DEEP BRAIN STIMULATION THINK TANK: UPDATES IN NEUROTECHNOLOGY AND NEUROMODULATION, VOLUME II

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DEEP BRAIN STIMULATION THINK TANK: UPDATES IN NEUROTECHNOLOGY AND NEUROMODULATION, VOLUME II

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EDITORIAL
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Editorial: Deep Brain Stimulation Think Tank: Updates in Neurotechnology and Neuromodulation, Volume II

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Editorial on the Research Topic

Deep Brain Stimulation Think Tank: Updates in Neurotechnology and Neuromodulation, Volume II

INTRODUCTION

The introduction of ever-newer technologies, improved software, and an increasing understanding of the cerebral anatomic and physiologic substrates involved in neurological and psychiatric conditions have all advanced research in neuromodulation, and its viable translation to clinical practice. In an effort to create a forum and nexus for stake and shareholders in techniques and technologies of deep brain stimulation (DBS) the group evolved into a freely interacting multidisciplinary group assembled to discuss challenges, problems, progress, and opportunities in the field. The first DBS Think Tank was convened in 2012 at the University of Florida, Gainesville FL. Since that initial meeting, the DBS Think Tank has grown, through the hybrid use of virtual and in-person resources to expand the involved number, and scope of worldwide participants from research, engineering, clinical, ethical-legal, and commercial disciplines. Since 2013, proceedings of the DBS Think Tank have been published and these highlight the most current and emerging work in the field. These published proceedings are open access and available to the public (https://fixel.ufhealth.org/research/deep-brain-stimulation-think-tank/think-tank-published-proceedings). Recognizing that different geographical regions often face unique needs and challenges, and to better understand the specific opportunities and limitations of DBS approaches upon the contemporary global stage, several researchers from Asia and Oceania initiated a separate meeting mirroring the spirit and structure of the original DBS Think Tank. The first East DBS Think Tank took place in June 2019 in Kyoto Japan, and this was followed by a virtual meeting in China in December 2020 (due to travel constraints imposed by the COVID-19 pandemic).

The DBS Think Tank should be seen as a genuine effort to conjoin multi-disciplinary perspectives to collaboratively crowd views, values, and issues in DBS research. Presentations and discussions have addressed a range of topics, including advocacy for DBS; improving clinical outcomes; technical and methodological, innovations and advancements; broadened understanding of neurophysiology, and neuropathology; and ethical questions, problems, and their potential solutions. As open dissemination of developments in DBS is both needed and critical for the advancement of science as a viable social good. Ongoing collaboration with Frontiers Editorial Office has afforded rapid yet nonetheless detailed review of work in the field.

In this spirit, this Editorial focuses upon the second volume. Twenty-three manuscripts were accepted within four different categories: (1) Clinical outcomes and DBS practice, (2) Neuromodulation for neuropsychiatric conditions [with particular emphases upon depression and OCD], (3) New insights toward integrating neuroimaging and DBS and (4) Progress in incorporating other neurotechnology in DBS research and clinical applications.

The Eighth annual DBS Think Tank Proceedings have been published. Vedam-Mai summarizes the discussions that took place in September 1st and 2nd, 2020. As in previous years, the meeting reviewed currently available advances in commercially offered DBS devices, and dedicated a section to discussing the ethical implications of (1) using DBS for rare diseases; (2) providing continued access to DBS—and supportive neuroscientific and technological methods after trials are completed; ongoing and future activities of the NIH BRAIN Initiative (inclusive of those NIH enterprises in ethics that are focused upon DBS). Discussions of the status of DBS for management of depression, development and use of novel approaches to identifying neurological node and network dysfunction in depressive signs and symptoms, and the use of neurophysiologic and neuroimaging techniques and tools to refine DBS targeting (see also below). Other advances were addressed and included the use of precision imaging and connectomic surgery; adaptive DBS; optogenetics methods for facilitating improved understanding of the molecular neurobiology of diseases; and the use of local field potentials (LFPs) as biomarkers for DBS control and programming.

ADVANCES IN DBS CLINICAL PRACTICE

Zhang et al. from Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China share their patients' experiences of the challenges encountered with DBS treatment during the early stages of the COVID pandemic. Indubitably, cancellations and delays of DBS surgeries were common as part of the initiatives to prevent the spread of the virus, and this disrupted the provision of neurological care—a reality that occurred not only in China, but subsequently in many other parts of the world. Of note was that that patients seeking DBS surgery during the initial phase(s) of the pandemic were predominantly as consequence of routine clinical referral; personal safety that could be provided by hospital care; and poor control of severe neurological symptoms through the use of other therapeutic modalities.

Multiple authors from different institutions, and presented by Mahajan et al. provide results of a comprehensive 58-question web-based practitioner survey conducted between December 2015 and May 2016 that focused upon DBS referral practices and peri-operative management. These results reveal considerable variability in the perceived best approaches for DBS selection, target selection, procedure type, and postoperative practices. As well, small, but significant differences in practice were noted across global regions, with differential utilization of multidisciplinary teams, and various (mood and cognitive) assessments prior to surgery.

Molina et al. report their experience using closed-loop DBS to treat medication-refractory freezing of gait (FoG) in Parkinson's disease (PD). Management of FoG. a paroxysmal phenomenon that provides an ideal framework for the possibility of "on demand " closed-loop DBS (CL-DBS), was noted to be challenging, with limited benefit achieved by accessing current targets [viz.- the pedunculopontine nucleus (PPN) for medication-refractory FoG]. Molina et al. compared the preoperative number of FoG episodes vs. the number of FoG episodes at 6 months post-DBS at the optimized settings in a gait lab. While the primary outcome variable was met in three of the five subjects who exhibited a >40% improvement in the number of FoG episodes from baseline to 6 months when on acute PPN CL-DBS, there were no significant differences between the pre-DBS and month 6 FoG counts at the group level. Moreover, there were numerous reports of side effects in this cohort, with 40% explantation due to delayed infection.

Investigators at the Cleveland Clinic and Case Western University in Ohio examined changes in PD patients' desired level of control of their DBS, and perception of global life control throughout DBS (Merner et al.). Participants reported decreased desired control of stimulation throughout DBS treatment, and significantly greater global life control. These findings highlight important distinctions between particular aspects of control, and suggest that patients may be more willing to share or cede certain domains of control as they gain greater global life control consequential to DBS intervention.

Sarica et al. provide a comprehensive review of key hardware and software specifications of commercially available IPG systems; offering a detailed account of challenges and developments related to DBS hardware, and highlighted strategies to improve IPG longevity and other practical problems.

Wong et al. detail the use of burst-cycling deep brain stimulation (BCDBS) for the management of FOG in PD. They reported benefit of BCDBS that was comparable to conventional DBS in measures of FOG, gait, functional mobility and other motor symptoms. These results support BCDBS as a feasible, safe, and well-tolerated intervention with considerable potential as a viable future DBS programming strategy.

The neuromodulation group at the University of Florida studied the effect of DBS on pallidal oscillatory activity and symptom severity in a PD patient implanted with the Medtronic Percept system (Cagle et al.). Using recordings of pallidal LFPs while delivering stimulation in a monopolar

configuration using stepwise increments (0.5 mA, every 20 s), it was found that electrical stimulation delivered to the target region elicited beta desynchronization. Beta power was strongly correlated to improved bradykinesia (when measured in the acute clinic setting). Interestingly, it was noted that beta power *rebounded* when the stimulation amplitude was increased, and this was associated with worsening bradykinesia. Although the mechanism for this phenomenon is unknown, their results can provide useful information to parametrize therapeutic windows for DBS programming.

Adult-onset truncal dystonia (ATD) is a rare presentation of this disorder, accounting for ∼10% of segmental dystonia affecting the trunk, inclusive of the paraspinal and abdominal wall muscles. ATD presents a clinical challenge, as response to treatment has been limited to date. Few reports have specifically addressed the potential role of DBS in the management of dystonic opisthotonos in the context of truncal predominant adult-onset dystonia. In this light, Tambirajoo et al. present outcomes of (three patients with) ATD managed with pallidal DBS, who showed a rapid and sustained clinical improvement of their symptoms with postoperative follow-up of 2–3 years.

Chen et al. discussed the importance, role, and value of large-scale data infrastructure in developing next-generation DBS therapeutics. Increasing challenges of managing massive (multi-scalar, and diverse) data include issues and problems in data acquisition, storage, organization, analysis, which are each and all instrumental to integrating complex neural time-series data with dynamic assessments of patients' clinical signs and symptoms. The authors reviewed Rune Lab, a scalable, HIPAA-compliant, cloud-based data platform designed for (1) time-synchronization and aggregation of multi-modal datasets (2) real-time data access, and (3) data analysis at the multiple terabytes scale directly in the cloud; and concluded that the system architecture, development process, and viability of shared data platforms afford considerable utility and value in both DBS research and clinical utility.

DBS THERAPEUTICS FOR NEUROPSYCHIATRIC CONDITIONS

Major depressive disorder is a common, often disabling disorder with high rates of treatment resistance, for which DBS continues to be explored as a valuable potential intervention. There is increasing evidence that depression is characterized by distributed network dysfunction that extends beyond a single brain region or neurochemical system. Computational advancements employing a network neuroscience framework have enabled brain activity to be modeled with greater granularity and complexity so as to better understand such distributed processes.

Scangos et al. studied whether application of a novel computational approach to large sample, high spatiotemporal resolution neural recordings in humans could demonstrate the functional organization and coordinated activity patterns of neurological networks involved in clinical depression. Using intracranial mapping with multi-channel iEEG for seizure localization as part of standard medical care while collecting clinical data regarding depressive symptoms, they elucidated two putatively contributory subnetworks. The first was characterized by left temporal lobe hypoconnectivity and pathological beta activity; the second was characterized by a hypoactive, but hyperconnected left frontal cortex. These novel findings have important implications for diagnosis, subtyping, and planning and monitoring treatment of depressive disorder(s).

Thomson et al. provided an exploratory study that employed a prospective qualitative design, and iterative thematic analysis to assess both patient perspectives of, and goals for DBS treatment (targeting the bed nucleus of the stria terminalis) of depression. It was found that patients' decision to undergo DBS was characteristically motivated by the intolerability of life with severe depression, and the exhaustion—and ineffectiveness—of other available treatment options. It was also reported that many patients expressed surprised by the lengthy process of establishing optimum stimulation settings, and felt the intervention was a "work in progress."

NEW INSIGHTS TO THE COMBINED USE OF NEUROIMAGING AND DBS

Schrock et al. presented a case report that reviewed the importance of lead localization within the targeted nucleus for achieving effective clinical benefit. Using 7T MRI and computational modeling it was shown that severe mood-related side effects (with minimal motor improvement) occurred in a PD patient following DBS in the limbic/associative territory of the STN. The patient experienced marked improvement in motor benefit, and resolution of mood side effects following repositioning of the lead within the STN sensorimotor territory. These findings served as a basis for a patient-specific anatomical model (provided in outstanding graphic depiction) of the STN with parcellation into distinct functional territories, which enabled computational modeling to evaluate the extent and effect(s) of activating particular target sites.

Chang et al. present their data from a single subject, and discussing the potential use of DBS of a closely related nucleus dorsal to the PPN—the cuneiform nucleus (CnF) as potentially important for gait control. Targeting guided by diffusion tensor imaging (DTI) and anatomical landmarks afforded neurosurgical details for targeting, which produced improved outcome metrics in gait, and in short-term reduction of FOG, which certainly warrant additional follow up studies.

Morishita et al. provide a case report of a patient with facial and palatal tremor due to craniofacial dystonia, and use normative connectome analysis to determine activation of specific fiber tracts *via* pallidal vs. thalamic DBS. Their results revealed that the fiber tracts associated with VTA of GPi DBS had different connections with the facial area of the motor cortex, which could explain differences in clinical outcomes, and help to guide future DBS intervention(s).

PROGRESS IN INCORPORATING NEUROTECHNOLOGY IN DBS

Tabacof et al. report the safety of a wearable, vibrotactile stimulation device for treating tremor in PD, noting that treatment of resting tremor is ineffective in a significant number of patients. In this work, a vibrotactile stimulation was delivered bilaterally to the wrists and ankles using four custom-built, wearable devices to evoke optimal full body vibrotactile stimulation. This system was shown to produce a moderate effect on tremor, with no reported adverse events, and appears to be safe and well-tolerated.

The effect of DBS on cerebellar vs. non-cerebellar tremor in a patient with multiple sclerosis was discussed by Xie et al. In this case report, a wearable accelerometer was applied to the index finger of each hand to quantitatively characterize kinetic tremor frequency and amplitude at the initiation and cessation of hand movement in a patient treated with thalamic DBS. In comparing both limbs in the ON and OFF stimulation state, they noted good responses, with reduction of cerebellar tremor, but only limited effect—with minimal functional benefit—on distal limb oscillation.

Chronically implanted, bidirectional, neural interfaces provide unprecedented access to, and assessment of human neurological function during activities of daily living in a range of disease and symptom states. To successfully optimize therapy for patients implanted with these devices, analyses must be conducted offline of the recorded neural data. The format, volume, and complexity of raw data from these devices necessitate conversion, parsing, and temporal reconstruction in advance of the time-frequency analyses and modeling required for evaluation toward such ends, Sellers et al. provide an open-source MATLAB toolbox capable of taking raw files (from the Summit RC+S device, available under investigational device exemption and employed in a range of clinical indications), transforming the data, and providing salient outputs and user functionality. This could be important for both researchers and clinicians, particularly as new commercial devices allow for prolonged (ecologically valid), assessment of brain signals relevant to sustainable therapeutic outcomes.

Taken together, these contributions afford a view of a leading edge of DBS research and its translational applications in clinical care. As mentioned above, a patient astutely noted that DBS is indeed a "work in progress." To be sure, the field and approaches gain precision and momentum from the cooperative efforts of the groups of engineers, scientists, clinicians, and those who inform and develop guidelines and policy to support ongoing experimentation, and therapeutic improvement. As we approach the decadal anniversary of launch of the US BRAIN Initiative (available online at https://www.braininitiative.org and https://obamawhitehouse.archives.gov/BRAIN) we believe it is important to let its titular invocation of "advancing innovative neurotechnology" serve as the cornerstone for investigation, invention, and safe, ethically sound clinical intervention. It is our hope that the DBS Think Tank—along with other focally dedicated efforts—will continue to provide nexus and vectors for such progress.

AUTHOR CONTRIBUTIONS

AR-Z, JG, CH, CB, and MO: draft manuscript preparation and revisions. All authors reviewed the results and approved the final version of the manuscript.

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CASE REPORT
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7T MRI and Computational Modeling Supports a Critical Role of Lead Location in Determining Outcomes for Deep Brain Stimulation: A Case Report

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Subthalamic nucleus (STN) deep brain stimulation (DBS) is an established therapy for Parkinson's disease motor symptoms. The ideal site for implantation within STN, however, remains controversial. While many argue that placement of a DBS lead within the sensorimotor territory of the STN yields better motor outcomes, others report similar effects with leads placed in the associative or motor territory of the STN, while still others assert that placing a DBS lead "anywhere within a 6-mm-diameter cylinder centered at the presumed middle of the STN (based on stereotactic atlas coordinates) produces similar clinical efficacy." These discrepancies likely result from methodological differences including targeting preferences, imaging acquisition and the use of brain atlases that do not account for patient-specific anatomic variability. We present a first-in-kind within-patient demonstration of severe mood side effects and minimal motor improvement in a Parkinson's disease patient following placement of a DBS lead in the limbic/associative territory of the STN who experienced marked improvement in motor benefit and resolution of mood side effects following repositioning the lead within the STN sensorimotor territory. 7 Tesla (7 T) magnetic resonance imaging (MRI) data were used to generate a patient-specific anatomical model of the STN with parcellation into distinct functional territories and computational modeling to assess the relative degree of activation of motor, associative and limbic territories.

Keywords: deep brain stimulation, subthalamic nucleus, Parkinson's disease, electrode location, ultra-high field MRI, computational modeling, case report

INTRODUCTION

Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is an effective therapy for the motor symptoms associated with Parkinson's disease (PD). Although STN DBS has been performed for PD for more than 30 years, the optimal site for implantation within the target remains under debate. In fact, in a recent survey thirty-three movement disorders specialists were presented with

the same canonical representation of the STN and were asked to indicate their preferred targeting location. While results showed that there was some clustering for the preferred target observed in the dorsolateral STN and subthalamic area, the suggested targets were heterogeneous, and no consensus existed. The authors concluded that the optimal target for STN DBS needed further verification (Hamel et al., 2017). Furthermore, while many have argued that the lead should be placed within the sensorimotor territory of the STN (Herzog et al., 2004; Wodarg et al., 2012; Horn et al., 2017), others report similar effects with leads placed in the associative or motor territory of the STN (Welter et al., 2014), and some assert that placing a DBS lead "anywhere within a 6 mm diameter cylinder centered in the presumed middle of the STN based on stereotactic atlas coordinates produces similar clinical efficacy" (McClelland et al., 2005). Still others have argued that the best location includes a region just dorsal to the STN (Plaha et al., 2006; Kasasbeh et al., 2013). These discrepancies likely contribute to the significant variability of clinical outcomes observed in clinical trials and day-to-day DBS therapy across centers (Deuschl et al., 2006; Follett et al., 2010; Vitek et al., 2020) as well as the unexpectedly high rate of documented DBS lead revisions (Rolston et al., 2016). Possible causes for these discrepancies and clinical observations include targeting preferences, image quality and the use of brain atlases that do not account for patient-specific anatomic variability.

Anatomical and imaging studies have divided the STN into three separate, though partially overlapping zones, serving motor, associative, and limbic function (Lambert et al., 2012; Haynes and Haber, 2013). 7 Tesla (7T) MRI techniques combined with post-processing analysis of diffusion weighted images have provided compelling evidence that the distribution pattern of these functional zones may be patient-specific (Plantinga et al., 2018).

Here, we take advantage of these patient-specific 7T MRI techniques as well as computational modeling of pathway activation to seize a unique opportunity to study a patient who developed severe, reversible depression after undergoing STN DBS with a lead placed in the associative/limbic territories. The patient subsequently required revision of lead location, which alleviated the mood side effects and improved motor function. We determined the location of individual stimulating contacts within the subterritories of the STN following the 1st and 2nd implantations. We then constructed a patient-specific computational model of the STN DBS settings to quantitatively estimate the degree of activation of specific neuronal pathways that were modulated at each clinical stimulation setting. Stimulation site within the STN was found to be a crucial determinant of this patient's motor outcomes and presence or absence of mood side effects, consistent with the hypothesis that DBS outcomes are critically dependent on lead location.

CASE PRESENTATION

A 52-year-old patient with a 14-year history of PD underwent bilateral STN DBS for treatment of motor fluctuations with severe rigidity and bradykinesia during off periods and frequent disabling dyskinesias when on, despite optimization of anti-parkinsonian medications. The patient reported longstanding baseline anxiety but had never required psychiatric treatment. There was no history of a mood disorder.

The patient was a participant in a clinical trial of STN DBS for the treatment of PD. The study was approved by the University of Minnesota's IRB board and the patient provided informed consent (University of Minnesota Twin Cities, MN, United States, RRID:SCR_011674).

With the patient awake, single unit microelectrode mapping was performed to define the borders and sensorimotor territory of the STN through identification of cells whose discharge was modulated by passive movements of the contralateral limbs. This was followed by intraoperative test stimulation from the DBS lead (BSC-DB-2201, Boston Scientific) to assess side effect thresholds. The left STN lead was implanted first. Test stimulation with the DBS lead at 130 Hz, 90 μs using contacts 2−/4+ elicited paresthesia at 4.0 mA, while tongue contractions were elicited using contacts 4−/2+ at 6 mA. Following implantation of the left STN, the right STN was mapped and the lead implanted. During test stimulation, however, the threshold for left face and chest paresthesia was unacceptably low (2.0 mA), suggesting proximity to medial lemniscal fibers running posteromedial to the STN. Thus, the lead was repositioned 2 mm anteriorly. Test stimulation at this location revealed transient paresthesia at 5.0 mA.

Shortly after programming the second (right) side (see **Table 1** for programming settings) the patient became hypomanic and severely anxious, requiring an urgent clinic appointment. The DBS settings were adjusted with reduction of the stimulation amplitude bilaterally and switching the right lead to activation of a more dorsal contact, following a strategy previously outlined (Greenhouse et al., 2011). On these settings, and despite a further dorsal shift of stimulation on the right lead, the patient developed severe depression, anxiety, and frequent crying. Four months after initial implantation, the patient attempted suicide with a pain medication overdose; the patient recovered without medical treatment. DBS was turned off on both sides at this time and the patient was hospitalized briefly for psychiatric treatment. Her mood significantly improved with DBS turned off.

The patient returned to clinic for formal assessment of stimulation effects on mood (see **Table 2**). Initial assessment with DBS OFF revealed the patient was euthymic with no depression, anxiety, or hypomania. For the subsequent evaluations the patient was blinded to the stimulation state. 2.5 h after taking morning medications, the right DBS lead was first activated to the settings the patient was on at the time of the suicide attempt. The left lead, which had not been associated with any mood changes when ON, remained OFF. Within 2 min of stimulation onset the patient reported feeling "a profound sadness, hopelessness, despair, and loss of trust. . . I don't think I can make it." At 3 min the patient started crying and the spouse observed "a noticeable change in her eyes, as if she is no longer my wife." At 4 min the negative mood effects seemed to peak, and the patient reported feeling "alone. I feel like I'm pulling away. It's hard to see things will ever get better." DBS was then turned OFF without notifying the patient, and immediately the patient said "I feel hopeful. The room just became brighter."

TABLE 1 | DBS programming settings and UPDRS III Motor Scores.

	Pre-surgical baseline		Initial settings (DBS is turned ON)	DBS with misplaced R STN lead on Low settings (due to mood side effects)	Settings at time of suicide attempt and formal mood testing	Pre-surgical baseline (Revision surgery)	DBS with revised R STN lead at optimized settings
Time from initial lead implantation	**(−)4 weeks**		**(+)4 weeks**	**(+)16 weeks**	**(+)24 weeks**	**(+) 30 weeks**	**(+)3 years; (+)2 years from R STN revision**
Left DBS lead	NA		Case+, 3−; 1.5 mA; 60 μs; 130 Hz	Case+, 3−; 0.9 mA; 60 μs; 130 Hz	Case+, 4−; 0.6 mA; 60 μs; 130 Hz	NA	Case+, 4−; 1.2 mA; 60 μs; 130 Hz
Right DBS lead	NA		Case+, 11−; 1.3 mA; 60 μs; 130 Hz	Case+, 12− (70%), 13− (30%); 0.6 mA; 60 μs; 130 Hz	Case+, 12− (70%), 13− (30%); 1.0 mA; 60 μs; 130 Hz	NA	Revised lead: Case+, 12−; 1.2 mA; 60 μs; 130 Hz
Medication state	OFF meds	ON meds	OFF meds	OFF meds	ON meds	OFF meds	OFF meds
UPDRS III LEFT body subscore (% improvement from pre-op baseline)	13	6	13 (0%; scored with DBS still OFF)	9 (30.77%)	NA	13	1 (92.31%)
UPDRS III RIGHT body subscore (% improvement from pre-op baseline)	17	7	14 (17%; scored with DBS still OFF)	8 (52.94%)	NA	14	2 (88.24%)
UPDRS III subscore (% improvement from pre-op baseline)	48	17	45 (6.25%; scored with DBS still OFF)	31 (35.42%)	NA	49	14 (70.83% compared to pre-DBS; 71.43% compared to pre-revision baseline)

DBS, Deep Brain stimulation; C+, Case as anode; 3−, Contact 3 as cathode; 12− (70%), Contact 12 as cathode receiving 70% of the current; UPDRS III denotes Unified Parkinson Disease Rating Scale Part 3 (motor subsection). The thick vertical line indicates the timepoint for DBS implantations.

Within 6 min of turning off the stimulation her mood had returned to baseline.

To assess the location of the lead contacts and correlate these to the clinical outcome we used a combination of high-resolution 7T MRI and post-operative CT [for details see Duchin et al. (2018) and **Figures 1A–D**].

CLINICAL AND IMAGING METHODS

Clinical Assessment

The motor effects of stimulation were assessed by calculating the sum of lateralized contralateral body Unified Parkinson's Disease Rating Scale Part 3 (UPDRS III) subscore (left body tremor, rigidity, and bradykinesia). UPDRS III summed scores are also presented in **Table 1**.

Scanning Protocol

In addition to the standard-of-care clinical imaging, the patient was also scanned with a 7T MRI (Magnetom 7 T Siemens, Erlangen, Germany) with SC72 gradients capable of 70 mT/m and a 200 T/m/s slew rate using a 32-element head array coil (Nova Medical, Inc., Burlington, MA, United States). The scanning protocol included: T1-weighted whole brain scan (0.6 mm^3 isotropic, 6.5 min), T2-weighted coronal slab covering the whole STN and substantia nigra (0.4 mm × 0.4 mm × 1.0 mm, 6.5 min), and diffusion-weighted images, covering the whole brain (50 directions, b-value = 1500 s/mm^2, 4 additional b0 volumes, 1.5 mm^3 isotropic). The diffusion images were acquired twice, each with different phase encoding directions: anterior-posterior and posterior-anterior (acquisition time = 2 × 4.5 min). The patient was awake and on her regular medical regimen during the scanning session. Full scanning protocols are described in great detail in previous publications (Plantinga et al., 2014; Duchin et al., 2018; Patriat et al., 2018). High resolution, post-operative computed tomography data (0.3 mm × 0.3 mm × 0.6 mm, Siemens Biograph 64) were used 4 weeks after the first and the second (revision) DBS surgery.

Image Processing and Analysis

Given the large variability in size, shape, and orientation of the STN (Duchin et al., 2018), manually segmenting the structure on the 7 T high-resolution images is more appropriate than utilizing a template. Therefore, three experts congruently performed the segmentation. Following our previously utilized techniques (Plantinga et al., 2018), probabilistic tractography was used as a primary tool to parcellate the STN into motor, associative, limbic, and "other" regions after performing motion, susceptibility and eddy current correction (FSL, RRID:SCR_002823). The post-operative CT and MRI images were non-linearly registered to

TABLE 2 | Formal assessment of mood effects from DBS.

DBS state (ON medication)	DBS settings	Mood assessment
DBS OFF	NA	Euthymic. No depression, anxiety, or hypomania.
Right DBS lead ON; Left DBS lead OFF	C+;12− (60%);13− (40%);1.0 mA;60 μs;130 Hz	2 min: Patient felt the onset of a profound sadness, sense of hopelessness, despair, and loss of trust. 3 min: Patient started to cry; husband reported a clear change in her eyes. 4 min: Depressed mood became overwhelming: "I feel like I'm pulling away. I feel alone. I don't see that things will ever get better. I don't think I could make it." DBS turned back OFF without warning: Immediately the patient reported "I feel more hopeful. The room seems brighter." 5 min after DBS turned OFF: Mood reported to be 80% back to baseline.
Right DBS lead OFF; Left DBS lead ON	C+;4−;0.6 mA;60 μs;130 Hz	3 min: Mild increase in right-sided dyskinesia. Mood unchanged, euthymic. No changes in mood during 10 min of monitored stimulation.

DBS, Deep Brain Stimulation; NA, Not Applicable; Min, minutes.

determine the final location of the electrode with respect to the patient's own anatomy (3D Slicer, RRID:SCR_005619; elastix, RRID:SCR_009619).

Computational Modeling

The anatomical portion of the model was constructed from segmentation of high field imaging data (7T) with post-operative CT scans for lead localization. The STN volumes were then populated with biophysical multi-compartment neuron models that were perturbed with clinical DBS waveforms whose amplitudes were calculated from simulations of the tissue voltages induced through an anisotropic and inhomogeneous finite element model (FEM, COMSOL Multiphysics 5.4, RRID:SCR_014767) (Pena et al., 2018) of the electrode-tissue interfaces for this patient. T1-weighted anatomical images data were used to manually extract the brain from the cranial and extracranial anatomy (called lumped head tissue hereafter). Then the white matter, gray matter and cerebrospinal fluid brain tissue were segmented. The STN volumes were then populated with multi-compartment biophysical neuron models with realistic morphologies of dendrites, soma and axon and were perturbed with clinical DBS waveforms (Pulse width: 60 μs, Freq: 130 Hz) in NEURON using extracellular mechanism (NEURON, RRID:SCR_005393). The FEM was parameterized using diffusion-weighted imaging data from the patient. Together, these models provided a quantitative estimate of which neuronal populations were directly modulated by each clinical stimulation setting.

OBSERVATIONS AND RESULTS

Using diffusion MRI data, a patient-specific tractography-based parcellation of the STN was performed (**Figures 1A,B**; Plantinga et al., 2018). This revealed a clear functional organization with partially overlapping zones, including a dorsal posterolateral motor region, a central associative region, and a smaller limbic region located anteromedially (**Figures 1A–D**). The left DBS lead was confirmed to be within the sensorimotor territory (**Figure 1C**). The right DBS lead was located in the anterior portion of the STN near the border between the limbic and associative territories (**Figures 1C,D**). Due to the stimulation-related adverse mood effects we chose to reposition the right lead posteriorly toward the sensorimotor region and the lead position was surgically revised. Following revision reconstruction of the right lead was confirmed to be within the STN sensorimotor territory (**Figures 1C,D**).

Motor benefit was measured by summing lateralized Unified Parkinson's Disease Rating Scale Part 3 (UPDRS III) subscores as well as the UPDRS III total score and the relative degree of activation of the functional territories were modeled and correlated to the patient's motor benefit and presence or absence of mood side effects (**Table 1**). Prior to DBS, the OFF medication left body UPDRS III subscore was 13 (Parkinson's medications were held for at least 12 h prior to assessment). At 16 weeks, with stimulation ON at very low settings, due to low thresholds for adverse mood effects, the left body (Right STN) motor subscore was reduced to 9 (31% improvement). After the right lead was repositioned posteriorly into the motor territory, the left body motor subscore was reduced to 1 (92% improvement) without associated depression or anxiety. Note that this marked reduction included the lateralized left body scores only. The right body scores were reduced from 17 to 8 at 16 weeks (53% improvement) and to 2 after optimization post revision surgery (88% improvement). The additional benefit to the right body following revision were likely due to the change in contact (from 3−/C+ to 4−/C+) and small increase in amplitude (0.9 to 1.2 mA) of the left STN combined with potential ipsilateral benefit resulting from the revised right STN implant. The UPDRS III score was reduced from 48 to 31 at 16 weeks (35% improvement) and to 14 after optimization of the revised lead (71% improvement).

These clinical improvements correlated with a patient-specific computational model of the STN DBS settings that included an anisotropic and inhomogeneous finite element model (FEM, COMSOL Multiphysics 5.4) (Pena et al., 2018) coupled with a multi-compartment biophysical model of STN neurons (Miocinovic et al., 2006). This provided a quantitative estimate of the percentage of each modeled neuronal pathway (i.e., motor, associative, limbic, or other pathways within STN)

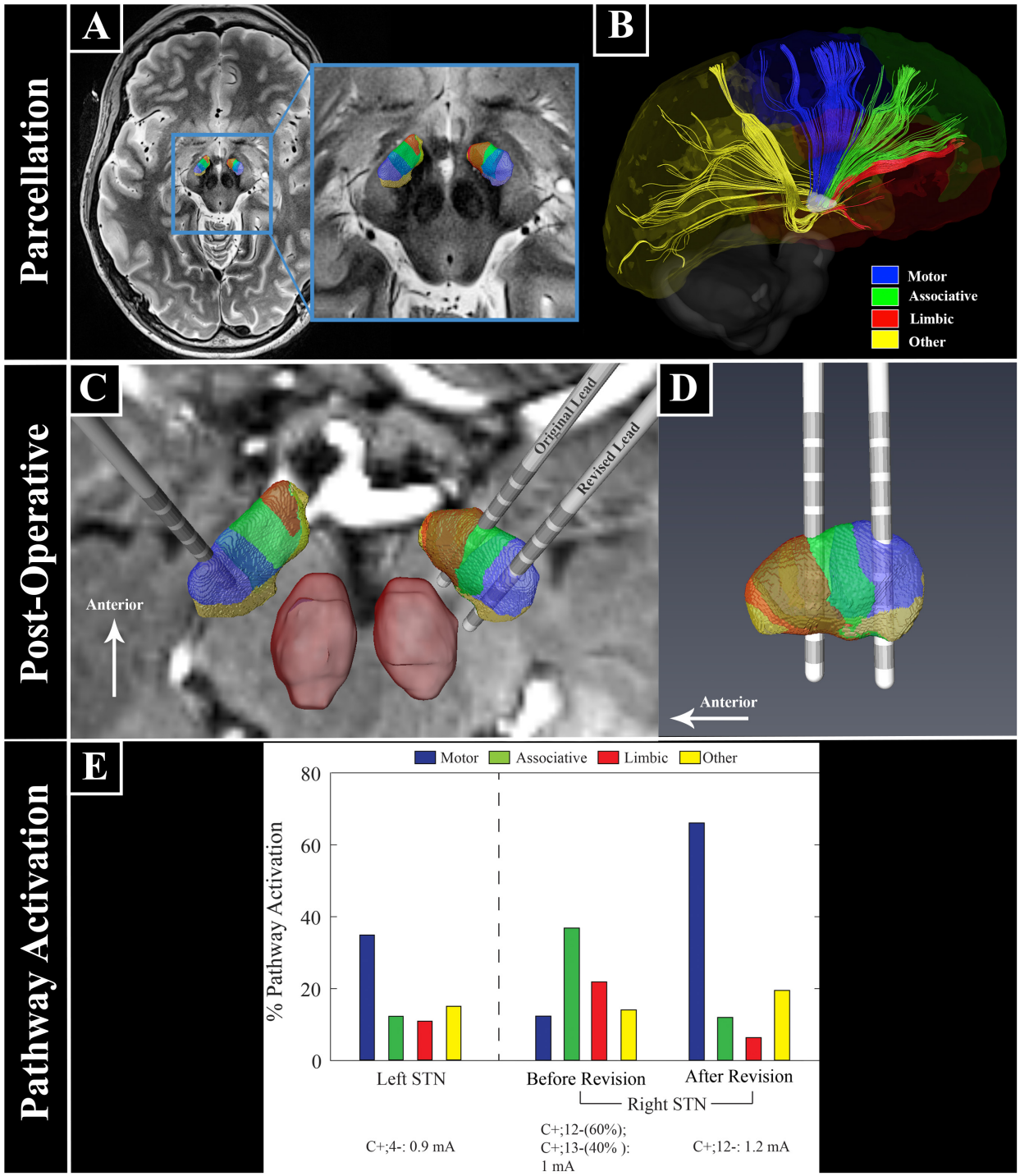

FIGURE 1 | Ultra high field 7 Tesla MR images for patient-specific STN parcellation, lead location, and computational modeling. **(A)** STN parcellation results. **(B)** Representation of white matter tracts between the STN and the cortex. **(C,D)** Lead locations with respect to the STN parcellation. **(E)** Patient-specific computational model of bilateral STN-DBS settings before and after right lead revision. The anatomical portion of the model was constructed from segmentation of high field imaging data (7T) with post-operative CT scans for lead localization. The STN volumes were then populated with biophysical multi-compartment neuron models that were perturbed with clinical DBS waveforms whose amplitudes were calculated from simulations of the tissue voltages induced through an anisotropic and inhomogeneous finite element model (FEM, COMSOL Multiphysics 5.4) of the electrode-tissue interfaces for this patient. The FEM was parameterized using diffusion-weighted imaging data from the patient. These models provided a quantitative estimate of the percentage of each neuronal pathway directly modulated by a clinical stimulation setting, with maximum possible activation of 100% for each pathway. Across all lead implants, the patient-specific models showed that stimulation of the motor STN was important to treat parkinsonian motor signs, while stronger activation of the associative and limbic territories resulted in the acute effects on mood.

modulated at each clinical stimulation setting. Before revision of the right STN lead settings, there was strong activation of both associative and limbic STN territories, with only weak activation of the motor territory (**Figure 1E**). In contrast, the clinical settings of the revised right lead as well as the left STN lead showed strong activation of motor STN neuronal populations, which correlated with greater motor benefit (**Figure 1E**).

DISCUSSION

This case report demonstrates the importance of lead location as a critical variable in determining STN DBS clinical outcomes. Using 7T MRI patient-specific STN parcellation, we provide a first-in-kind within-patient demonstration of superior motor outcomes with lead placement within the sensorimotor territory, while stimulation within associative and limbic regions provided less motor improvement and was associated with severe mood side effects. The significant improvement in motor benefit seen after repositioning the lead into the sensorimotor territory, is in agreement with previous studies that have suggested optimal motor benefit with stimulation of the dorsolateral motor STN (Wodarg et al., 2012). However, this result is in stark contrast to others who have argued that similar outcomes can be produced with stimulation anywhere within the STN (McClelland et al., 2005; Kasasbeh et al., 2013), or that the greatest motor improvements are seen in the most anterior electrode locations, closer to or in the associative territory (Welter et al., 2014).

This discrepancy may reflect the fact that these studies did not have the visualization tools that would allow for accurate determination of lead location with respect to individualized patient STN anatomy.

Previous studies were limited by: their use of low (McClelland et al., 2005) or intermediate (Kasasbeh et al., 2013; Welter et al., 2014) field MR imaging data making it difficult to accurately visualize the borders of the STN; imaging analyses that were not patient-specific (McClelland et al., 2005; Kasasbeh et al., 2013; Welter et al., 2014); utilizing AC-PC coordinates (McClelland et al., 2005) or Schaltenbrand atlas-based (Kasasbeh et al., 2013) lead localizations. Welter et al. (2014) used MR tractography, but employed a deformable atlas and theoretical STN subdivisions were extrapolated from tract tracings in non-human primates (Haynes and Haber, 2013; Welter et al., 2014), which does not take into account the significant between-patient variability of subcortical structures (Duchin et al., 2018; Plantinga et al., 2018).

Our finding of partial motor benefit with the lead placed more anteriorly was similarly reported in a recent study of STN DBS lead revisions in select patients with suboptimal motor benefit [as defined by inferiority to the patients suprathreshold ON medication motor scores (Nickl et al., 2019)]. This finding of partial motor improvement with lead location in the associative territory may help explain why some have argued that there is no difference between associative or motor territory stimulation (Welter et al., 2014). If we accept the baseline assumptions that: (1) there exist meaningful inter-individual anatomic variability of subcortical structures (Duchin et al., 2018; Plantinga et al., 2018), (2) imaging tools, until recently, have had limited ability to detect these differences, and (3) the STN functional territories include zones of considerable overlap (Haynes and Haber, 2013; Plantinga et al., 2018), then not only is the unresolved controversy over DBS lead location understandable, but we can also provide one additional explanation for why there has been such remarkably high variability of DBS outcomes within and across studies (Deuschl et al., 2006; Follett et al., 2010; Vitek et al., 2020).

In our patient, stimulation of the associative STN with spread into the limbic STN territory was likely responsible for her reversible disabling depression, transient hypomania, and feelings of euphoria before morphing into more persistent feelings of helplessness and depression. A remarkably similar case, the first reported in 1999, also observed the peak of negative mood effects 4 min after stimulation was turned on. However, the ability to determine the relative distribution of pathway activation responsible for the adverse effects was limited by the imaging and modeling technology of the time (Bejjani et al., 1999). Stimulation-induced hypomania is a well-recognized potential adverse mood effect of STN DBS (Mallet et al., 2007; Welter et al., 2014) that has been attributed to spread of stimulation into the putative limbic or associative STN territories. Our patient-specific imaging data (**Figures 1A–D**) and patient-specific computational models (**Figure 1E**) strongly support this hypothesis.

Reviewing the approach used for DBS lead placement we believe the low thresholds for stimulation induced paresthesia was the result of using a new device. With this device rather than abruptly scaling current amplitude up and down with a screener system to look for stimulation evoked muscle twitch, we assessed the patient for capsule effects associated with stimulation by disconnecting and reconnecting the stimulation cable. In retrospect this likely induced a capacitive discharge leading to the induction of intolerable paresthesia at low thresholds necessitating moving the lead from its initial implant site to a more anterior location.

While one could interpret the data based on a volume of tissue activated (VTA) approach, there is a growing number of studies showing that the VTAs are significantly less accurate than the pathway-specific approach adopted in this study (Gunalan et al., 2017; Howell et al., 2019). Additionally, the use of volumes is a misnomer when considering neuronal responses to stimulation, which have shown that electrical stimulation results in a sparse density map of neuronal activation (Histed et al., 2009; Xiao et al., 2018; Michelson et al., 2019).

This work is not without its limitations. Although this case report contains a cutting-edge imaging data set and analytics, e.g., 7T MRI patient-specific parcellation and modeling pathway activations, the work is based on a single patient. In support of the findings presented here, however, there are previous reports of mood changes during DBS that resolved when DBS was discontinued. The current study provides direct evidence in support of these studies while providing additional findings related to the relative effect of motor, associative and limbic pathway activations on clinical outcomes and side

effects. Another potential limitation is movement artifact(s) associated with scanning movement disorder patients when using high-resolution MRI. To mitigate this problem scanning protocols were developed to minimize sensitivity to head motion [see (Duchin et al., 2018)]. A typical concern when scanning at 7T is an increased impact of susceptibility artifacts on diffusion data, especially in the phase encoding direction. To attenuate this issue, we followed the HCP (Glasser et al., 2013) scanning and preprocessing guidelines which include acquiring the diffusing "blip up" and "blip down" and using FSL topup/eddy current to minimize these distortions. Last while our imaging data were acquired with resolution higher than most clinical settings, partial volume of the diffusion imaging voxels may impact our ability to sharply define the borders between functional territories results given the relatively small volume of the STN.

CONCLUSION

We are entering an era of rapid technological advance in the field of neuromodulation, with the development of powerful imaging technologies (Duchin et al., 2018; Plantinga et al., 2018), innovative segmented lead designs, tailorable programming capabilities, multiple current source devices, and predictive computational models of pathway activation (Gunalan et al., 2017; Pena et al., 2018). In this study, consistent with the hypothesis that DBS outcomes are critically dependent on lead location, we provide evidence that, in many cases, suboptimal DBS outcomes can be rationally explained, and corrected, on an individualized basis with only millimetric intra-target adjustments in DBS lead location (Nickl et al., 2019). Using ultra high field (7T) MRI, recently approved for clinical use, we present a tool with which we may be able to answer previously unresolved questions in the field, and by its very nature will bring us one step closer to patient-specific DBS.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (JLV). The data are not publicly available due to them containing information that could compromise research participant privacy/consent.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Minnesota's IRB board. 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

LES and RP contributed equally to this work. LES, RP, NH, and JLV designed the study, performed the majority of the analysis, and co-wrote the manuscript. MG, JK, and MDJ performed the computational modeling and participated in editing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: LES has served as a consultant for Medtronic and Boston Scientific. RP is a consultant for Surgical Information Sciences, Inc. NH is a co-founder and shareholder in Surgical Information Sciences, Inc. JLV serves as a consultant for Medtronic, Boston Scientific, and Abbott, and serves on the scientific advisory board for Surgical Information Sciences, Inc.

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BRIEF RESEARCH REPORT
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Changes in Patients' Desired Control of Their Deep Brain Stimulation and Subjective Global Control Over the Course of Deep Brain Stimulation

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Objective: To examine changes in patients' desired control of the deep brain stimulator (DBS) and perception of global life control throughout DBS.

Methods: A consecutive cohort of 52 patients with Parkinson's disease (PD) was recruited to participate in a prospective longitudinal study over three assessment points (pre-surgery, post-surgery months 3 and 6). Semi-structured interviews assessing participants' desire for stimulation control and perception of global control were conducted at all three points. Qualitative data were coded using content analysis. Visual analog scales were embedded in the interviews to quantify participants' perceptions of control over time.

Results: Participants reported significant increases in their perception of global control over time and significant declines in their desired control of the stimulation. These changes were unrelated to improvements in motor symptoms. Improvements in global control were negatively correlated with a decline in desired stimulation control. Qualitative data indicate that participants have changed, nuanced levels of desired control over their stimulators. Increased global life control following DBS may be attributed to increased control over PD symptoms, increased ability to engage in valued activities, and increased overall self-regulation, while other domains related to global control remained unaffected by DBS.

Conclusions: There are few empirical data documenting patients' desire for stimulation control throughout neuromodulation and how stimulation control is related to other aspects of control despite the growing application of neuromodulation devices to treat a variety of disorders. Our data highlight distinctions in different types of control and have implications for the development of patient-controlled neurostimulation devices.

Keywords: deep brain stimulation, control, ethics, neuromodulation, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is often characterized by the acronym TRAP representing the cardinal motor symptoms: tremor, rigidity, akinesia, and postural instability. Patients with PD often use language that suggests they feel "trapped" with limited control over their body and lives due to the motor symptoms and/or unpredictable motor fluctuations. Paradoxically, in seeking to gain greater control of their symptoms and the ability to participate in valued activities and behavioral goals, patients with PD who undergo deep brain stimulation (DBS) need to relinquish some bodily control by partnering with the DBS team to share control over the brain stimulator. Patients are provided with the basic option to turn the stimulation on or off, as necessary for medical procedures, in case of emergencies, to check the batteries, or to preserve battery life in some conditions (e.g., essential tremor). Guidelines in the field advocate for maintaining constant stimulation to treat PD symptoms since motor symptoms are constant, particularly for patients implanted in the subthalamic nucleus (STN; Deuschl et al., 2006). The DBS team relies on the patient's feedback at regularly scheduled appointments to adjust stimulator parameters similar to patients undergoing medication titration. Nonetheless, there may be differences in the patients' perception of control of the DBS stimulator due to the invasiveness of the procedure and biotechnological properties.

This topic has generated interest in the neuroethics literature with some arguing that DBS results in self-estrangement and a loss of control vs. others who assert that DBS can enhance autonomy and control (e.g., Gisquet, 2008; Glannon, 2014; Gilbert et al., 2017). Most of the literature regarding device control *per se* has focused on patients' perceptions of control in the context of closed-loop DBS (e.g., for a recent review see Aggarwal and Chugh, 2020) or brain-computer interfaces (BCI; see Burwell et al., 2017 for a scoping review). Data specifically addressing this question in open-loop DBS are relatively scarce. Briefly, Klein et al. (2016) conducted focus groups with eight participants and more detailed individual interviews with seven patients who were implanted with open-loop DBS systems as part of clinical trials to treat either treatment-resistant depression or obsessive-compulsive disorder. The goal of the Klein et al.'s (2016) study was to explore patients' perspectives on closed-loop systems. One of the themes that emerged was related to control over the device function. Of most relevance to the current study, there was a range of responses regarding having control over the device with the majority of patients indicating that they would not be comfortable having sole or primary control over the stimulation and preferred that the stimulation settings be controlled by the clinical team. Goering et al. (2017) elaborated on these data and framed the participants' responses in the context of relational autonomy. Others (e.g., Gilbert et al., 2019) relied on a phenomenological approach in a small group of patients (n = 6) to explore patients' experiences with BCI in the context of treating uncontrolled seizures. Themes associated with control were evident in these data with patients indicating that the technology-enhanced feelings of control and some patients reporting the converse. Most of the available data addressing device control are qualitative data drawn from convenience samples. Reliance on convenience samples has the potential to increase bias and not reflect the experiences of the majority of patients who undergo DBS.

We prospectively examined the relationship between patients' desired control of the stimulator settings and their perception of global life control before and following DBS surgery as part of a larger study examining patients' goals and perceptions of control of their symptom and behavioral goals (Kubu et al., 2017). Participants were drawn from a consecutive series of patients scheduled for DBS surgery from a large academic medical center. We hypothesized that patients' desire for control of the stimulator would increase after surgery as would their perception of global control.

MATERIALS AND METHODS

The current study was part of a larger study on patients' goals for DBS (Kubu et al., 2017).

Participants

A consecutive series of 59 patients approved for DBS were approached from July 2009 to June 2011 to participate in a study examining patients' goals for DBS and perceptions of control. Most patients (n = 52, 88%) agreed to participate. Details regarding the patients who declined participation as well as inclusion/exclusion criteria are documented in our previous report (Kubu et al., 2017).

Measures

All participants completed a semi-structured interview before surgery that included questions regarding their desired control of the stimulator as well as their perception of global life control. Embedded within the structured interview were visual analog scales (VAS) in which participants indicated the extent to which they desired control of their stimulator with 10 representing complete control and zero representing no control. Concerning desired stimulation control patients were asked to, "indicate (on the VAS) the degree to which they desire to control the programming (e.g., stimulation settings) of their DBS stimulation device," and then were asked to elaborate on why they placed the mark where they did. Similarly, participants indicated the extent to which they believed they had complete control of their life (10) vs. absolutely no control (zero, similar to someone in a coma) on a separate VAS and asked to elaborate on their responses Participants completed the interview and VASs before DBS and at Post-Operative Months 3 and 6. The interview was approximately 1 h in length; it included additional questions and rating scales discussed in our previous report (Kubu et al., 2017).

Participants also completed standard clinical research outcome measures including the Parkinson's Disease Quality of Life scale (PDQ; Jenkinson et al., 1997; Baseline, Month 6), the Unified Parkinson's Disease Scale (UPDRS-II; Fahn and Elton, 1987; approximately Baseline, Month 3, Month 6) and UPDRS-III (Off medication at Baseline, Off medication-On stimulation 1-month post-DBS).

TABLE 1 | Demographic and Parkinson's disease (PD) outcome measures.

Variable	Baseline *N* = 52 *N* = 52	Post-op month 3 *N* = 47 *N* = 47	Post-op month 6 *N* = 45 *N* = 45
Gender	75% Men (*n* = 39)		
Age	61.3 years (sd = 9.3)		
Duration of PD	9.1 years (sd = 4.1)		
UPDRS-II	17.2 (SE = 1.0)	12.5 (SE = 1.0)	12.0 (SE = 1.1)
UPDRS-III	38.7 (SE = 1.5)	*20.1 (SE = 1.2)	
PDQ	47.9 (SE = 3.3)		25.1 (SE = 2.5)

*sd, standard deviation; SE, standard error. *UPDRS-III Off medication on stimulation scores were collected at the 1-month post-operative visit. Note: N = 45 for Post-op UPDRS-III; N = 38 for 6 month PDQ variable due to lack of post-op standard neuropsychological assessment; N = 41 6 month UPDRS-II variable.*

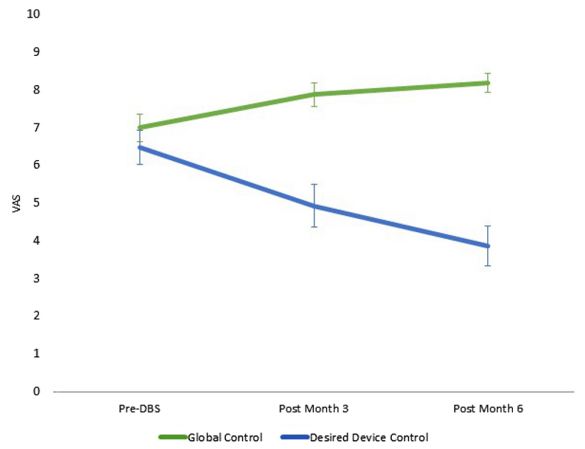

FIGURE 1 | Quantitative changes in global and stimulation control over time. Note: 10, maximum control, 0, no control; vertical lines represent standard error. Data reported are the estimated means from the generalized estimating equation (GEE) models. Desired stimulator control ratings were not available at Month 3 for two participants due to examiner error.

Quantitative Analyses

Generalized estimating equation (GEE) models were used to examine changes over time on the VASs. Autoregressive working correlations were used for the error terms with Time as the fixed effect. Models were constructed with and without a change in the UPDRS-III as a covariate to ascertain if changes in motor symptoms significantly impacted changes in the stimulation and global life control VAS measures over time. Two sets of GEE models were constructed with the VAS variables treated as either linear or ordinal variables. The results did not change; consequently, the linear analyses are reported. Both Spearman Rho (non-parametric) and Pearson (parametric) correlations were used to assess the relationships between changes on the control measures. There was no difference in the pattern of relationships; consequently, the Pearson correlations are reported.

Qualitative Analyses

Data from the semi-structured interviews underwent thematic content analysis to inductively and iteratively identify recurring participant-reported themes related to participants' levels of desired control over the stimulation and their perceptions of global life control. A coding structure was developed based on recurring themes in participant interviews using content analysis by one coder. All transcripts were reviewed and large themes were identified. This was followed by a closer reading in which more nuanced and specific codes were defined that fell within those larger themes or nodes (Elo and Kyngäs, 2008). Once this coding structure was finalized, a second-rater coded a subset of the interviews to determine interrater reliability for the coding structure. Frequency distributions representing the different codes were examined at each time point to provide additional insights into participant-reported changes in desired stimulation control and global life control.

RESULTS

Participant Characteristics

Fifty-two participants completed the baseline assessments. Data were available on 47 of the participants at Month 3 and 45 at Month 6 (three participants withdrew for personal reasons and the remaining four did not complete the study because they did not have surgery at our center within the study timeframe). Due to technological difficulties, interviews for six participants were not recorded; thus, those qualitative data were not available for analysis. Besides, only data from participants who completed all three research interviews were included in the qualitative analyses to allow for assessment of changes in individual participants over time. The final sample included in qualitative analyses (N = 39; Interview transcripts = 117) was still a sufficient sample to reach data saturation (Guest et al., 2006; Tran et al., 2017). The subthalamic nucleus was the surgical target in all but one of the participants. The participants' demographic data, UPDRS, and PDQ scores are reported in **Table 1**.

Control Ratings

Participants reported a significant improvement in their self-ratings of global life control ($\chi^2_{(2,N=144)} = 11.11$, $p = 0.004$). Similarly, significant declines in desired stimulation control were evident over time ($\chi^2_{(2,N=142)} = 18.36$, $p < 0.001$; **Figure 1**). Change in the UPDRS-III score was not a significant covariate in either model (p's = 0.157, 0.879). Changes in global control were significantly correlated with changes in desired stimulator control such that as ratings of global life control increased, desired stimulation control ratings decreased over time ($r = -0.31$, $p = 0.038$). Changes in the control measures were not significantly correlated with changes in the UPDRS-III

TABLE 2 | Stimulation control theme definitions and exemplar quotes.

Stimulation control themes	Definition and exemplars
Primary control	*Definition: Participant wants to be in full control of stimulator, including programming settings*.
	"When it comes to my body I want to control it."
	"I would love to have full control. . .I'm a quick learner. I think I could learn what my body's telling me vs. what the simulation values are fairly quickly and be able to adapt to that."
	"I don't want someone else having a remote telling me what to do."
	"I'd like to be able to, if I need to dial it up or dial it down, I'd want to have the ability to do that."
	"Well, I'd like to have control at all times. I'd like to be in charge of my life again."
Shared control	*Definition: Participant wants to share control with DBS team, either by controlling the device themselves with assistance from the team, or providing input to the DBS team who controls the stimulator*.
	"I don't want to control all of it because I want to have someone backing me up. . .I want to be able to say, "Look, I am having a problem. What can we do about this?"
	"Right now I feel a very good sense of partnership. . .She knows the technology, but she doesn't know how I feel. I have to provide input."
	"[I] just want to be able to communicate with them how well it's doing, if it needs to be adjusted up or down or whatever would be my input."
	"I expect this would be a 50/50 adventure. If I have a problem with where it's set I want to be able to tell them that and get some serious consideration about changing it."
No control	*Definition: Participant wants to have no control over the stimulator (beyond basic ON/OFF) and the DBS team controls all aspects of the device programming*.
	"I don't want any [control]. I want the doctor to do it."
	"I don't really want control of it. I'd rather leave that up to the professionals who know what they're doing."
	"I don't have any desire to control the settings on it at all. I don't think I'm qualified to do any of that at all. I think I have a lot of faith and confidence in the technicians to do that. That's their job, not mine."
	"I want no control because she [programmer] does it and that's working great."

(Desired Control, $r = -0.10$, $p = 0.518$; Global Control, $r = 0.02$, $p = 0.903$).

Qualitative Thematic Analyses

After the coding structure was finalized a second-rater coded a subset of interviews (36/117) to determine the reliability of the coding structure. Cohen's kappa (κ) was 0.86, indicating excellent agreement (Cicchetti et al., 2006).

Themes Related to Stimulator Control

Participants identified several reasons for desiring more or less control over their DBS stimulators. These themes fell under three broader categories including Primary Control, Shared Control, and No Control. Participants often identified multiple themes at each time point, therefore the percentages of participants endorsing each theme will add to over 100% at each time point. Definitions and exemplar patient quotes can be found in **Table 2**. Frequency distributions illustrating the relative changes in the presence of each category can be found in **Figure 2**.

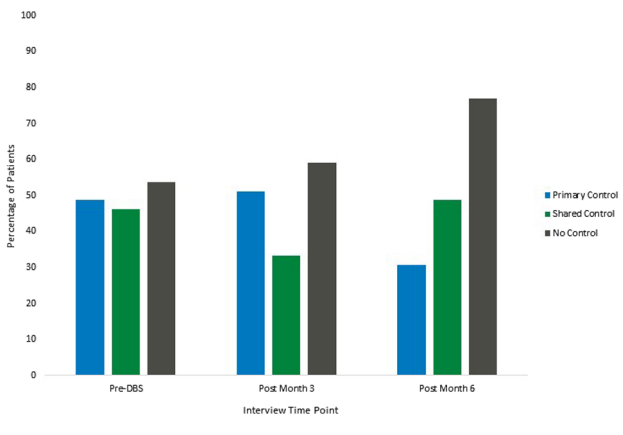

FIGURE 2 | Participant themes related to desired control of stimulation. Note: participants reported more than one theme at each time point, therefore percentages of participants at each time point will add to over 100%.

Primary Control

Several participants discussed reasons for desiring primary control over their stimulators. At the baseline interview, which took place before surgery, 48.7% of the participants discussed themes indicating their desire to have primary control of the stimulator. Themes in this category included participants desiring control over their bodies, wanting the ability to adjust parameters to control fluctuating symptoms, eliminating or reducing the amount of travel and number of visits to receive programming, and several participants felt confident they could be trained to program their stimulators if given the proper education. The percentage of participants endorsing themes related to primary control of the stimulator remained relatively stable from the baseline interview to the first post-surgical interview at 3 months (51.2%) and decreased at the final 6-month interview (30.8%).

Shared Control

Participants also identified several themes that demonstrated a desire to have a partnership with the surgical team

and programmer, with some individuals desiring to control stimulator settings with the team's guidance, and others desiring their input to be used to guide programming. Several individuals also expressed satisfaction with having the ability to turn the stimulator on and off and check batteries, while leaving the programming in the hands of the team. At the baseline appointment, 46.2% of the participants discussed the desire for some form of shared control between the participant and the DBS team. The percentage of patients who discussed themes related to shared control decreased from baseline to the 3-month interview (33.3%) and increased at the 6-month interview (48.7%).

No Control

Participants discussed several reasons for desiring no control over the stimulation. These themes were related to trust in the team and the team's expertise, as well as satisfaction with how the stimulator was working. Participants also discussed their apprehensions about having control over their stimulators, with many saying they would not want to harm themselves or break the stimulator, and stating they were not qualified to program the stimulator and they do not want that responsibility. At the baseline appointment, 53.8% of the participants discussed themes related to having no desire to control the stimulation. The percentage of participants that discussed these themes increased slightly at the 3-month interview (59.0%) and increased further at the 6-month interview (76.9%).

Themes Related to Global Life Control

Participants identified many different aspects of their lives that contributed to enhancing or diminishing their feelings of global life control. These themes fell under six broader categories including Parkinson's Disease Symptoms and Challenges (diminish control), Reliance on Support Systems (mixed effects on control), Internal Self-Regulation (mixed effects on control), Continued Ability to Engage in Activities (enhance control), Symptoms Managed/General Health (enhance control), and Other (diminish control). Frequency distributions illustrating the relative changes in the presence of each category can be found in **Figure 3**.

PD Symptoms and Challenges

Participants identified several ways in which PD symptoms and challenges diminished their overall level of global life control. Themes in this category included fluctuating PD symptoms, ways in which the various PD symptoms make patients' lives more challenging, participants feeling as though PD has taken over their bodies, and an awareness that PD is a progressive disease without a cure so their condition will continue to worsen. At the baseline interviews, 53.8% of participants discussed themes in this category. After DBS surgery, the presence of these themes in participant interviews decreased, with 23.1% of participants discussing themes related to PD symptoms and challenges at 3 months and 23.1% again at 6 months.

Reliance on Support Systems

Participants identified several ways in which reliance on various support systems either enhanced or diminished their feelings of global life control. These themes have been separated into enhancing or diminishing control in **Figure 3** for ease of interpretation. Participants discussed themes surrounding the notion that God is in control of their lives and how their reliance on others to help with daily activities, the DBS stimulator or medication, or reliance on the programmer or DBS team diminish the sense of control. At baseline, 38.5% of participants discussed themes related to ways in which reliance on support systems diminished their feelings of global control. The percentage of participants endorsing these themes fluctuated after surgery, with 25.6% of participants discussing these themes at the 3-month interview and 35.9% at the 6-month interview. In contrast, participants identified several themes in this category that enhanced participants' perceptions of control included having a good support system of friends and family, feeling more in control because God is helping them, and the impact of the stimulator or medications in restoring control. At baseline, 20.5% of participants discussed themes related to how reliance on support systems enhanced feelings of global life control. After surgery, the percentage of patients discussing these themes fluctuated, with an initial increase at the 3-month interview (25.6%) and then a decrease at the 6-month interview (12.8%).

Internal Self-Regulation

Participants identified several ways in which aspects of internal self-regulation either enhanced or diminished their feelings of global life control. These themes have been separated into enhancing or diminishing control in **Figure 3** for ease of interpretation. Themes in this category that diminished perceptions of control included participants' feelings of uncertainty regarding their physical limitations and feelings of anxiety or fear when trying to engage in different activities. At baseline, 5.1% of participants discussed themes related to ways in which internal self-regulation diminished their feelings of global control. The percentage of participants endorsing these themes remained stable after surgery, with 5.4% at the 3-month interview and then a decrease to 2.6% at the 6-month interview. Themes related to internal self-regulation that enhanced participants' perceptions of control included being cognitively in control, having the ability to make important decisions in their lives including the decision to seek different treatment options, being in control of their outlook and attitude, feeling an overall sense of independence, having control over when they ask for help and being able to communicate how they feel, and having less fear and anxiety about physical limitations. At baseline, 61.5% of participants discussed themes related to how internal self-regulation enhanced feelings of global life control. After surgery, the percentage of participants discussing these themes increased at the 3-month interview (82.1%) and increased again at the 6-month interview (92.3%).

Continued Ability to Engage in Activities

Participants discussed their ability to engage in various activities as something that enhanced their feelings of global life control. Activities included engaging in personally-meaningful hobbies, working and volunteering, and interacting with friends and family members. At the baseline interview, 10.3% of the participants discussed themes that fell into this category. After surgery, the percentage of participants endorsing these themes

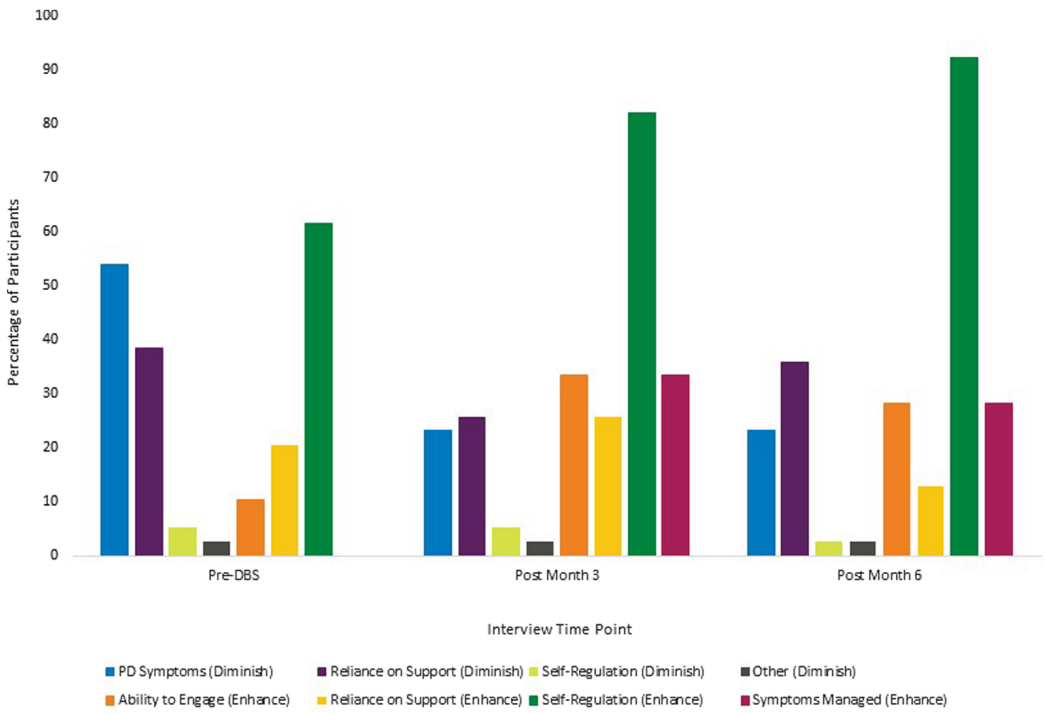

FIGURE 3 | Participant themes related to global life control. Note: participants reported more than one theme at each time point, therefore percentages of participants at each time point will add to over 100%. Categories that contained themes related to both enhanced control and diminished control have been divided and reported separately in the figure.

fluctuated, with an initial increase to 33.4% at the 3-month interview and then a decrease to 28.2% at the 6-month interview. It is worth noting that although two fewer participants discussed themes related to their continued ability to engage at the 6-month interview, this remains an overall increase from pre-DBS to post-DBS.

Symptoms Managed/General Health

Participants cited feeling generally healthier, having better control of their symptoms, and feeling more in control of their bodies as reasons for enhanced feelings of global life control. At baseline, none of the participants discussed these themes. However, after surgery, 33.4% of the participants discussed themes in this category in the 3-month interview and 28.2% of the participants identified these themes at the 6-month interview.

Other

There were only three total instances (less than 1% of themes present at all of the time points) when participants provided reasons they felt their global life control had been diminished that did not fit into the existing coding structure. These included the need to continue to work and responsibilities for others, both of which resulted in perceived decreased control.

DISCUSSION

Participants reported decreases in their desired control of stimulation throughout DBS treatment. Simultaneously, participants reported significantly greater global control over their lives. The changes in desired stimulation control and global life control were negatively correlated such that as desired stimulation control declined, the participants' perception of global control increased over time. Quantitative findings demonstrate that changes in control ratings were unrelated to improvements in the patient's motor symptoms as measured using the UPDRS-III. This is the first report, to our knowledge, that systematically assessed a large, consecutive series of PD patients' desire for stimulator control as well as the perception of global control throughout DBS treatment.

The qualitative responses from the patients provide insight into factors that influenced the changes in the control ratings. Many patients indicated that their reduced desire to control the DBS stimulator, including stimulator settings, reflected a sense of collaboration with, trust in, and respect for the DBS team's expertise. These findings are very similar to those documented in the work by Klein et al. (2016) and support a relational autonomy framework as articulated by Goering et al. (2017). For example, many patients indicated that their input regarding stimulation effects was critical in helping the team optimize stimulation. Some patients also indicated that they felt that turning the stimulator on and off was sufficient control for them and they relied on the team for controlling other aspects of the stimulation.

A review of the qualitative global control data indicated that increases in global life control may be partially attributed to

a reduction of PD symptoms, a finding that contradicts our findings that improvements in global control were unrelated to changes on the UPDRS-III. This discrepancy highlights the importance of approaching these questions using a mixed-methodology to gather a more holistic view of the participants' experiences and also illustrates that the standard clinical outcome measures used to assess treatment efficacy, such as the UPDRS-III, may not fully capture patients' experiences (see Kubu et al., 2017). The reduction in PD symptoms also came with an increase in the number of participants citing their ability to engage in valued activities as a reason for increased perceptions of global life control. Although these factors are important drivers of change in ratings of global life control from pre- to post-DBS surgery, participants also highlighted other themes that impacted their sense of control. Our data demonstrate that beyond the management of PD symptoms, participants rely on their relationships with others (including God, family, and the DBS team) once again highlighting the relational aspect of control, as well as their ability to internally self-regulate across cognitive, affective, and interpersonal domains to maintain a sense of control over their lives. Participants reported their reliance on relationship supports remained relatively unchanged before and after DBS surgery, meaning the surgery does not diminish their control in this highly personally relevant domain. Further, the qualitative data demonstrate an overall increase in the percentage of patients who discuss enhanced internal self-regulation, with 36 of the 39 participants (92.3%) endorsing themes related to feeling a sense of independence at the 6-month interview compared to 61.5% before surgery. Taken together these findings indicate that participant-identified themes related to relationships and the belief in one's own ability to control one's behavior work in conjunction with improved symptom management for an overall increased sense of global life control.

These findings are limited by the relatively brief follow-up period. It may be that patients' desire to control the stimulator may decline even more over time as they habituate to the stimulator or patients' desire to control the stimulator may increase as symptoms progress. It is also possible that feelings of control may change as the need to undergo battery replacements arise. Second, participation in a study specifically designed to explore patients' expectations surrounding control may have resulted in a positive bias toward the team resulting in greater trust and/or willingness to share control with the team. Third, these data represent patients' desired stimulation control when actual stimulator control was limited to turning it on/off. In our center, rarely, DBS patients with PD would regularly choose or be advised to turn their stimulator off. This is consistent with expert guidelines in the literature (Deuschl et al., 2006) and reflects the fact that most DBS candidates with PD can experience their primary motor symptoms constantly if not treated. Thus, although they had control to turn the stimulator on or off, most participants would be unlikely to exercise that option. Nonetheless, even in this simple example, our data highlight the need to study patients' preferences for stimulation control throughout DBS as those preferences may change, and what patients define as primary, shared, and no control can change as they learn more about the stimulator and experience DBS. For example, several patients identified having the ability to turn their stimulators on/off as having no control at the baseline interview, but by the end of the study felt this ability gave them primary control over the stimulator. Future studies should follow patients for longer periods, include other centers, and compare devices that offer differing options for patient control of stimulation to further explore and understand how desired control of the stimulator settings and perceptions of global control over one's life are related and, if our findings are replicated, what drives those relationships. Finally, although our participants reflect the gender demographics of PD and are similar to other largescale outcome DBS studies, our sample was heavily skewed toward Caucasian men. Consequently, these findings should not necessarily be generalized onto other demographic groups whose sense of control may be influenced by sociocultural factors related to gender, ethnicity, and race[1]. Similarly, these findings should not be generalized to other patient groups with different disorders and stimulation targets since all of these important variables may influence patients' perceptions of control (Kubu et al., 2019).

Despite these limitations, our findings suggest that reductions in desired stimulation control do not correspond to parallel reductions in perceived global control over one's life in the context of DBS for the treatment of motor symptoms in PD. These data highlight the important distinction between different aspects of control and suggest that patients may be more willing to share or cede one aspect of bodily control (i.e., changing stimulation settings of an implanted brain device) to the medical team as they gain greater global control over their lives following DBS surgery. We hope that these empirical data can help inform future conceptual, neuroethical analyses which are beyond the scope of this brief report. Our data provide support to the perspectives that DBS can supplement a patient's sense of autonomy and control *via* a model of shared control (Glannon, 2014) or relational autonomy (Goering et al., 2017). The data are also consistent with Klein et al.'s (2016) observations that most patients in their sample preferred to defer control of the stimulation parameters to the medical experts. Also, our data illustrate the importance of recruiting a consecutive series of patients to obtain a better understanding of most patients' experiences. Finally, our findings also have implications for the development of patient-controlled neuromodulation devices and highlight the importance of assessing patients' perceptions surrounding control throughout DBS. Quite simply, patient-rated measures collected before surgery may not reflect patients' rated stimulation control preferences after they have experienced DBS.

DATA AVAILABILITY STATEMENT

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

[1]We are grateful to an anonymous reviewer for raising this important point.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Cleveland Clinic. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ARM, TF, and BL: data analysis and interpretation, writing and critical revision of the manuscript. SC, AM, JV, and PF: study concept and design, writing and critical revision of the manuscript. CK: study concept and design, data analysis and interpretation, writing and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Closed-Loop Deep Brain Stimulation to Treat Medication-Refractory Freezing of Gait in Parkinson's Disease

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Background: Treating medication-refractory freezing of gait (FoG) in Parkinson's disease (PD) remains challenging despite several trials reporting improvements in motor symptoms using subthalamic nucleus or globus pallidus internus (GPi) deep brain stimulation (DBS). Pedunculopontine nucleus (PPN) region DBS has been used for medication-refractory FoG, with mixed findings. FoG, as a paroxysmal phenomenon, provides an ideal framework for the possibility of closed-loop DBS (CL-DBS).

Methods: In this clinical trial (NCT02318927), five subjects with medication-refractory FoG underwent bilateral GPi DBS implantation to address levodopa-responsive PD symptoms with open-loop stimulation. Additionally, PPN DBS leads were implanted for CL-DBS to treat FoG. The primary outcome of the study was a 40% improvement in medication-refractory FoG in 60% of subjects at 6 months when "on" PPN CL-DBS. Secondary outcomes included device feasibility to gauge the recruitment potential of this four-lead DBS approach for a potentially larger clinical trial. Safety was judged based on adverse events and explantation rate.

Findings: The feasibility of this approach was demonstrated as we recruited five subjects with both "on" and "off" medication freezing. The safety for this population of patients receiving four DBS leads was suboptimal and associated with a high explantation rate of 40%. The primary clinical outcome in three of the five subjects was achieved at 6 months. However, the group analysis of the primary clinical outcome did not reveal any benefit.

Interpretation: This study of a human PPN CL-DBS trial in medication-refractory FoG showed feasibility in recruitment, suboptimal safety, and a heterogeneous clinical effect in FoG outcomes.

Keywords: freezing of gait (FOG), Parkinson's disease, pedunculopontine nucleus, closed-loop, deep brain stimulation

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INTRODUCTION

Medication-refractory, or unresponsive, freezing of gait (FoG) is among the most difficult and disabling symptoms to address in advanced Parkinson's disease (PD; Moore et al., 2007). The unresponsive FoG phenomenon occurs when PD patients freeze despite optimized dopaminergic medications and improvement in other PD motor symptoms (Espay et al., 2012). Although exercise, physical therapy, and assistive devices have demonstrated clear benefits for FoG (Cosentino et al., 2020), neuromodulation strategies such as deep brain stimulation (DBS) applied in both the globus pallidus internus (GPi) and the subthalamic nucleus (STN) have fallen short in providing therapeutic benefit for medication-refractory FoG and its associated symptoms, such as falling (Deuschl et al., 2006; Okun et al., 2009; Moro et al., 2010b; Williams et al., 2010; Odekerken et al., 2013). Several attempts have been made to alleviate unresponsive freezing by utilizing pedunculopontine nucleus (PPN) and PPN + STN DBS. Overall, these small sample studies have yielded inconclusive findings (Stefani et al., 2007; Strafella et al., 2008; Moreau et al., 2009; Ferraye et al., 2010; Moro et al., 2010a; Acar et al., 2011; Thevathasan et al., 2011, 2018; Wilcox et al., 2011; Khan et al., 2012).

Due to the paroxysmal and heterogeneous nature of FoG, improved clinical outcomes may be achieved with closed-loop DBS (CL-DBS; Rosin et al., 2011; Little et al., 2013, 2016; Rosa et al., 2015, 2017; Piña-Fuentes et al., 2017; Tinkhauser et al., 2017; Arlotti et al., 2018; Molina et al., 2018; Swann et al., 2018; Houston et al., 2019; Velisar et al., 2019; Petrucci et al., 2020). In this technique, stimulation is delivered in response to a specific electrophysiological brain marker that represents periods of activity in which stimulation would be needed (i.e., gait). We aimed to test the safety and feasibility of a closed-loop approach for PPN DBS and to document effects on medication-refractory FoG as well as to collect PPN electrophysiology to serve as our biomarker for CL-DBS. Our strategy also employed conventional open-loop GPi DBS (OL-DBS), which has not been shown to consistently modulate axial symptoms in humans (Ghika et al., 1998; Rocchi et al., 2012; Schrader et al., 2013), to address the levodopa-responsive PD motor symptoms.

MATERIALS AND METHODS

Subjects

This safety and feasibility study was approved for five subjects who all provided written informed consent. The trial was registered with the University of Florida (UF) Institutional Review Board (IRB #201400951) and https://clinicaltrials.gov (NCT02318927), which includes the full inclusion and exclusion criteria. There was also an FDA investigational device exemption (IDE, G140181) in place. An interdisciplinary team at the Norman Fixel Institute for Neurological Diseases at UF screened, reviewed, and approved DBS implantation. Through this process, eight candidates were screened and three failed to meet the inclusion criteria (**Figure 1**). Subjects were required to have greater than two freezing episodes per month, a score of greater than 1 on item 3 of the Freezing of Gait Questionnaire (FOGQ#3; Giladi et al., 2000), and to exhibit five or more FoG episodes during a provocation screening protocol in the "on" and "off" dopaminergic states. The FoG provocation protocol included stepping in place, walking at a self-selected pace, walking over an obstacle, dual tasking (carrying a tray, answering questions, etc.), turning while walking, and walking through a narrow passage. The off-medication state was defined as a 12-h withdrawal of dopaminergic (L-DOPA) medications, whereas the on-medication state was 45–60 min post-medication administration. The five enrolled subjects had a confirmed medical history of FoG which occurred both "on" and "off" dopaminergic medication, despite aggressive medication optimization by a movement disorders-trained neurologist (**Table 1**). Furthermore, our subjects had a history of falling, which was confirmed through both extensive chart review and clinical visits.

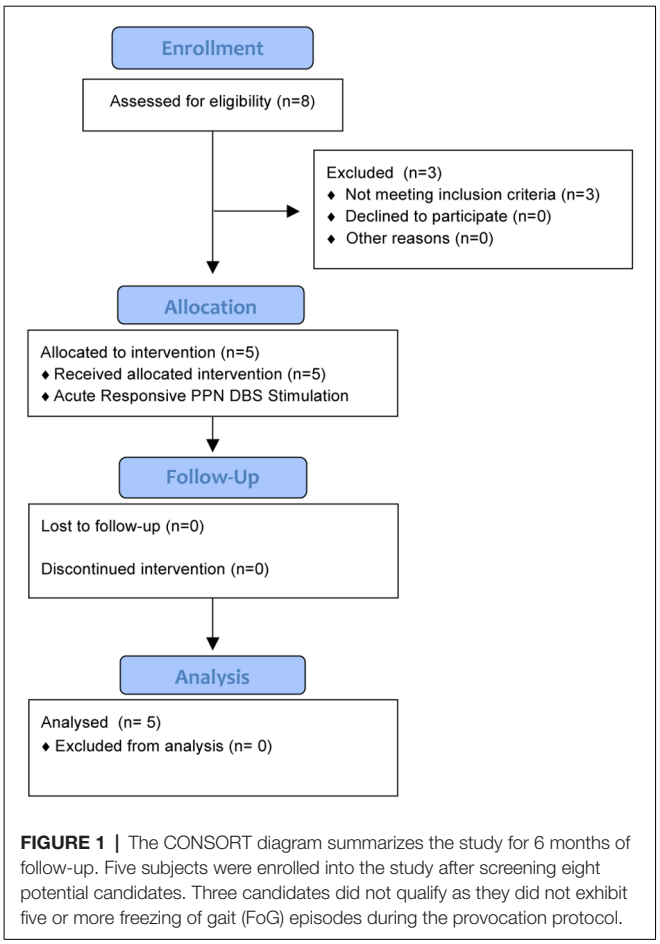

FIGURE 1 | The CONSORT diagram summarizes the study for 6 months of follow-up. Five subjects were enrolled into the study after screening eight potential candidates. Three candidates did not qualify as they did not exhibit five or more freezing of gait (FoG) episodes during the provocation protocol.

Assessments and Device Programming

Information regarding device and surgical implantation can be found in Molina et al. (2020). Briefly, electrodes were implanted bilaterally in both the GPi (Medtronic 3387 leads) and PPN (Medtronic 3389 leads) and the implantation procedure was divided into three stages. In the first stage, two leads (PPN + GPi) were unilaterally implanted; in the second stage of the operation 2–4 weeks later, the other two leads were implanted in

TABLE 1 | Subject demographics.

Subject	Gender	Age (years)	Diagnosis (year of first symptom)	Disease duration at surgery	LEDD (screening/ 6 months)		UPDRS II (screening /6 months)		UPDRS III off-med/on-GPi DBS only (screening/ 6 months)		UPDRS III on-med/on-GPi DBS only (screening/ 6 months)		UPDRS IV (screening/ 6 months)	
1	F	50	2009 (2001)	6 (14)	502.5	577.5	26	22	38	24	23	19	5	7
2	M	52	2008 (2006)	7 (9)	622.5	607.5	23	17	31	37	21	31	5	3
3	M	74	2008 (2005)	7 (10)	275	350	30	40	42	57	34	52	5	6
4	M	60	1995 (1994)	20 (21)	625	625	24	21	49	46	30	41	14	5
5	F	60	2013 (2011)	2 (4)	427.5	405	35	33	40	48	28	42	5	6

UPDRS scores were performed On-GPi DBS only. PPN DBS was not activated during these scales. UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; GPi, globus pallidus internus; DBS, deep brain stimulation.

the contralateral hemisphere. In one subject (subject 3), two PPN leads were placed in stage 1 and the two GPi leads in stage 2. In the final stage, which occurred approximately 4 weeks after stage 2, GPi DBS leads were connected to one Medtronic Activa PC + S (Medtronic PLC, Minneapolis, MN, USA), the implantable neurostimulator (INS), and secured in a sub-clavicular pocket, while the PPN leads were connected to a separate Activa PC + S. Postoperative CT images co-registered with preoperative MRI were used to confirm the postoperative position of the active contacts (**Supplementary Table 1**). At the end of the study, patients whose systems were not explanted kept both implantable neurostimulators. If the patient and clinician decided not to use the PPN leads after study conclusion, they were deactivated.

Monthly visits were initiated 4 weeks after the last surgical phase and occurred until month 10, followed by visits at months 12 and 18. During monthly visits, the subjects performed clinical evaluations and biomechanical studies while "off" and then "on" L-DOPA medications. Every month included the FOGQ, the Gait and Falls Questionnaire (GFQ; Giladi et al., 2000), the Activities-Specific Balance Confidence Scale (ABC; Powell and Myers, 1995), the Parkinson's Disease Quality of Life Questionnaire (PDQ)—39 (Peto et al., 1998), and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987).

The primary outcome variable was a comparison of the preoperative number of FoG episodes vs. the number of FoG episodes at 6 months post-DBS at the optimized GPi OL-DBS and PPN CL-DBS settings (**Table 2**). Two tasks were used to quantify the primary outcome of the study: (1) stepping in place (SIP; Nantel et al., 2011); and (2) gait at a self-selected pace (SSP). SIP was collected first during visits. The SIP protocol consisted of three trials of 90 s of SIP in which the subjects were asked to raise their legs alternately at a self-selected pace. During SSP, the subjects were asked to walk at their comfortable, preferred pace over-ground across an 8-m walkway a total of 10 times. Changes in stamina and disease state necessitated a normalized FoG count. The "on" and "off" medication condition FoG counts were normalized to the number of trials from each task, which ranged from 1 to 6 (mean, 3.4) for SIP and from 10 to 22 (mean, 9.6) for SSP, in each respective medication state, and were then summed. The percent improvement was then calculated from the total combined count. Not all subjects completed the tasks at each month in each condition due to the inability to perform the tasks off medication (subject 3) or due to fatigue. In order to meet the predetermined primary outcome variable, 60% of the subjects (three of five) were required to show a greater than 40% improvement from baseline on the combined "on" and "off" medication normalized FoG counts. An independent, blinded movement disorders-trained neurologist reviewed video recordings of the subjects performing the FoG provocation protocol and labeled freezing events (Nutt et al., 2011).

Secondary outcome measures included feasibility of recruitment, safety, and adverse events. All adverse events (AEs) were recorded and scored by a physician to determine whether they were related to the study procedure. AEs were scored for severity and outcome. Other outcome variables were the changes from baseline to 6 and 12 months on the FOGQ, GFQ, ABC, PDQ, Berg Balance Scale (BBS; Berg et al., 1992),

TABLE 2 | Stimulation parameters at 6 months.

Nucleus	GPi				PPN					
Subject	Active contacts	Amp. (V)	PW (μs)	Freq. (Hz)	PPN recording side	Recording contact	Active contacts	Amp. (V)	PW (μs)	Freq. (Hz)
1	2-C+	3.4	90	185	Right	8–10	1-C+	0.8	60	65
	10-C+	2.2	90	185			9-C+	0.8	60	65
2	1-C+	2.1	90	180	Left	0–2	1-C+	0.7	60	65
	10-C+	2.2	90	180			9-C+	0.7	60	65
3	2-C+	3.5	90	135	Right	8–10	1-C+	0.8	60	65
	9–10-C+	2.1	90	135			9-C+	0.8	60	65
4	2-C+	1.8	100	135	Left	0–2	1-C+	0.4	60	65
	11-C+	2.8	100	135			9-C+	0.4	60	65
5	1–2+	2.6	90	180	Left	1–3	2-C+	0.6	60	65
	9–10+	2.6	60	180			9-C+	0.6	60	65

Amp., Amplitude; PW, Pulse width; Freq., Frequency. PPN recording side is the electrode side which contains the recording contacts for the ambulation biomarker. Recording contacts are the sensing contacts on the respective recording electrode. Active contacts are those that delivered stimulation.

UPDRS III, total UPDRS scores, and L-DOPA response, which we defined as the difference between the UPDRS-III off and on medication total score divided by the UPDRS-III off medication total score.

During the monthly visits, electrophysiology data from bilateral GPi and PPN were collected using the Activa PC + S. The neural data were aligned to external sensors (Trigno, Delsys Inc., Natick, MA, USA) and video recordings, and subsequently used to develop the PPN CL-DBS paradigm. Gait performance was assessed using 3D motion capture (Vicon Motion Systems, Oxford, UK) and spatiotemporal parameters of interest were calculated using custom MATLAB software (2016a Mathworks, Natick, MA, USA) based on definitions from Whittle's Gait Analysis (Levine et al., 2012). Participants wore retroreflective markers on the lower extremity to measure gait speed and stride length, which were calculated based on standard definitions. Specifically, gait speed was the average stride velocity across an 8-m walkway when participants were walking at a "steady" pace (i.e., not accelerating or decelerating), and stride length was the horizontal distance between subsequent heel strikes along the line of progression.

Closed-Loop Implementation

From month 4 onward, we used the Medtronic Nexus-D platform (Afshar et al., 2013), which is a telemetry wand that allows a direct interface to the DBS INS and enables real-time neural data streaming to a host computer. This platform facilitated not only the acquisition of the neural data needed to identify a CL-DBS biomarker but also the delivery of acute PPN CL-DBS in the laboratory setting. CL-DBS stimulation was delivered to the PPN and was triggered by an increase in power of the 1- to 8-Hz band from the PPN region (Molina et al., 2020), which was identified to modulate most consistently with gait.

The acute PPN CL-DBS paradigm was used to establish the parameters for long-term PPN CL-DBS, in which the subjects received PPN CL-DBS outside of the laboratory. Long-term PPN CL-DBS was delivered *via* the Nexus-E firmware, which allowed a similar Nexus-D operation, but was completely embedded within the Activa PC + S (i.e., the INS). However, the Activa PC + S onboard classifier uses a linear discriminant analysis approach, which permits the use of only two power bands with a minimum and a maximum bandwidth of 5 and 32 Hz, respectively. Therefore, the center frequency of our CL-DBS power band was 5 Hz with a bandwidth of 5 Hz (i.e., 2.5–7.5 Hz) to capture our 1- to 8-Hz gait signal within the PPN. Once the 2.5- to 7.5-Hz signal exceeded a predefined threshold, which was derived from the training data during off-stimulation periods and was extracted from a receiver operating characteristic curve (ROC) that maximized specificity and sensitivity, PPN stimulation would initiate and consistently stimulate for 3.5 s after the onset of detection. By sweeping through various hold times, 3.5 s was chosen since it maximized the ROC area under the curve (AUC), which was delineating walking and rest. Longer hold times did not increase the AUC (i.e., the performance of the detector). Since the PPN gait signal did not always produce

a large or sustained power increase and was overcome with noise from the stimulation pulse, we defined hold times from a histogram of inter-detection intervals during walking (**Supplementary Figure 1**).

For both acute and long-term PPN CL-DBS, a 65-Hz frequency setting with a 60-μs pulse width was chosen for all subjects based on previous FoG studies (Mazzone et al., 2005; Plaha and Gill, 2005; Stefani et al., 2007; Ferraye et al., 2010; Moro et al., 2010a; Thevathasan et al., 2011) and also empirical programming that yielded minimal stimulation artifacts. Both Nexus-E and Nexus-D solutions sensed unilaterally and delivered stimulation bilaterally from 0 V to the individual target's therapeutic voltage (**Table 2**, PPN settings). The side chosen for unilateral PPN sensing was based on which nuclei had the more robust gait biomarker. For GPi stimulation, patients underwent standard-of-care DBS parameter optimization. The same clinical settings were used for GPi stimulation throughout either acute or long-term PPN CL-DBS. For subjects 1 and 5, long-term CL-PPN DBS was initiated at months 12 and 8, respectively. Therefore, secondary outcome measures at month 18 for subject 1 and at months 9, 10, and 12 for subject 5 were all conducted when the patient was on CL-PPN DBS (**Supplementary Table 2**).

Statistical Analysis

Significant changes in the primary outcome variable (i.e., FoG count), stride length, velocity, and BBS between baseline and month 6 were evaluated using a repeated measures ANOVA. To evaluate changes between screening, 6 months, and 12 months, a mixed model was used for the following outcome variables: FOGQ, FOGQ#3, GFQ, PDQ-39 total score, PDQ-39 mobility subscore, ABC, total UPDRS (both on and off medication), UPDRS III (both on and off medication), levodopa (L-DOPA) response, and medication doses (i.e., levodopa equivalent daily dose, LEDD). We chose a mixed model instead of a repeated measures ANOVA since subject 2 is missing data from month 12 due to device explantation. *Post hoc* pairwise comparisons were adjusted with Bonferroni correction. Significance was defined as a p-value < 0.05. All statistics were completed in R 3.5.2. Additionally, given the small sample size and variable follow-ups, we have focused on individual outcomes as well as group outcomes at screening, 6 months, and 12 months.

RESULTS

Feasibility and Safety

The feasibility of recruiting patients with both "on" and "off" medication FoG was achieved. However, the safety profile was suboptimal, with a 40% device explantation rate due to infection. Of 54 AEs reported, 14 were related to either the implanted device or to the study procedure (**Figure 2**). From the related AEs, seven were determined to be severe. The numbers of infection and scalp erosion events reflect the initial event and subsequent difficulty with wound healing, which occurred in two subjects, 2 and 4. Subjects 2 and 4 were withdrawn from the study before long-term closed-loop PPN stimulation could be implemented and had their entire DBS systems explanted at months 12 and 16, respectively, due to infections. Thus, the final follow-up visits for subjects 2 and 4 were months 10 and 12, respectively. Subjects 3 and 5 reported worsening of symptoms, specifically gait and balance impairments, immediately following the first lead implantation. Subject 3's worsening subsided before undergoing his second bilateral implantation; however, he was lost to follow-up after month 12. Vasogenic edema was observed by imaging following the first surgical phase (PPN and GPi left lead implantation) in subject 5, which may have led to the worsening of PD symptoms pertaining to gait and balance that persisted throughout the study. Subject 1 experienced a worsening of gait and balance following the second surgical phase (PPN and GPi right lead implantation), which persisted throughout the study.

Primary Outcome Variable—FoG Episode Counts

The primary outcome variable was met in three of the five subjects who exhibited a greater than 40% improvement in the number of FoG episodes from baseline to 6 months when on acute PPN CL-DBS (**Table 3**). There was no significant difference between the pre-DBS and month 6 FoG counts at the group level ($F_{(1,4)} = 0.053$, $p = 0.0829$).

Secondary Outcome Measures

Group Analysis

There were no significant differences for any measure between pre-DBS, month 6, and month 12 (**Figure 3**), except a worsening of L-DOPA response ($F_{(2,7.32)} = 12.83$, $p < 0.01$), in which *post hoc* comparisons demonstrated a significant decrease from pre-DBS to month 6 ($t = 3.77$, $p_{adj.} = 0.020$) and pre-DBS to month 12 ($t = 4.74$, $p_{adj.} = 0.005$). Additionally, there was no significant difference found for LEDD between any time point ($F_{(2,7.02)} = 0.38$, $p = 0.70$). Gait metrics were compared between baseline and 6 months while the subjects were on levodopa (**Figure 4**). Overall, the subjects' velocities (baseline, 0.84 ± 0.24; month 6, 0.59 ± 0.30; $F_{(1,4)} = 4.07$, $p = 0.11$) and stride lengths (baseline, 0.97 ± 0.24; month 6, 0.75 ± 0.41; $F_{(1,4)} = 3.29$, $p = 0.14$) did not change from baseline to 6 months.

Individual Outcomes

Individual clinical measures prior to DBS and throughout the entirety of the study are summarized in **Figure 5**. At 6 months, subjects 2 and 4 experienced improvements from screening to their last visit and month 9, respectively, in the FOGQ, FOGQ#3, GFQ, PDQ-39 total score, PDQ-39 mobility subscore, and ABC (**Figure 5**). Subject 1, who initiated long-term PPN CL-DBS after her month 12 visit, improved in FOGQ, FOGQ#3, and GFQ, from both baseline and month 12 at month 18, or after 6 months of long-term PPN CL-DBS. Furthermore, she slightly improved in her PDQ-39 total score and PDQ-39 mobility subscore from month 12 to 18. All other subscores worsened or remained the same from both baseline and month 12 at month 18 (**Figure 5**). Subject 5 began long-term PPN CL-DBS after month 8, in which she improved from month 8 to 9 in FOGQ, FOGQ#3, GFQ, ABC, and the UPDRS-III gait subscore; however, these initial

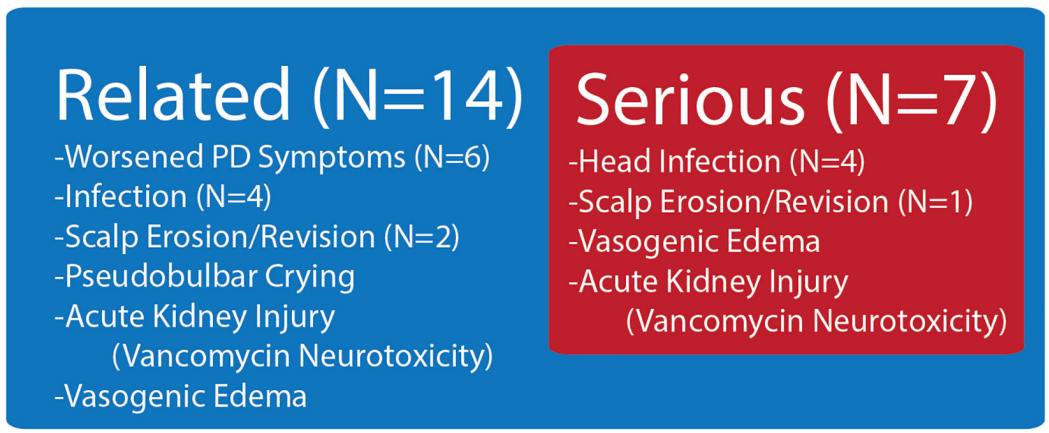

FIGURE 2 | Device- and procedure-related adverse events (AEs) in the study, which were drawn from all AEs. Shown in the figure are the number of AEs related to the device or study protocol and from the related number of those AEs that were severe.

TABLE 3 | Primary outcome of the FoG episode count.

	FoG count			No. of SIP trials (pre-DBS/6 months)				No. of SSP trials (pre-DBS/6 months)			
Subject	Pre-DBS	Month 6	Improvement (%)	Off		On		Off		On	
1	4.3	7.0	−63	3	3	2	3	10	10	6	10
2	1.8	0.2	89	5	0	4	3	10	10	0	0
3	6.7	2.0	70	0	0	3	1	0	0	10	10
4	4.1	0.3	93	3	0	3	6	10	10	10	12
5	11.2	16.4	−46	3	6	1	6	10	10	5	10

The FoG count, which was our primary outcome variable, was completed by a movement disorder neurologist who was blinded to all stimulation conditions. Subjects 2, 3, and 4 met the 40% improvement criteria for a positive trial (highlighted in the table). Counts were normalized to the number of trials and combined in the "on" and "off" L-DOPA state.

improvements were not consistent across these and all other subscores up until her last visit (**Figure 5**).

DISCUSSION

We present the feasibility, safety, and clinical results of a PPN CL-DBS GPi OL-DBS trial in five individuals with unresponsive freezing of gait. Recruitment was feasible and the primary outcome was met; however, it resulted in a suboptimal safety profile, which included a 40% explantation rate due to delayed infection. Since other DBS studies have successfully applied four-lead approaches (PPN + STN; Stefani et al., 2007; Mazzone et al., 2009; Ferraye et al., 2010), it is likely that our specific atypical and fragile patient population of markedly disabled unresponsive freezers in the early to moderate stages of their disease were negatively impacted by this surgical approach. Another study that implanted bilateral PPN leads in patients with FoG experienced significant surgical side effects in two of six patients, leading to one explantation (Welter et al., 2015). This evidence, combined with our previous experiences (Okun et al., 2009), indicates that the choice of two sets of bilateral leads may be high risk in patient populations with atypical PD symptoms (refractory freezes) who are at a greater risk of falling. The primary clinical outcome of greater than 40% improvement in medication-refractory FoG in three of five subjects was achieved at 6 months when "on" acute PPN CL-DBS. However, the group analysis of the change in FoG counts from pre-DBS to month 6 on acute PPN CL-DBS did not reveal a significant benefit.

An important aspect to the study was the rigid inclusion criteria. During the planning phase, we reasoned that if available medications or DBS could greatly improve or resolve "off" medication FoG, then PPN therapy would not be necessary. Therefore, the more critical need for the PD community was a therapy targeting medication-refractory FoG, which usually presents with patients displaying both on-medication and off-medication FoG. One potential issue with this selection criterion is that PD patients with on-medication FoG may be

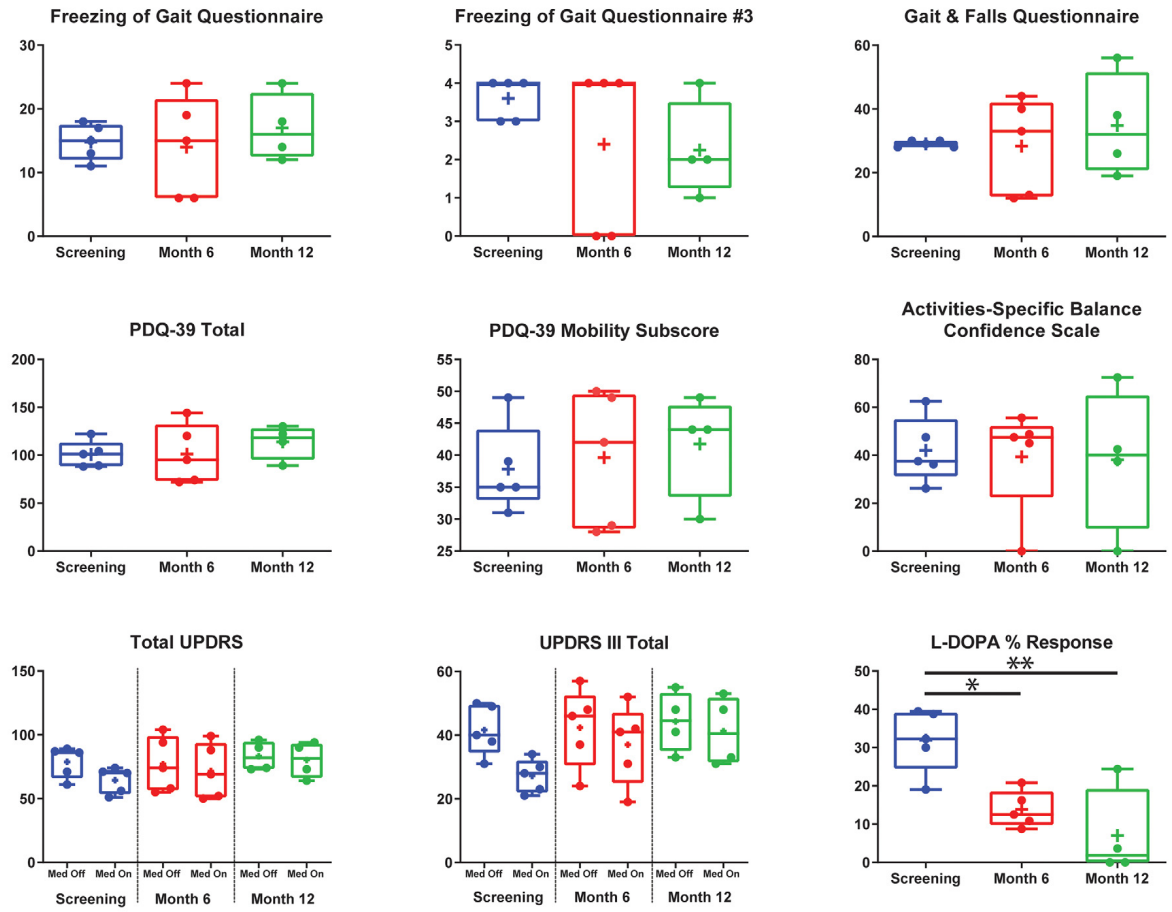

FIGURE 3 | Group summary of clinical outcome measures. This figure addresses the entire cohort before deep brain stimulation (DBS) implantation (*blue*) after 6 (*red*) and 12 (*green*) months post-implantation on the Freezing of Gait Questionnaire (FOGQ), FOGQ#3, Gait and Falls Questionnaire (GFQ), Parkinson's disease (PD) Quality of Life Questionnaire—3 (PDQ-39) total, PDQ-39 mobility, Activities-Specific Balance Confidence Scale (ABC), total Unified Parkinson's Disease Rating Scale (UPDRS), UPRS-III, and L-DOPA percent response. All graphs are standard box plots, with *dots* indicating individual scores, and *plus signs* indicating means. FOGQ question #3 was "Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?" *Off Med*, off dopaminergic medication; *On Med*, on dopaminergic medication. All clinical measures were performed on globus pallidus internus (GPi) open-loop DBS. Pedunculopontine nucleus DBS was not activated during secondary outcome measures, except at month 12 for subject 5. $^{*}p < 0.05$, $^{**}p < 0.01$.

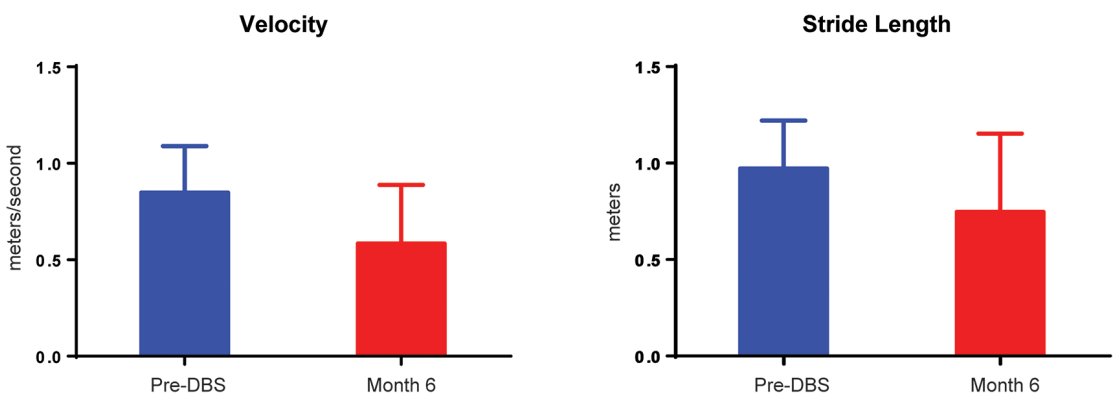

FIGURE 4 | Velocity and stride decrements in five subjects. A comparison of pre-DBS (*blue*) and 6 months (*red*) demonstrated no significant changes in gait velocity (in meters per second) or stride length (in meters). All data are plotted as μ + SD.

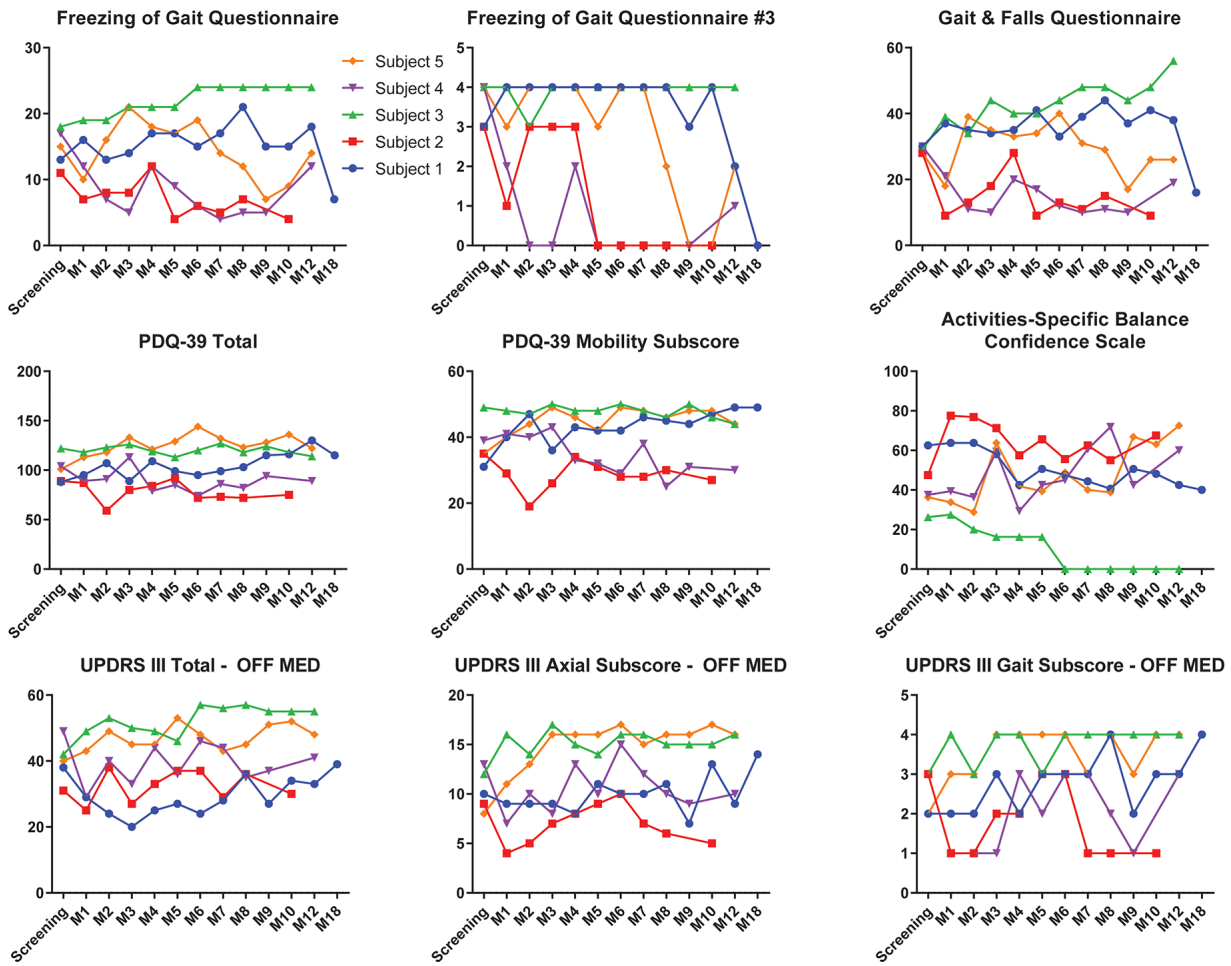

FIGURE 5 | Clinical outcome scores of each individual subject pre-deep brain stimulation (DBS) until the last available follow-up. Individual outcomes for each individual subject on the Freezing of Gait Questionnaire (FOGQ), FOGQ#3, Gait and Falls Questionnaire (GFQ), PD Quality of Life Questionnaire—3 (PDQ-39) total, PDQ-39 mobility, Activities-Specific Balance Confidence Scale (ABC), Unified PD Rating Scale III (UPDRS-III) off dopaminergic medication, UPDRS-III axial subscore (items 18, 27–30) off medication, and UPDRS-III gait subscore (item 29) off medication. Subjects 1 and 5 were on long-term pedunculopontine nucleus (PPN) closed-loop DBS (CL-DBS) during their 18- and 9- to 12-month visits, respectively. All other subjects did not have their PPN DBS activated. GPi open-loop DBS (OL-DBS) was activated during all outcomes.

more clinically fragile and suffer from more comorbidities. Thus, it is likely that the culmination of the atypical patient population (i.e., medication-refractory FoG patients and high-risk fallers) and the four-lead approach, which had immediate impacts in three of the five patients in the study and persistent effects in two of five likely contributed to our suboptimal safety profile.

There were no significant differences between baseline and 6 or 12 months in any secondary outcome variables, except a decline in L-DOPA response. Although this may point to disease progression, we believe that this is due to the assessments being performed under GPi stimulation or a lesion effect from surgery. Additionally, the gait metrics were not significantly different from baseline and were within the range of metrics from another large cohort study (N = 310; Hass et al., 2012), in which the subjects of this study were within the PDQ mobility subscore, UPDRS motor subscore, and disease duration range of the larger cohort.

All outcome variables, besides the FoG counts, were performed when patients were on only GPi OL-DBS settings, with the exception of month 18 for subject 1 and months 9, 10, and 12 for subject 5; thus, these effects were primarily driven by the GPi OL-DBS settings. For subject 1, PPN CL-DBS did improve the subjective measures of failing and freezing, including the FOGQ, GFQ, and PDQ-39. However, on the objective measurements of UPDRS-III, PPN CL-DBS led to a worsening of the total score as well as the axial (items 18, 27–30) and gait (item 29) subscores from 12 to 18 months (**Figure 5**). Yet, this worsening may have stemmed from disease progression rather than PPN CL-DBS over those 6 months or from the paroxysmal nature of FoG. Subject 5 experienced an alleviation of scores on the FOGQ and GFQ after 1 month of PPN CL-DBS;

however, the effects were inconsistent at her remaining visits (**Figure 5**). Overall, the effects of PPN CL-DBS have been proven to be modest in these two subjects.

This article established a PPN CL-DBS paradigm driven by a gait biomarker, which was defined as an increase in 1- to 8-Hz power within the PPN (Molina et al., 2020). An increase in low-frequency oscillations (7–10 Hz) within the PPN has been previously described in patients with PD during gait (Thevathasan et al., 2012). A potential limitation of this biomarker is that it may be due to movement artifact rather than gait; however, we do not believe that this is the case. During gait, we did not observe a broadband increase in PPN or GPi activity (**Supplementary Figure 2**). Furthermore, if the signal we were identifying was in fact an artifact produced from the device, it would also be observed within the GPi recordings.

Various continuous stimulation PPN DBS studies have produced varied results, and there has been recent cautious optimism about the possibility of addressing FoG (Stefani et al., 2007; Strafella et al., 2008; Moreau et al., 2009; Moro et al., 2010a; Acar et al., 2011; Thevathasan et al., 2011; Wilcox et al., 2011; Khan et al., 2012). Although there are published PPN studies with acute improvement, most subjects have failed to maintain positive long-term outcomes (Mestre et al., 2016), similar to the two subjects in this study who underwent long-term PPN CL-DBS. Within other studies that selected patients with unresponsive FoG (Thevathasan et al., 2011) or patients with gait disturbances in progressive supranuclear palsy (Doshi et al., 2015), benefits in gait and balance until 24 and 18 months, respectively, were perceived. However, their cohorts only received bilateral PPN stimulation, whereas in our subjects, we may have perceived inconsistent benefits due to co-stimulation of the GPi (Thevathasan et al., 2018). Our lack of chronic benefit and heterogeneous clinical results in our two long-term PPN subjects was similar to other studies delivering stimulation to multiple targets (Ferraye et al., 2010; Goetz et al., 2019). Furthermore, the failure to maintain benefit from PPN DBS could be a result of many factors including patient selection, microlesion effects, balance dysfunction, disease progression, and electrode locations (Goetz et al., 2019) as well as whether continuous vs. closed-loop DBS programming approaches have been applied.

There were several limitations with the approach in this study. First, eliciting FoG in the laboratory setting is difficult (Nieuwboer et al., 2001; Giladi and Nieuwboer, 2008). Additionally, many FoG episodes are ambiguous and can lead to labeling difficulty, even for experienced movement disorders-trained neurologists. Second, we developed and implemented a new CL-DBS algorithm without knowing whether there would be a consistent and robust physiological signal, which would ultimately define who would undergo long-term PPN CL-DBS. Accomplishing this task in a human population as well as with a new DBS device (Activa PC + S) was non-trivial, and we explored many possible algorithms to identify the best approach for each patient based on their individual physiology. The study sample was small and lacked a control group, which would be helpful to judge the clinical results. Furthermore, we did not test the primary outcome variable with GPi-DBS turned both on and off in order to elucidate the effects of PPN-DBS. Finally, though all five patients met the criteria for a diagnosis of PD, it is possible given the disease progression and complications that some of this cohort may have had other parkinsonism-related diagnoses. Without postmortem confirmation from any of the patients, we cannot be certain of the diagnoses.

In conclusion, FoG as a paroxysmal phenomenon provides an ideal framework for closed-loop DBS; however, the approach resulted in heterogeneous clinical and physiological outcomes and did not reach a reasonable safety standard to warrant a follow-up study. A safer approach may be to limit patient selection to "off" freezers only while implanting and developing closed-loop DBS in a single deep brain target (e.g., PPN).

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request.

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by the University of Florida Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM contributed to the conceptualization, methodology, software, formal analysis, investigation, resources, data curation, writing of the original draft, review and editing, and visualization. CH helped with the conceptualization, methodology, review and editing, supervision, and funding acquisition. SC performed formal analysis, revisions, and review and editing. KS, AS, and JR helped with the validation, formal analysis, investigation, and review and editing. DM-R performed formal analysis, data curation, and review and editing. EO helped with the methodology, software, formal analysis, and investigation. CWH and RE helped with the formal analysis and review and editing. KF, AG, and MO contributed to the conceptualization, methodology, resources, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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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.2021.633655/full#supplementary-material.

SUPPLEMENTARY FIGURE 1 | Example of local field potential recordings from PPN. **(A)** Real-time detection of gait demonstrating the intermittent spiking nature of the gait feature. Inter-detection intervals defined the 3.5 s hold out. Blue areas denote when the subject was walking. **(B)** Fully implemented responsive PPN-DBS. The top panel is the right and left foot acceleration, the middle panel is the raw PPN signal, and finally the bottom panel is the gait feature band. The algorithm successfully detected walking, and subsequently turned on stimulation, maintained stimulation for the majority of the walking task, and turned stimulation back off when ambulation stopped.

SUPPLEMENTARY FIGURE 2 | Spectrograms from GPi and PPN in one participant. **(A)** One representative spectrogram of GPi activity before and after the onset of walking (n = 20 trials). The onset of walking is denoted by the black vertical line at 0 s. **(B)** Spectrogram of PPN activity before and after the onset of walking. Note the increased power within the PPN is confined to lower frequencies rather than a broadband sharp increased across frequencies. Similar, no artifact is present within the GPi recordings from the same trials.

SUPPLEMENTARY TABLE 1 | Lead locations of the active contacts.

SUPPLEMENTARY TABLE 2 | Stimulation protocol at each month.

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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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Global Variability in Deep Brain Stimulation Practices for Parkinson's Disease

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Introduction: Deep brain stimulation (DBS) has become a standard treatment option for select patients with Parkinson's disease (PD). The selection process and surgical procedures employed have, to date, not been standardized.

Methods: A comprehensive 58-question web-based survey was developed with a focus on DBS referral practices and peri-operative management. The survey was distributed to the Parkinson's Foundation Centers of Excellence, members of the International Parkinson's Disease and Movement Disorders Society, and the Parkinson Study Group (Functional Neurosurgery Working Group) between December 2015 and May 2016.

Results: There were 207 individual respondents (20% response rate) drawn from 59 countries and 6 continents, of whom 64% received formal training in DBS. Thirteen percent of centers reported that DBS could proceed despite a confidence level of $< 50\%$ for PD diagnosis. A case-based approach to DBS candidacy was applied in 51.3% of centers without a cut-off for levodopa-responsiveness. Surprisingly, 33% of centers regularly used imaging for diagnostic confirmation of idiopathic PD. Thirty-one percent of centers reported that neuropsychological evaluation did not affect DBS target selection. Approximately half of the respondents reported determination of DBS candidacy based on a multidisciplinary committee evaluation and 1/3rd reported that a committee was used for target selection. Eight percent of respondents felt that psychosocial factors should not impact DBS candidacy nor site selection. Involvement of allied health professionals in the preoperative process was sparse. There was high variability in preoperative education about DBS outcome expectations. Approximately half of the respondents did not utilize a "default brain target," though STN was used more commonly than GPi. Specific DBS procedure techniques applied, as well as follow-up timelines, were highly variable.

Conclusion: Results revealed high variability on the best approaches for DBS candidate selection, brain target selection, procedure type, and postoperative practices. Cognitive and mood assessments were underutilized. There was low reliance on multidisciplinary teams or psychosocial factors to impact the decision-making process. There were small but significant differences in practice across global regions, especially regarding multidisciplinary teams. The wide variability of responses across multiple facets of DBS care highlights the need for prospective studies to inform evidence-based guidelines.

Keywords: DBS (deep brain stimulation), Parkinson's disease, intra-operative, practices, international

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder with both motor and non-motor symptoms and medical and surgical treatment options (Hughes et al., 1992; Postuma et al., 2015). The incidence of PD in the United States doubled between 1997 and 2017 (Collaborators et al., 2020). It has been estimated that there will be 1.64 million cases by 2037 (Yang et al., 2020). Although there are many approved medications for PD symptoms, select patients may require deep brain stimulation (DBS) surgery (Lozano et al., 2019; Ramirez-Zamora et al., 2019). DBS has been recognized as a treatment of choice for specific symptoms (tremor, dyskinesia, on-off fluctuations, off time) by several national and international guideline committees and expert consensus. Accordingly, DBS has been included in several professional society best-practices recommendations (National Collaborating Centre for Chronic Conditions, 2006; Pahwa et al., 2006; Fox et al., 2011; Ferreira et al., 2013).

Deep brain stimulation evaluation practices have gradually evolved over the past three decades. The original practices were borrowed from the core evaluations formulated by consensus for CAPIT (Langston et al., 1992) and CAPSIT-PD, which were initially developed for PD tissue transplantations (Defer et al., 1999). Initially, published "surgical" referral criteria were quite stringent, including proposing preoperative hospitalization in some instances (Broggi et al., 2003). In contrast, modern practices are such that most preoperative evaluations are completed in the outpatient setting.

Multiple groups have reported on their expert approaches (Pinter et al., 1999; Lang and Widner, 2002; Abboud et al., 2014) and posited exclusion criteria for DBS (Lopiano et al., 2002). Practices have been reported to vary widely across DBS centers in the areas of preoperative evaluation, candidate selection, brain target selection, and procedural techniques. The variability in DBS practices has limited generalizability in the extrapolation of DBS outcomes.

The current study utilized a comprehensive survey-based approach in collaboration with the International Parkinson's Disease and Movement Disorders Society (MDS), the Parkinson's Foundation Centers of Excellence (PF COE), and the Parkinson Study Group (PSG) Functional Neurosurgery Working Group. The study was international and aimed to uncover the variations in global DBS practices to inform future prospective outcome-directed research on DBS practices.

METHODS

A 58-question web-based survey (**Supplementary File 1**) on global DBS practice(s) was constructed. The survey focused on various aspects of the DBS referral pathway, including: initial referral mechanism, indications for DBS, adequacy of medication trials, method(s) of neuropsychiatric and neuropsychological evaluation, use and members of a multidisciplinary screening committee, brain target site selection, intra-, and postoperative imaging as well as postoperative management.

Questions regarding DBS referral and peri-operative management were formulated by a consensus of six practicing DBS experts at three centers. Discrepancies were addressed by consensus discussion among survey authors. The survey was distributed between December 17, 2015, and May 28, 2016, to the PF COEs, the MDS Functional Neurosurgery Committee members, and PSG functional neurosurgery working group members. An online survey system was used, with only one response from each participating DBS center permitted. When more than one response from a center was received, the authors identified a single representative response, typically the response from the practitioner's response with the most years of experience in DBS. Results were tabulated and presented as a choice probability of response (denominator as the total number of question respondents). The complete dataset is available upon request to the corresponding author. Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

RESULTS

Respondent Demographic Information

There were 207 individual respondents (20% of the sample) from 59 countries across six continents (**Figure 1**). Fifty-eight (58%) of respondents classified themselves as movement disorders neurologists (MDN) and 15% as neurosurgeons (**Supplementary File 2**). The average center experience for DBS surgery was 11.3 years (range: < 1 year to 32 years) and the average monthly number of surgeries was 3.3 (range: 0–15). Sixty-four percent of respondents received formal training in DBS (126/197), and 62%

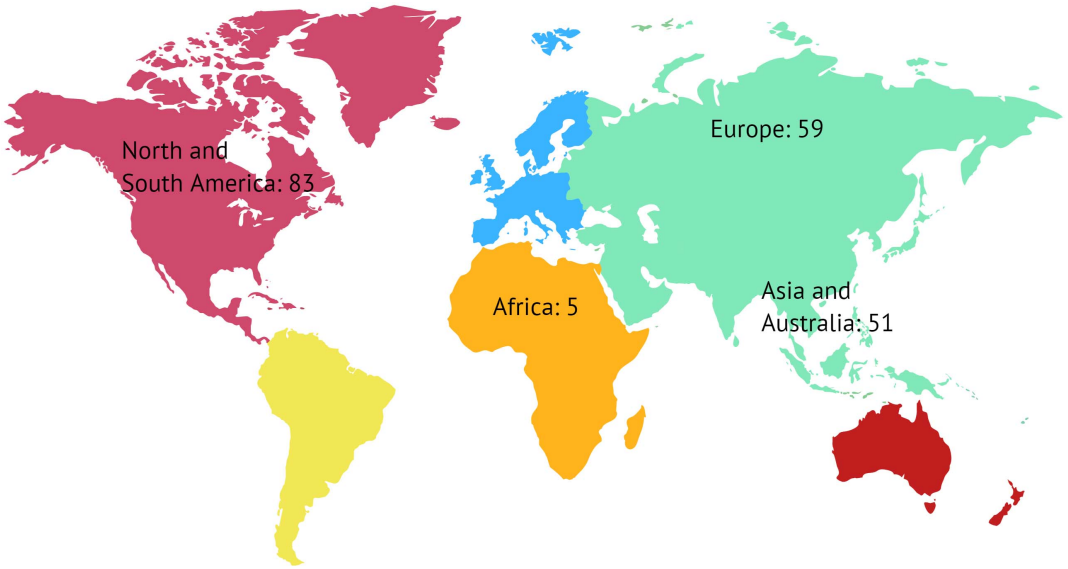

FIGURE 1 | The survey had respondents from 4 regions representing 6 continents and 59 countries.

(78/126) reported a DBS manufacturer (i.e., industry) assisted in some role in their training (e.g., course).

Referral Pathway

There were 91.5% (172/188) of respondents who responded that their center required an MDN evaluation before DBS surgery. Referrals directly to surgery could be made by general neurologists or outside MDNs in 11.2% (21/188) and 19.7% (37/188) of the sample, respectively, without evaluation by an internal neurologist or multidisciplinary committee. Sixty-seven percent (126/188) accepted self-referrals and 66.5% (125/188) accepted referrals from non-neurologists. About 50% (77/188) of respondents reported participating in direct-to-patient advertising for DBS surgery services.

Pre-surgical Evaluation – Diagnosis

Responding centers reported 7.2 DBS referrals (range: < 1 to 42) and conducting an average 3.3 DBS procedures (range: < 1 to 15) a month. Besides PD, 83.5% (142/170), 79% (134/170), 70.6% (120/170) and 37.6% (64/170) of respondents reported performing DBS procedures for essential tremor, generalized dystonia, focal or segmental dystonia and Tourette's syndrome/tics, respectively. Several other indications were also reported. Thirty-three percent (56/170) of respondents reported the use of functional imaging (including DaT SPECT imaging, PET, etc.) to confirm the diagnosis of idiopathic PD. Thirteen percent (22/170) of centers proceeded with DBS with a diagnostic confidence level of PD at ≤ 50%.

Pre-surgical Evaluation – Medication Trials

Approximately 93% (147/158) of respondents reported a process for determining the adequacy of pharmacotherapy before surgery. Almost half of the respondents (78/158) considered candidacy for intestinal gel-based levodopa (Duopa^{TM}) simultaneously with DBS during the pre-surgical evaluation. 82% (129/158) felt immediate-release carbidopa/levodopa *must* be tried, while only 2.5% (4/158) felt it was unnecessary (see **Figure 2** for details). The majority (86%) agreed that DBS should be considered if fluctuations were present despite dosing at least 5–6 times daily. While 18% (28/158) felt that there should be no minimum disease duration for consideration of DBS, 81% (128/158) felt it should be at least 3–4 years and 6.3% (10/158) felt that it should at least be seven years. Ninety percent (143/158) reported an OFF-ON Levodopa challenge as part of their DBS evaluation. A post-levodopa improvement on the Unified Parkinson Disease Rating Scale (UPDRS) or MDS-UPDRS of > 50% or > 33% were required in 15.2% (24/158) and 37.3% (59/158) of respondents, respectively. In contrast, 51.3% (83/158) of respondents reported a case-based approach without absolute cut-off of levodopa response.

Pre-surgical Evaluation – Non-motor Features

Less than half the respondents (71/147) used specific, absolute cut-offs for a cognitive screen. Notably, 12.2% (18/147) respondents reported no formal neuropsychological evaluation required before DBS surgery. A formal neuropsychological evaluation was performed only if a cognitive screen suggested dysfunction at 68 (out of 147, 46.2%) centers. Suicidal ideation was not routinely assessed by 15.6% (23/147) of respondents.

There were questions to explore how the preoperative evaluation influenced decision-making regarding brain target or whether bilateral leads would be implanted simultaneously or staged. In 36% (53/147) of responses, mood evaluation never affected DBS target selection. In 30.6% (45/147) of

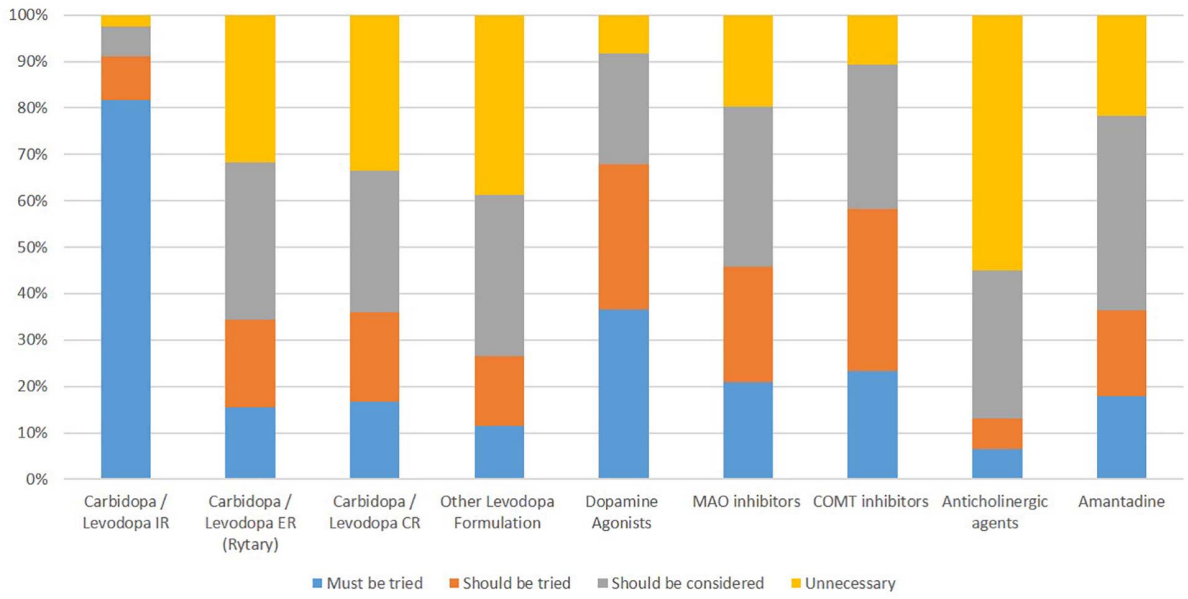

FIGURE 2 | Percentage of respondents reporting pharmacotherapy use prior to Deep Brain Stimulation for Parkinson's disease.

responses, neurocognitive evaluation never affected DBS target selection (**Supplementary File 2**). Twenty-four percent (35/147) of respondents reported that procedures were never staged. Mood or neurocognitive evaluations would not have affected the decision to stage DBS in 49% (72/147) and 42.2% (62/147) of respondents, respectively (**Supplementary File 2**).

Pre-surgical Evaluation – Rehabilitative and Psychosocial

Allied health professionals and rehabilitation staff were involved in the minority of preoperative evaluations: physical therapy (PT) 48%, occupational therapy (OT) 23.6%, speech therapy (SLP) 38.2%, social work 20.8%, case managers 13.2%, and registered nurses (34%, total number of respondents = 144). Eighty-five percent (124/144) of the responding centers' evaluated psychosocial support and socioeconomic factors before DBS surgery, and only 7.6% (11/144) of respondents felt that these factors never affected DBS candidacy or site selection. On a question with multiple answers allowed (total number of respondents = 144), respondents reported that patients learned about DBS outcomes expectations from a variety of sources, including the referring neurologist/physician (40.3%), group seminar (27%), MDN (93%), a neurosurgeon (82%), psychiatrist (12.5%), neuropsychologist (28.5%) and registered nurse (32.6%).

DBS Committee and Decision

Respondents considered various team members to be part of the "required" preoperative evaluation, though more and different specialists were variably available for evaluation (**Figure 3**). Ultimately, the candidacy for DBS for PD was determined by a DBS committee (46.5%; 67/144), MDN alone (18.7%; 27/144), MDN and neurosurgeon *without* a DBS committee (24.3%; 35/144), or by the neurosurgeon alone (10.4%; 15/144) across respondents. Likewise, the DBS target and procedure type was determined by a DBS committee (36.8%; 53/144), a MDN alone (13.2%; 19/144), an MDN and a neurosurgeon *without* a DBS committee (32%; 46/144), or a neurosurgeon alone (18%; 26/144). The final decision to proceed with DBS could be made via consensus-building (80%; 115/144), a veto by MDN (13.2%; 20/144), a veto by a neurosurgeon (16.6%; 24/144), a decision-making tool (1.4%; 2/144) or another modality (3.5%; 5/144).

DBS Procedure

The following intra-operative technique(s) were reported to be utilized to evaluate or to confirm micro- or macro-electrode position (total number of respondents = 143): Microelectrode recording or MER (91.6%), Image guidance-CT (25.2%), and image guidance-MRI (40.5%) (**Figure 4**). Several centers performed more than one type of lead localizing procedure. 49% of the respondents reported using MER only. 9.8% used MER with iCT, 21% used MER with iMRI, and 12.6% used all three modalities (MER, iCT, and iMRI). No respondent reported using iCT alone, whereas 4.2% of respondents reported using iMRI alone. 1.4% reported using iCT and iMRI without MER use.

Via multiple response questions with more than one response allowed, MER recording and analysis were performed by a neurologist (62.9%), a neurosurgeon (37%), a physiologist (30.8%), or others (7%). Relatedly, the preoperative and peri-operative stereotactic planning for the DBS target was reported as performed by a neurologist (26.6%), a neurosurgeon (92.3%); a physiologist (7%), a radiologist (4.9%), or by a representative from a medical device company (9%).

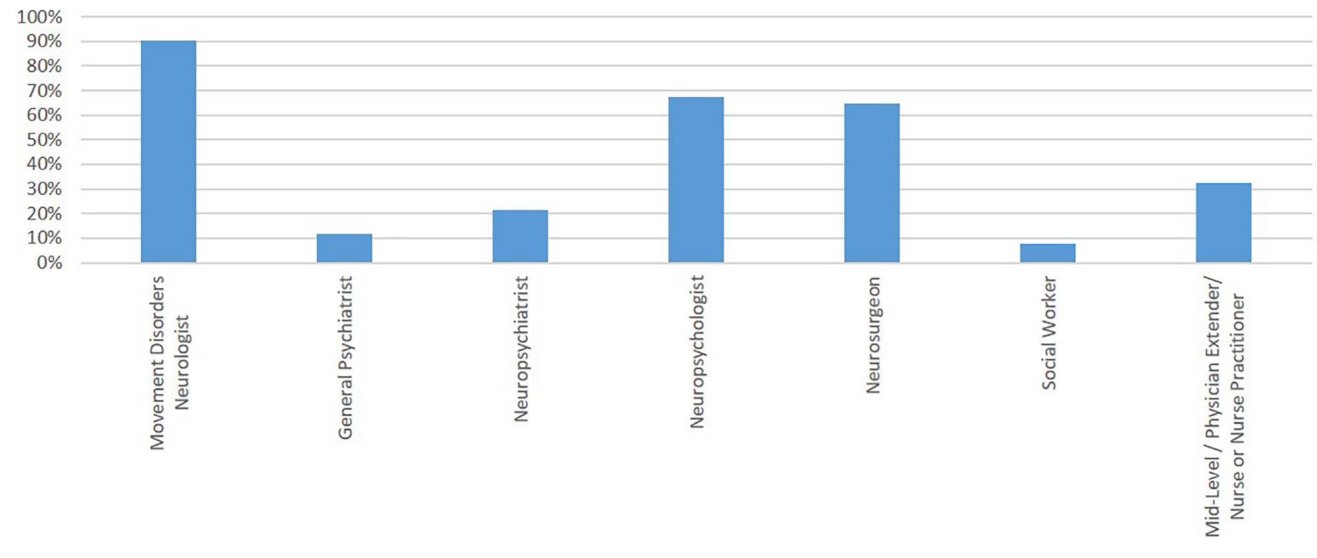

FIGURE 3 | Team members reported as a part of the "required" preoperative evaluation. Y-axis represents the percentage of respondents reporting involvement of that team member.

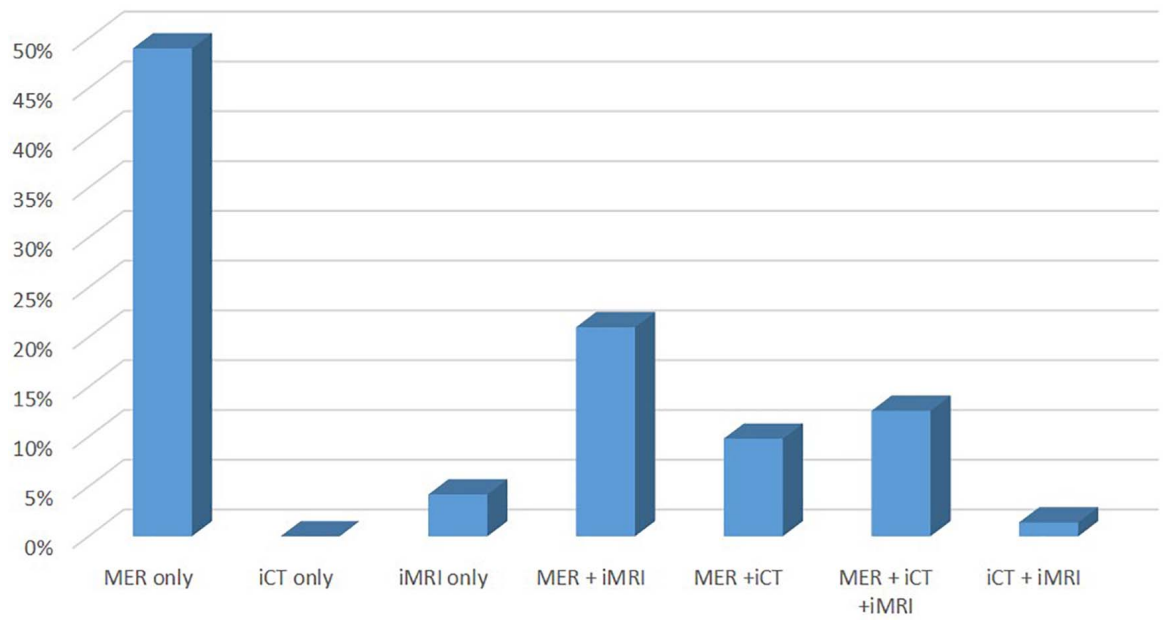

FIGURE 4 | The intra-operative technique reported to be utilized to evaluate and/or to confirm micro-macro-electrode position. Y-axis represents percentage of respondents reporting use of that technique. More than one technique may be used in a given institution. Abbreviations: MER, microelectrode recording; iCT, intraoperative computed tomography; iMRI, intraoperative magnetic resonance imaging.

Approximately half of the respondents (51%) did not utilize a "default target." STN was used more commonly than GPi as a target. Few centers used alternative targets (**Figure 5**). Many centers (45.4%) targeted STN for 81-100% of PD cases, while only 2.8% (65/143) targeted GPi and 0.7% (1/143) targeted Vim with that frequency. PPN was reported to be used 21-40% of the time by three centers and cZI by seven centers at that proportion of cases. Other targets were also pursued in some participating centers.

Post-implantation and Follow-Up Care

Postoperative imaging was obtained within 24 h by 66.4% (95/143) of centers, while 7.7% (11/143) of centers did not routinely obtain postoperative imaging. Overall, CT was used by 73.4% (105/143) and MRI by 36.4%

(52/143) of respondents. No respondent reported using ventriculography. Feedback to the referring physician about clinical efficacy was provided by the MDN (78.3%; 112/143), a neurosurgeon (14.7%; 21/143), or was not provided (7%; 10/143). Seventy-three percent (105/143) of respondents routinely evaluated mood or cognitive disability/sequelae postoperatively. While a pre-specified schedule for follow up was reported by 43.3% (62/143) of respondents, 12% (17/143) reported no specific routine follow-up. The following services did not participate in the routine postoperative evaluations in nearly 40% (57/143) of centers: PT, OT or SLP, social workers, case managers, psychiatrists/neuropsychiatrists neuropsychologists. Only 31% (44/143) of centers had a formal DBS specific mortality-morbidity conference.

Regional Variability

The regional variability of key DBS practices are as follows. The African region only had five responses limiting further data exploration (**Table 1**).

Respondent Demographic Information

North and South America

The average center experience of DBS surgery was 11.7 years. Sixty-seven percent (51/76) of respondents received formal training in DBS.

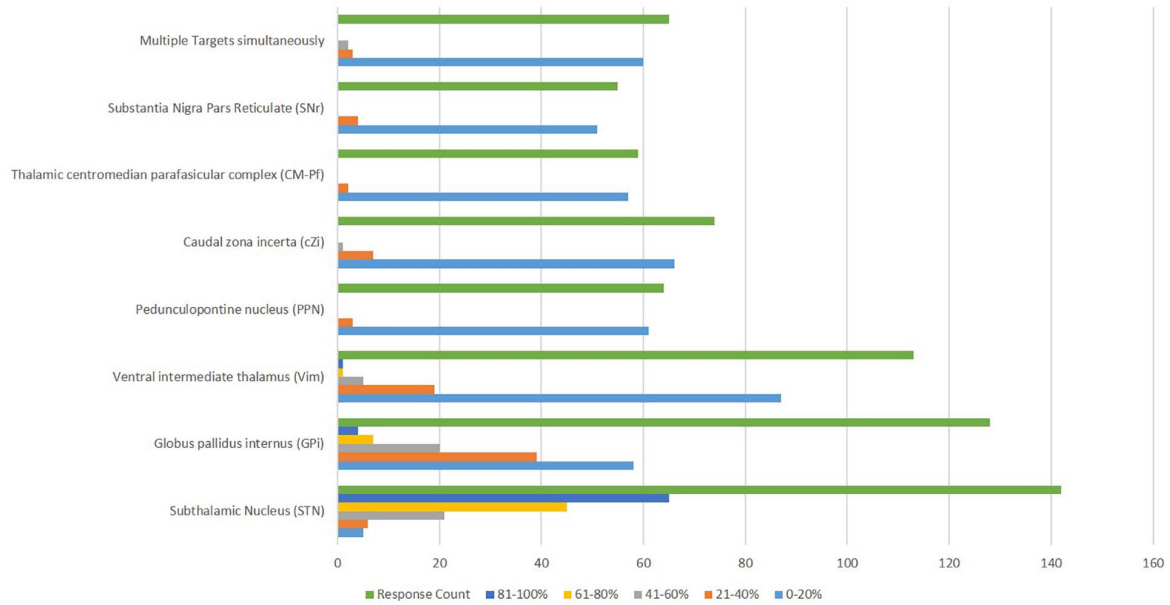

FIGURE 5 | Deep Brain Stimulation targets reported to be utilized for the management of Parkinson's disease.

TABLE 1 | Regional variability in Deep Brain Stimulation practices in Parkinson's disease.

	North and South America	Asia and Australia	Europe	Africa
Number of respondents	83	51	59	5
Movement disorders neurologists respondents	57%	53%	65.5%	20%
Center experience (years)	11.7	9.4	12.4	2
Formal DBS training	67%	63%	67%	20%
Number of DBS referrals per month for PD	9	5	6.8	1.2
Number of DBS procedures per month for PD	4.3	2.2	2.7	0.2
Assessment of pharmacotherapy adequacy prior to DBS	97%	97%	91%	50%
No cut-off for disease duration prior to DBS	22%	16%	9%	0%
No absolute cut-off for motor improvement for DBS consideration	54%	57%	41%	0%
No formal neuropsychological testing prior to DBS	7.5%	5%	5%	50%
Default target for DBS in PD	43%	56%	50%	50%
DBS candidacy decided based on a multidisciplinary committee	40%	69%	69%	50%
Use of intra-operative MER in the institution	89%	100%	90%	100%
Pre-specified schedule clinic follow up post DBS	42.4%	31.2%	56.4%	100%

Abbreviations: DBS, Deep Brain Stimulation; PD, Parkinson's disease; MER, Microelectrode recording.

Asia and Australia

The average center experience of DBS surgery was 9.4 years. Sixty-three percent (31/49) of respondents received formal training in DBS.

Europe

The average center experience of DBS surgery was 12.4 years. Seventy-one percent (41/58) of respondents received formal training in DBS.

Referral Pathway and Pre-surgical Evaluation – Diagnosis

North and South America

For 92% (67/73) of respondents, an MDN evaluation was necessary before DBS surgery.

Responding centers reported receiving an average number of 9 DBS referrals and conducting an average of 4.3 DBS procedures a month.

Asia and Australia

For 91.5% (43/47) of respondents, an MDN evaluation was necessary before DBS surgery.

Responding centers reported receiving an average number of 5 DBS referrals and conducting on an average 2.2 DBS procedures a month.

Europe

For 98% (53/54) of respondents, an MDN evaluation was necessary before DBS surgery.

Responding centers reported receiving an average number of 6.8 DBS referrals and conducting on an average 2.7 DBS procedures a month.

Pre-surgical Evaluation - Medication Trials

North and South America

Whether a trial of levodopa/carbidopa immediate must be tried before DBS for PD was endorsed by 87% ($n = 60$), whereas none felt it was unnecessary. While 22% (15/69) felt that there should be no minimum disease duration for DBS consideration for PD, 6% (4/69) felt that it should be more than seven years. While 7% (5/69) required at least 50% improvement on UPDRS or MDS-UPDRS before proceeding with DBS, 54% (37/69) reported a case-based approach with no absolute cut-off.

Asia and Australia

Whether a trial of levodopa/carbidopa immediate must be tried before DBS for PD was endorsed by 81% (30/37), whereas none felt it was unnecessary. While 16% (6/37) felt that there should be no minimum disease duration for DBS consideration for PD, 8% (3/37) felt that it should be more than seven years. While 11% (4/37) required at least 50% improvement on UPDRS or MDS-UPDRS before proceeding with DBS, 57% (21/37) reported a case-based approach with no absolute cut-off.

Europe

Whether a trial of levodopa/carbidopa immediate must be tried before DBS for PD was endorsed by 75% (33/44), whereas 4.5% (2/44) felt it was unnecessary. While 9% (4/44) felt that there should be no minimum disease duration for DBS consideration for PD, 7% (3/44) felt that it should be more than seven years. While 29.5% (13/44) required at least 50% improvement on UPDRS or MDS-UPDRS before proceeding with DBS, 41% (18/44) reported a case-based approach with no absolute cut-off.

Pre-surgical Evaluation – Non-motor Features

North and South America

98.5% (66/67) of respondents reported cognitive symptoms routinely screened pre-DBS. Only 7.5% (5/67) of respondents reported no requirement of formal neuropsychological evaluation before DBS surgery. 43% (29/67) of respondents reported using a default brain target for DBS for PD.

Asia and Australia

Ninety five percentage (33/34) of respondents reported cognitive symptoms routinely screened pre-DBS. Only 5% (10/34) of respondents reported no requirement of formal neuropsychological evaluation before DBS surgery. 56% (19/34) of respondents reported using a default brain target for DBS for PD.

Europe

Ninety five percentage (38/40) of respondents reported cognitive symptoms routinely screened pre-DBS. Only 5% (2/40) of respondents reported no requirement of formal neuropsychological evaluation before DBS surgery. 50% (20/40) of respondents reported using a default brain target for DBS for PD.

DBS Committee and Decision

North and South America

A committee determined DBS candidacy for PD in 40%, brain target, and procedure type in 30% of centers. The final decision to proceed with DBS was established by consensus building in 82% (55/67).

Asia and Australia

A committee determines DBS candidacy for PD in 69%, brain target, and procedure type in 22% of respondents. The final decision to proceed with DBS was established by consensus building in 75% (24/32).

Europe

A committee determines DBS candidacy for PD in 69%%, brain target, and procedure type in 56.4% of respondents. The final decision to proceed with DBS was established by consensus building in 87% (34/39).

DBS Procedure

North and South America

The following intra-operative technique(s) were reported to be utilized to evaluate and confirm micro-macro-electrode position (total number of respondents = 67): Microelectrode recording or MER (89%; 60/67), Image guidance-CT (28.3%; 19/67), and image guidance-MRI (42%; 28/67).

In a question with multiple options allowed (total number of respondents = 67), the recording and analysis of MER was reported to be performed by the neurologist (54%; 36/67),

neurosurgeon (40.3%; 27/67), physiologist (33%; 22/67) and others (6%; 4/67).

In a question with multiple options allowed (total number of respondents = 67), the preoperative and peri-operative stereotactic planning for the selected DBS target was reported to be performed by the neurologist (21%; 14/67), neurosurgeon (91%; 61/67); physiologist (7.5%; 5/67) and radiologist (3%; 2/67).

Asia and Australia

The following intra-operative technique(s) were reported to be utilized to evaluate and confirm micro-macro-electrode position (total number of respondents = 32): Microelectrode recording or MER (100%; 32/32), Image guidance-CT (16%; 5/32), and image guidance-MRI (34.4%; 11/32).

In a question with multiple options allowed (total number of respondents = 32), the recording and analysis of MER were reported to be performed by the neurologist (78%; 25/32), neurosurgeon (44%; 14/32), and physiologist (28%; 9/32).

In a question with multiple options allowed (total number of respondents = 32), the preoperative and peri-operative stereotactic planning for the selected DBS target was reported to be performed by the neurologist (44%; 14/32), a neurosurgeon (84%; 27/32); physiologist (9.4%; 3/32) and radiologist (6.2%; 2/32).

Europe

The following intra-operative technique(s) were reported to be utilized to evaluate and confirm micro-macro-electrode position (total number of respondents = 39): Microelectrode recording or MER (90%; 35/39), Image guidance-CT (26%; 10/39), and image guidance-MRI (41%; 16/39).

In a question with multiple options allowed (total number of respondents = 39), the recording and analysis of MER were reported to be performed by the neurologist (69%; 27/39), neurosurgeon (26%; 10/39), physiologist (31%; 12/39) and others (10%; 4/39).

In a question with multiple options allowed (total number of respondents = 39), the pre-operative and peri-operative stereotactic planning for the selected DBS target was reported to be performed by the neurologist (20.5%; 8/39), neurosurgeon (100%; 39/39); physiologist (2.6%; 1/39) and radiologist (7.7%; 3/39).

Post-implantation and Follow-Up Care

North and South America

Postoperative imaging was not obtained by 7.6% of centers routinely (unless there were unexpected signs or symptoms), and 9% reported no specific routine to follow-up with DBS check whenever needed or during PD follow-up visit.

Asia and Australia

Postoperative imaging was not obtained by 12.5% of centers routinely (unless there were unexpected signs or symptoms), and 22% reported no specific routine follow-up with DBS check whenever needed or during PD follow-up visit.

Europe

Postoperative imaging was not obtained by 2.6% of centers routinely (unless there were unexpected signs or symptoms), and 5% reported no specific routine follow-up with DBS check whenever needed or during PD follow-up visit.

DISCUSSION

The data from this global survey revealed variability in international DBS practice, including preoperative motor evaluation, preoperative non-motor evaluation, DBS decision-making, procedure type, and postoperative assessment of outcomes. The involvement of respondents from 59 countries, spread across six continents and the four regional sections (acknowledged by the International Parkinson's disease and Movement Disorder Society) strongly supported the survey's global intentions. While a survey-based methodology could be susceptible to several sources of bias, there were clear and expected areas of variability that warrant further inquiry.

One potential source of variability in DBS practice(s) is the wide variety of pathways through which providers receive training in the management of DBS patients. It was somewhat concerning that 36% of respondents reported *no* formal training in DBS during post-graduate, subspecialty training, or fellowship experience. DBS was first approved by the United States Food and Drug Administration in 1997 and even earlier in Europe. As the average duration of practice among respondents was 11.3 years (range < 1 to 32y), many respondents likely began managing DBS patients before widespread clinical use and training (movement disorders neurology or functional neurosurgery fellowships). However, these data did suggest that most respondents may have finished training within the last two decades. This would correspond to when DBS education should have likely been integrated into post-residency programs. Interestingly, a majority of respondents (62%) reported training by industry. Though device manufacturer-sponsored courses are valuable, most experts would agree that they should not be the main drivers of education in the field. There are three FDA- and CE-approved DBS manufacturers with 20 + companies in the DBS development pipeline internationally (DelveInsight's, 2020). The involvement of industry as a primary source of DBS education will introduce a major source of variability in DBS practice given that each device manufacturer may emphasize different management principles (imaging-based, neurophysiology-based, segmented leads, etc.). Some of the heterogeneity in training may be related to restricted access to movement disorders training programs, though we did not explore this issue within our dataset. There is wide variability in the availability of training for DBS; for instance, the world's second most populous country, India, has only 8-10 movement disorders fellowships and one functional neurosurgery training program, which is far less than what is needed (Zhang et al., 2020). Collectively, the data suggest that there may be space for improvement in the standardization of essential educational elements expected in DBS training. We also would advocate that the influence of industry education on trainees' education should be more closely monitored.

The variability in diagnostic confirmation techniques for PD was particularly notable. The most recent clinical diagnostic criteria for PD supports a diagnosis of probable or

clinically established PD, based mainly on history and physical examination (Postuma et al., 2015), with ancillary testing only necessary when there is an accompanying suspicion of a secondary cause of parkinsonism (Berg and Adler, 2018). Therefore, the use of functional imaging to confirm PD diagnosis by 33% of respondents was surprising and may be driven by the recent shift toward earlier DBS (Schuepbach et al., 2013; Hacker et al., 2020). On the other hand, 13 centers reporting proceeding with DBS for PD when diagnostic certainty was < 50% demonstrates that there is still high variability across centers regarding their degree of concern over diagnostic certainty. Lack of standardization to guide pre-DBS candidacy determination may lead to adverse outcomes (Mari, 2020).

The survey results offer insight into the decision-making processes employed at many DBS centers. A slight majority (51.3%) of centers used a patient-centered approach to candidacy and did not employ cut-offs for the degree of levodopa response (Kleiner-Fisman et al., 2006). The data supports a growing acknowledgment that using a 33% improvement in UPDRS or MDS-UPDRS Part III as a cut-off will limit DBS access, especially in patients with medication-refractory tremor (or other unique symptom profiles). We posit that the use of hard cut-offs on UPDRS scales may inadvertently exclude specific patients who may benefit from DBS, and systems of care should investigate the extent to which these criteria may inadvertently introduce an undue burden on clinicians and patients. Individual patient symptoms and expectations must be taken into consideration before making decisions pertaining to DBS surgery and assessing outcomes.

Rather than using strict cut-offs, consensus recommendations from DBS experts promote the use of a pre-DBS multidisciplinary team to review the motor, cognitive, psychiatric, and psychosocial status in the development of a risk-benefit estimate (Abboud et al., 2014; Higuchi et al., 2016; Akbar and Asaad, 2017). However, only half of the respondents reported using a multidisciplinary committee to determine DBS candidacy. Furthermore, 12.2% of respondents did not require neuropsychological evaluation, with 46.2% if deficits were uncovered mandating a conditional neuropsychological evaluation after a cognitive screening examination (Rothlind et al., 2015; Cernera et al., 2019; Kenney et al., 2020). The literature is evolving but supportive of the notion that brain target selection can impact cognitive or and mood outcomes following DBS (Okun et al., 2009; Rothlind et al., 2015; Kenney et al., 2020) and that baseline cognitive performance predicts post-DBS cognitive decline and quality of life (Odekerken et al., 2015; Kenney et al., 2020). The survey revealed room for potential improvement in utilizing multidisciplinary teams with patient-centered assessments, including neuropsychological and psychosocial function, rather than relying on strict rating scale cut-offs, permitting more inclusiveness for patients who may benefit from DBS.

The involvement of allied health professionals varied considerably across centers. More than half of respondents reported that routine physical therapy assessments were not utilized. The utility of preoperative PT assessments will warrant further study given that the types and severity of baseline gait and postural abnormalities could potentially inform the DBS team (and patient), particularly in postoperative gait and balance expectations (Nantel et al., 2012). Only 20.8% and 13% of respondents reported social workers or case managers' were involved in the DBS preoperative process, though our survey did not quantitate why these professionals were not utilized. With training in assessment of care partner burden and psychosocial challenges, social workers or case managers might better prepare the DBS team's expectations for having a patient and care partner who facilitate successful DBS therapy, or they might help to identify and mitigate social determinants of health in order to optimize outcomes. Understanding the barriers or reluctance to use these allied health professionals in perioperative DBS management will be a potential area for future study.

The preoperative education on outcome expectations was highly variable among our respondents, with only about $1/4^{th}$ (27%) of centers using a formalized educational format such as a seminar or lecture to supplement education from neurologists (40.3%) and neurosurgeons (82%). Educational programs such as ParkEduStim might help to align patient expectations with potential results from surgery (Valérie Fraix and Schmitt, 2021). Patient and care partner expectation management will be integral to achieving patient satisfaction with DBS and other surgical procedures (Maier et al., 2013; Knoop et al., 2017). Whether the presence or absence of structured DBS educational programs in the preoperative evaluation changes decision-making at the patient or provider level is unclear, but current evidence suggests that it increases patient satisfaction. In a recent retrospective analysis of DBS cases referred for second opinions, nearly half of the "unsatisfied patients" complained of symptoms that DBS could not address, including cognitive impairment, imbalance, dysarthria, and dysphagia (Kluger et al., 2011). Use of a formal education seminar, internally or directed to reliable external sources (Parkinsons Foundation, 2020) may lead to more concurrence between patient and provider expectations. Whether cultural issues drove the gap in education and management of preoperative expectations, availability of services or other factors was unclear.

The brain target variability matches the literature suggesting STN or GPi targets can be used for PD (Deuschl et al., 2019). However, some respondents predominantly used a specific brain target (45.4% of centers used STN in 81–100% of cases). Approximately half of the respondents (51%) did not utilize a "default target," though STN was used more commonly than GPi. We suspect technical considerations such as familiarity with MER, access to intraoperative imaging, surgical experience, or center-specific outcome trends can potentially influence target choice. Interestingly, some centers reported a high frequency of implanting alternative targets such PPN (21–40% of cases at three centers) or cZI (21-40% at seven centers). Since there are many factors in choosing a DBS target, our results were unsurprising.

We stratified responses to the survey by region (excluding Africa, which only provided five responses), and by analyzing the data in this fashion, we observed only small inter-region variability across most questions. Centers located in the Americas tended to be less likely to use a specific cut-off for disease duration for DBS candidacy (22% of centers in the Americas,

16% in Asia/Australia, versus 9% in Europe). American region centers were also less likely to decide on DBS candidacy based on a multidisciplinary committee (40% of centers in the Americas, 69% in Asia/Australia, versus 69% in Europe. We speculate that payor systems or cultural norms may have driven these differences; however, we could not uncover the rationale from the dataset.

Centers in the Americas had a lower rate (43%) of a "default target" as compared to Europe (50%), Asia (55%), and Australia (67%). We speculate that this could be sequelae of differences in outcomes between the two largest trials comparing brain targets. The North American trial (Follett et al., 2010) showed equipoise regarding motor symptom outcomes when comparing STN and GPi DBS, while the Dutch/European trial favored STN for the secondary outcome of motoric benefit (Odekerken et al., 2013). Thus, using a default target might seem more appropriate if greater weight is given to the latter trial. Only 40% of the Americas' centers reported using a multidisciplinary committee for decision-making, while 69% of centers in both Asia/Australia and Europe used a committee. We do not know how many solo or small group DBS practices exist in the Americas, especially North America when compared to other countries. We suspect healthcare systems outside of the Americas' to more commonly use centralized hubs of healthcare (Ridic et al., 2012), potentially providing more consistent access to a multidisciplinary team.

Our study was not without limitations, the foremost of which is that surveys are usually susceptible to selection bias. To counteract this issue, we attempted to reach as many providers as possible by dissemination through the International Parkinson's disease and Movement Disorders society and other major organizations. While our survey probably over-represents larger or academic DBS centers, there were many respondents with low volumes of only 1-2 surgeries per month, suggesting we also captured small and mid-size programs. Additionally, surveys can also be susceptible to information bias based on the question's wording. We developed the survey with input from six experienced providers, including representatives from psychiatry, neurology, and neurosurgery, to address this issue. Another issue was duplicate responses from the same surgical center. We addressed this issue by only considering a single response per center, and we prioritized based on the respondent's experience. Our survey focused on DBS practices and did not inquire about the availability, expertise or utilization of stereotactic lesioning because (a) we wanted to minimize attrition by keeping the survey as short as possible, (b) lesioning is widely used but perhaps not completely overlapping with DBS centers so a parallel question set would have been required, and (c) the risk assessment performed for DBS is potentially different than invasive or non-invasive lesioning procedures, and thus would have required separate responses.

In summary, the survey results reflect wide variability and a lack of consensus in many critical areas of PD DBS practice. Though variability can be important to improve surgical procedures, we would argue that the presentation of this and other future datasets may be useful in guiding the field toward better outcomes. The dialog should include discussing issues where a more homogenous approach across centers may improve overall outcome(s). Finally, we propose that similar surveys, perhaps coupled with outcome registries, be circulated periodically as a monitoring tool for the DBS field.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AM did the analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. AB did the acquisition, analysis or interpretation of data, and critical revision of the manuscript for important intellectual content. MO did the analysis or interpretation of data, and critical revision of the manuscript for important intellectual content. ZM did the concept, acquisition, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, and supervision. KM did the acquisition, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, and supervision. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.667035/full#supplementary-material

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BRIEF RESEARCH REPORT
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Deep Brain Stimulation for Parkinson's Disease During the COVID-19 Pandemic: Patient Perspective

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Background: Public health guidelines have recommended that elective medical procedures, including deep brain stimulation (DBS) surgery for Parkinson's disease (PD), should not be scheduled during the coronavirus (COVID-19) pandemic to prevent further virus spread and overload on health care systems. However, delaying DBS surgery for PD may not be in the best interest of individual patients and is not called for in regions where virus spread is under control and inpatient facilities are not overloaded.

Methods: We administered a newly developed phone questionnaire to 20 consecutive patients with PD who received DBS surgery in Ruijin Hospital in Shanghai during the COVID-19 pandemic. The questionnaire was designed to gather the patients' experiences and perceptions on the impact of COVID-19 on their everyday activities and access to medical care.

Results: Most of the patients felt confident about the preventive measures taken by the government and hospitals, and they have changed their daily living activities accordingly. Moreover, a large majority of patients felt confident obtaining access to regular and COVID-19-related health care services if needed. Routine clinical referral, sense of security in the hospital during the outbreak, and poor control of PD symptoms were the three main reasons given by patients for seeking DBS surgery during the COVID-19 pandemic.

Conclusion: The COVID-19 pandemic has considerably impacted medical care and patients' lives but elective procedures, such as DBS surgery for PD, do not need to be rescheduled when the health care system is not overloaded and adequate public health regulations are in place.

Keywords: deep brain stimulation, Parkinson's disease, COVID-19, Person-centered care, elective surgery

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INTRODUCTION

The ongoing coronavirus (COVID-19) pandemic is rapidly changing how we live and practice medicine globally. Most public health guidelines developed to deal with the COVID-19 pandemic recommend that inpatient facilities reschedule elective clinical examinations and surgeries as a preventive measure for the virus (Collaborative Covids, 2020b). In line with this general

recommendation, many medical centers are postponing elective procedures and deferring non-urgent clinic visits to conserve hospital resources and prevent further spread of COVID-19 (Collaborative Covids, 2020a). The surgical implantation of deep brain stimulation (DBS) electrodes for select patients who suffer from Parkinson's disease (PD) is considered an elective procedure and hence, should not be scheduled while public health preventive measures for COVID-19 are in place (Gross et al., 2020; Miocinovic et al., 2020). Only patients with PD who have already undergone DBS surgery and encounter a sudden interruption of the implantable pulse generator or a DBS system-related infection are generally viewed as the ones who require urgent hospital care or, in rare cases, emergency surgery (Miocinovic et al., 2020). Yet, rescheduling and delaying DBS surgery for patients who suffer from advanced and medication-refractory PD may not be in the best interest of individual patients.

Public health guidelines for COVID-19 vary across countries, states/provinces, and local municipalities and can change rapidly according to new scientific insights, public health policies, and changing circumstances (del Rio and Malani, 2020). Indeed, public health guidelines initially put forward should not be seen as fixed and universal but need to be continuously updated and adapted to the current situation. Correspondingly, depending on federal and local regulations, the virus spread, and availability of medical resources, some elective and time-sensitive therapeutic procedures may be prioritized in certain regions and hospitals to maintain or reinstate the delivery of regular health care (Thomas et al., 2020), and to admit new patients with PD referred for specialized DBS surgery and treatment. In our hospital, this option was considered because we were not overcrowded with COVID-19 patients and were able to maintain regular health care delivery. Thus, all functional neurosurgeries, as well as face-to-face and remote programming, remained available upon request during the COVID-19 pandemic (Zhang et al., 2020a). Although we were uncertain about the volume of new patients with PD who would be seeking DBS surgery and treatment amidst the COVID-19 pandemic and the implemented public health preventive measures, a substantial number of patients did seek and receive this neurosurgical intervention for PD in our hospital.

We were intrigued by the patients' perspectives on the COVID-19 pandemic and their own medical risk, as well as on the impact that the COVID-19 crisis may have had on their daily living activities, access to clinical care, and health care costs while they were seeking DBS surgery and treatment for PD during the virus outbreak. Given the uncertain nature of COVID-19 (e.g., future outbreaks) and that other parts of the world not having COVID-19 under control, understanding what PD patients who are seeking DBS think about COVID-19 has important implications for supporting the clinical needs of this sensitive population pre- and post-operatively. In this study, therefore, we examined the perceptions and experiences of a series of PD patients who sought and received DBS surgery and postoperative management in our hospital during the COVID-19 pandemic.

METHODS

Participants

This study enrolled 20 consecutive patients who had received DBS surgery for PD from February 3, 2020 to April 7, 2020 at the Center for Functional Neurosurgery of Ruijin Hospital in Shanghai. The Ruijin Hospital Institutional Ethical Review Board approved study procedures. All patients had provided written informed consent for the surgical procedure and postoperative follow-ups. Patients admitted to the hospital during the COVID-19 pandemic were mainly local residents because national travel restrictions made it difficult for out-of-town patients to enter the city. They were often accompanied by young family members who, according to national public health policy, could take sufficient vacation to accompany their elderly family members to the hospital for clinical examination and surgical treatment if needed. Hospital appointments had been scheduled during the COVID-19 outbreak and none of the patients opted for rescheduling the surgery.

Initially, a trained health professional called by phone all patients with PD who had undergone DBS surgery during the period of interest and invited them to participate in this survey study. Once a patient accepted the invitation and provided verbal informed consent in the phone call, a structured phone questionnaire was administered by the health professional to acquire information about the patient's perspective on the COVID-19 pandemic and its impact while he or she was seeking and receiving DBS surgery and treatment for PD. The questionnaire typically took less than 25 min to complete. The phone interviews were done from April 28, 2020 to May 14, 2020.

COVID-19 Exposure and Impacts Questionnaire

We developed a structured phone questionnaire, referred to as the COVID-19 Exposure and Impacts Questionnaire (CEIQ), to collect information about patient perceptions, attitudes, and experiences in relation to the COVID-19 pandemic (see **Tables 1–3**). We employed the following four sections of the CEIQ: (1) COVID-19 Personal Status, involving dichotomously scored items about the patients' health status and medical risk related to the COVID-19 virus; (2) COVID-19 Impact on Living Conditions, consisting of dichotomously or polytomously scored items about the impact of the COVID-19 crisis and associated public health preventive measures on patients' daily living activities (e.g., occupational or educational functioning), including regular medical visits, and the behavioral changes they personally made to prevent virus infection in public places and at work or home; (3) COVID-19-related Health Care Costs, consisting of dichotomously and quantitatively scored items about patients' actual or expected direct and indirect personal costs for receiving COVID-19-related health care; and (4) COVID-19 Attitudes and Information, composed of items rated using a 5-point Likert scale (ranging from 1 = strongly disagree to 5 = strongly agree), focusing on patients' attitudes and perceptions on: (a) the preparedness of the patient self, the city, and the global community for the

COVID-19 pandemic; (b) the level of confidence in the city's preventive approach; (c) the level of trust in COVID-19-related information provided by official sources; (d) the health risk conferred by contracting the virus; and (e) the ability to get access to regular or specialized health care services. Furthermore, we gathered demographic data as well as the main reasons for seeking DBS surgery and treatment during the COVID-19 virus outbreak.

Hospital Preventive Measures

At the hospital, all patients and accompanying family members were first screened for COVID-19 virus infection. In line with national public health policy, they all possessed carry-on digital codes that documented whether they had traveled to a high-risk area in the past two weeks. All patients also underwent preoperative chest CT screening to detect asymptomatic infections and to ensure that no individuals with COVID-19 were admitted into the general ward. Importantly, management measures (temperature measurement, real-name system recording, and health checks of accompanying personnel) were carried out in single rooms.

Medical personnel's protection in the hospital was also crucial. We took several measures for enhancing their safety, including the development of nursing guidelines related to COVID-19, along with training, facilitating communication skills, and updating of knowledge on diagnostics, therapeutics, and levels of protection needed to interact with a particular patient. Specifically, first-level protection (wearing disposable surgical masks and disposable head covering) was used for patients with no fever in the ward. Second-level protection measures were used for patients with fever, who received timely referrals to a specialized COVID-19 clinic according to protocol. Also, for some invasive and aerosol-generating procedures, the doctor wore goggles and used closed suction tubes to reduce infection risk. Other preventive measures implemented included standardized procedures for disinfection and physical distancing in operating rooms and rest areas, as well as dividing meals into multiple time slots to reduce the risk of cross-infection.

RESULTS

Patient Sample Characteristics

Participants consisted of 20 patients with PD (11 women, 9 men; mean age = 61.4 years, SD = 9.6) (**Table 1**). Most patients (n = 14, 70%) had completed middle school as the highest level of education attained. Also, most patients were married (n = 16, 80%) and had either one child (n = 10, 50%) or two or three children (n = 8, 40%). The majority of patients were retired (n = 16, 80%), one patient was employed, and the remaining were unemployed before the COVID-19 pandemic (n = 3, 15%). Five patients (25%) reported having experienced mental health problems, mainly anxiety or mood disorder, during their lifetime (**Table 1**). One patient was treated with medication for anxiety and depression. None of the patients with PD contracted the COVID-19 virus during the hospitalization.

TABLE 1 | Patients' demographics and clinical information (N = 20).

Characteristics	Value (Percentage)
Age (years)	
mean ± SD	61.4 ± 9.6
range	35–76
Gender (Male/Female)	9/11 (45%/55%)
Level of education	
Middle school	14 (70%)
High school/Special secondary school	5 (25%)
Undergraduate	1 (5%)
Clinical features	
MDS USPRS-III at med-OFF state	55.8 ± 12.4
MDS USPRS-III at med-ON state	29.3 ± 10.3
BDI-II	14.2 ± 8.6
BAI	11.3 ± 7.9
LEDD (mg)	881.5 ± 406.6
Combined household income per year (10 thousand CNY)	
2–5	1 (5%)
5–10	3 (15%)
10–30	10 (50%)
30–50	3 (15%)
50–100	3 (15%)
Marital status	
Single	1 (5%)
Married	16 (80%)
Divorced	1 (5%)
Other	2 (10%)
Employment status	
Full-time work	1 (5%)
Retired	16 (80%)
Unable to work	3 (15%)
Number of children	
0	2 (10%)
1	10 (50%)
2	6 (30%)
3	2 (10%)
History of mental disorders	
No	15 (75%)
Yes	5 (25%)
Generalized anxiety disorder	1
Social anxiety disorder	1
Other anxiety disorder	3
Obsessive-compulsive disorder	1
Depression	2
Bipolar disorder	1
Eating disorder	1

COVID-19 Exposure and Impacts Questionnaire (Sections 1–3)

Table 2 presents the patients' CEIQ data involving Section 1 (COVID-19 Personal Status), Section 2 (COVID-19 Impact on Living Conditions), and Section 3 (COVID-19-Related Health Care Costs). Before DBS surgery and at study entry, none of the patients had been infected by the COVID-19 virus or had any

TABLE 2 | COVID-19 Exposure and Impacts Questionnaire – Sections 1–3.

COVID-19 Exposure and Impacts Questionnaire	Number (Percentage) for positive response
Section 1. COVID-19 personal status	
1. Have you ever contracted COVID-19?	0 (0%)
2. Do you receive immunosuppressive therapy for respiratory diseases, diabetes or other diseases except for PD?	1 (5%)
3. Is your caregiver a member of an at-risk group for more serious COVID-19 illness (such as being immunosuppressed, over 65 years of age, have pre-existing respiratory disease, diabetes, or other)	1 (5%)
4. Have you previously been impacted by SARS, MERS, H1N1, Ebola, or other serious emerging infectious diseases (that is; you got sick, knew someone who got sick, or lived in an area with cases of the disease)?	0 (0%)
Section 2. COVID-19 Impact on Living Conditions	
1. Has your employment been affected by COVID-19?	
Yes, unemployed due to COVID-19 pandemic	0 (0%)
Yes, working hours reduced	0 (0%)
Yes, working hours increased	0 (0%)
Yes, with salary reduction	0 (0%)
Yes, with remote working	0 (0%)
Yes, major events canceled in company or organization	1 (5%)
No, without impact	0 (0%)
Not relevant (retired or unemployed before COVID-19 pandemic)	19% (95%)
2. Have your daily activities been impacted by any of the following?	
Primary/Middle School closures	1 (5%)
University closures	0 (0%)
Transition to online learning	0 (0%)
Inability of being hospitalized or operated in hospital	3 (15%)
Doctor's appointment canceled or postponed	2 (10%)
Shortage of food and other supplies	5 (25%)
Avoid going to restaurants or stores	8 (40%)
Avoid participating large gatherings (e.g., sport events, cinema)	9 (45%)
Avoid meeting people suspected of having recently visited high-risk areas	6 (30%)
Avoid having international air travel	5 (25%)
Avoid having domestic air travel	5 (25%)
3. Have you voluntarily changed your behaviors due to COVID-19 pandemic?	
Increase the frequency of handwashing	19 (95%)
Use additional or stronger disinfectants/cleaners at home or work	8 (40%)
Consult regularly the websites with COVID-19 information	8 (40%)
Take the disinfectants with you to clean objects that may be contaminated by the virus	4 (20%)
Talk with doctors about health issues related to COVID-19	3 (15%)
Purchase face masks	16 (80%)
Wear the protective mask or other equipment in public	10 (50%)
Section 3. COVID-19-related Health Care Costs	
1. Have you incurred any direct costs due to COVID-19 testing and/or treatment?	15 (75%)
If yes, please estimate your direct costs [Median (Range)]	150 (120–300,000) CNY
2. Have you incurred any indirect costs due to COVID-19, e.g., loss of income, additional childcare expenses, costs of necessary travel, preparing for quarantine/isolation?	4 (20%)
If yes, please estimate your indirect costs [Median (Range)]	325 (20–2,000) CNY

other emerging serious infectious disease. One patient, however, received immunosuppressive therapy for diabetes, making this patient at high risk for developing serious or life-threatening COVID-19 symptoms or complications if infected. Seven other patients and one caregiver were similarly at high risk due to advanced age (>65 years) or the presence of a comorbid medical condition.

The COVID-19 outbreak and its preventive measures profoundly affected the patients' daily behavior in both public places and their home setting (**Table 2**). A large proportion of patients reported that they avoided public events (85% of all patients), avoided large gatherings (45%), and avoided restaurants or stores (40%). Many patients also decided to increase their frequency of handwashing (95%), to purchase a face mask (80%), to wear a protective mask or other gear in public (50%), to use extra or stronger disinfectants at home or work (40%), and to visit a web site to gather more information about COVID-19 (40%). Additionally, several patients encountered problems with acquiring food and other product supplies (25%) (**Table 2**).

Relatively few patients canceled doctor appointments (10%) or were unable to get admitted to the hospital for surgery (15%) during the pandemic. Only a few patients (15%) had talked with a doctor about the health issues related to COVID-19 (**Table 2**).

Fifteen patients (75%) incurred direct expenditures due to COVID-19 testing or treatment (median = 150 CNY, range = 120–300,000 CNY) (**Table 2**). Four patients (25%) reported to have incurred indirect expenditures, such as loss of income or extra expenses for necessary travel, due to COVID-19 and associated restrictions (median = 325 CNY, range = 20–2,000 CNY).

COVID-19 Exposure and Impacts Questionnaire (Section 4)

Figure 1 summarizes the patients' CEIQ data involving Section 4 (COVID-19 Attitudes and Information). Almost all patients (95%) felt that they were well prepared for the COVID-19 outbreak. Most patients also felt that the government (85%) and international community (65%) were well prepared. A large majority of patients (85%) reported to have had access to information about the COVID-19 pandemic (e.g., via websites, television) and all patients (100%) trusted the information provided by official sources. Almost all patients (95%) were confident that the government would adequately handle the virus outbreak within several months, and most patients (60%)

TABLE 3 | Reasons for seeking deep brain stimulation surgery.

Questions	Number (Percentage) for positive response
1. What's the main reason for you to choose surgery during the pandemic?	10 (50%)
Doctor appointment with referral	5 (25%)
There are few patients and it is more secure in the hospital	4 (20%)
Poor control of PD symptoms with medical therapy	1 (5%)
Medical insurance referral	1 (5%)
No specific reason	
1. Did you make any special preparations for the surgery, such as taking self-protective measures like wearing a face mask or using antiseptic solution?	7 (35%)

believed that the worst of the crisis was over. Surprisingly, most patients (65%) believed that the risk of COVID-19 was exaggerated, but the other patients (35%) were uncertain or neutral about this statement.

Most patients reported that they had easily access to basic COVID-19 medical care (70%) and intensive medical care (60%) if needed, but other patients (30 and 40%, respectively) were not so certain about their access to these special types of health care. Furthermore, about half of the interviewees (55%) reported that they could afford COVID-19 medical care if required, but many patients did not agree (20%) or were unsure (25%). Less than half of the patients (40%) reported that their COVID-19 medical care would be sufficiently covered by the health care system or private health insurance, whereas the other patients were either uncertain (35%) or disagreed (25%) with this statement.

Reasons for Seeking DBS Surgery

Table 3 presents the main reasons mentioned by the patients for seeking DBS surgery and treatment during the COVID-19 pandemic, along with the personal safety preparations they made before receiving DBS surgery. Clinical referral by the primary health provider, with the hospital appointment scheduled during the pandemic, was the most common reason mentioned among patients (n = 10, 50%). Other patients (n = 5, 25%) reported that the low regional number of COVID-19 patients and the known well-established protective regimen in the hospital formed the main reason. Four patients (20%) sought DBS treatment because their PD symptoms had become too severe to manage with routine treatment. Finally, most patients (60%) reported that major changes had occurred in their life as a consequence of the COVID-19 pandemic, but the other patients (40%) had experienced no major life changes in relation to the pandemic (**Table 3**).

DISCUSSION

In this study, we examined the perceptions and experiences of a series of elderly patients with PD who sought and received DBS surgery and treatment during the COVID-19 virus outbreak in China. Understanding the perceptions and experiences of this group has important implications for personalizing care and optimizing treatment outcomes. The three main reasons given by the patients for seeking DBS surgery during the virus outbreak were routine clinical referral, personal safety provided by hospital care, and poor control of severe PD symptoms. Most patients felt that they, as well as the government, were well prepared for the COVID-19 virus outbreak. Many patients had changed their behavior accordingly, such as avoiding public events, wearing face masks, and increasing the frequency of handwashing. Moreover, the hospital provided indeed a safe health care setting since none of the patients with PD contracted the COVID-19 virus during hospitalization. Thus, in the context of adequate and timely public health preventive measures, the COVID-19 outbreak did not seem to pose a major obstacle

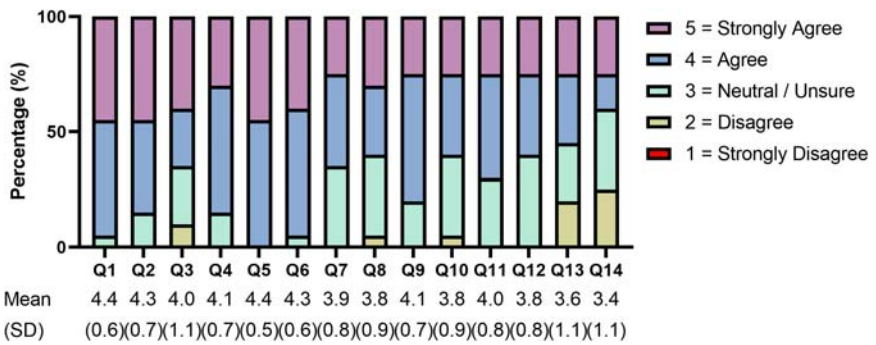

FIGURE 1 | COVID-19 Attitudes and Information. Items were rated using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The items are listed below. Q1: I am well prepared for COVID-19. Q2: The local government is well prepared for COVID-19. Q3: The international community is well prepared for COVID-19. Q4: I can access enough information about COVID-19. Q5: I trust information about COVID-19 from official sources. Q6: I am confident that the local government will cope with COVID-19 over the coming months. Q7: The risk of COVID-19 has been exaggerated. Q8: The worst period of the COVID-19 pandemic is over. Q9: I can access the regular (not related to COVID-19) medical care that I need. Q10: If needed, I can easily access COVID-19 testing. Q11: If needed, I can easily access basic medical care for COVID-19. Q12: If needed, I can easily access intensive medical care for COVID-19 (such as hospitalization or respiratory support). Q13: If needed, I can afford treatment for COVID-19. Q14: If needed, I am sufficiently covered by public or private insurance for COVID-19 treatment.

for this series of patients to get access to DBS surgery and treatment for PD. These observations qualify general public health guidelines recommending that elective procedures, such as the surgical implantation of DBS electrodes, should not be scheduled and performed during the COVID-19 pandemic.

Additionally, most patients mentioned that they could get access to regular medical care if needed, despite the COVID-19 outbreak and associated restrictions, but one-fifth of the patients was not sure about this option. Similarly, the majority of patients felt that they had easily access to basic and intensive COVID-19-related medical care if needed, but more than one-third of patients was not so certain about getting access to these special types of health care. Furthermore, a small majority of patients reported that they could afford COVID-19-related medical care if required, but again a substantial portion of patients did not share this view. In relation to the latter observation, such a social- or income-based disparity in health care access should be addressed because lack of access to high-quality health care not only results in poorer patient outcomes but is also a main driver of population-level health disparities and results in higher health care system costs (Wasserman et al., 2019).The patients hold a relatively optimistic view toward the outcome of the COVID-19 outbreak. Almost all patients were confident that the government would adequately control the COVID-19 virus outbreak within a couple of months, and most patients felt that the worst of the crisis was over. The patients had learned of the COVID-19 pandemic from public health officials, along with gathering information via television and internet. Only a few patients had actually talked with a doctor about the health issues related to COVID-19. The latter observation may explain the unexpected finding that most patients felt that the health risk of the COVID-19 virus was exaggerated. This finding is troublesome but illustrates the importance of direct and clear doctor-patient communication addressing the health issues involved and ensuring patients to not underestimate (or overestimate) their own medical risk of contracting the virus (Malecki et al., 2020).

Nevertheless, in contrast to the clinical management and experiences of patients with PD described in this study, the COVID-19 pandemic has profoundly disrupted the delivery of routine clinical care to neurological patients in many other parts of the world. For example, postponed clinical examinations, increased levels of anxiety and depression, and worsening of seizures have been observed in patients with epilepsy during the COVID-19 outbreak and lockdown in Italy (Assenza et al., 2020). The disruption of routine health care provision due to COVID-19 has similarly resulted in clinical worsening and decreased quality of life in many patients with other chronic brain diseases (Lin et al., 2020; Moro and Fernandez, 2020). Fortunately, telemedicine such as virtual visits and remote patient monitoring can help to maintain routine health care during the COVID-19 pandemic by delivering clinical care to neurological patients in their own home setting (Lin et al., 2020; Moro and Fernandez, 2020; Zhang et al., 2020b).

Finally, it should be acknowledged that the present study has certain limitations, which form threats to the external and internal validity of the results. For example, all patients in this study mentioned that they trusted the information about the COVID-19 pandemic provided by official public health agencies. This high level of trust in government is in marked contrast to the lower levels of trust currently evident in many other countries and cultures. Furthermore, in addition to differences in public health policy, the health care system in China differs greatly from the health care systems in other countries. Correspondingly, it remains to be seen to what extent the perspective and experiences of the patients with PD reported in this study can be generalized to other societal cultures and health care systems. Similarly, the study was cross-sectional and included a relatively small number of participants. These study limitations make it uncertain whether the results are robust and can be generalized to patients who live in other areas in China. Moreover, we examined patients with PD who opted for undergoing DBS surgery during the COVID-19 outbreak. This poses another threat to the external validity because these patients who sought and received DBS surgery during the outbreak may have had sufficient financial capacity to control their circumstances and risk of infection. If true, the results cannot be generalized automatically to patients who do not have such financial capacity. Yet, despite its limitations, the present study shows that it is feasible to maintain the delivery of routine pre- and postoperative clinical care to patients with advanced PD who underwent DBS surgery during the COVID-19 pandemic.

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/s.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

BS, CZ, and ES: study concept and design. XQ, YZ, and ES: questionnaire development. JZ, YZ, and ZL: collection, analysis, and interpretation of data. JZ, XQ, YZ, and CZ: drafting of the manuscript. BS, CZ, ZL, PH, YP, ES, and DL: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Proceedings of the Eighth Annual Deep Brain Stimulation Think Tank: Advances in Optogenetics, Ethical Issues Affecting DBS Research, Neuromodulatory Approaches for Depression, Adaptive Neurostimulation, and Emerging DBS Technologies

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We estimate that 208,000 deep brain stimulation (DBS) devices have been implanted to address neurological and neuropsychiatric disorders worldwide. DBS Think Tank presenters pooled data and determined that DBS expanded in its scope and has been applied to multiple brain disorders in an effort to modulate neural circuitry. The DBS Think Tank was founded in 2012 providing a space where clinicians, engineers, researchers from industry and academia discuss current and emerging DBS technologies and logistical and ethical issues facing the field. The emphasis is on cutting edge research and collaboration aimed to advance the DBS field. The Eighth Annual DBS Think Tank was held virtually on September 1 and 2, 2020 (Zoom Video Communications) due to restrictions related to the COVID-19 pandemic. The meeting focused on advances in: (1) optogenetics as a tool for comprehending neurobiology of diseases and on optogenetically-inspired DBS, (2) cutting edge of emerging DBS technologies, (3) ethical issues affecting DBS research and access to care, (4) neuromodulatory approaches for depression, (5) advancing novel hardware, software and imaging methodologies, (6) use of neurophysiological signals in adaptive neurostimulation, and (7) use of more advanced technologies to improve DBS clinical outcomes. There were 178 attendees who participated in a DBS Think Tank survey, which revealed the expansion of DBS into several indications such as obesity, post-traumatic stress disorder, addiction and Alzheimer's disease. This proceedings summarizes the advances discussed at the Eighth Annual DBS Think Tank.

Keywords: DBS (deep brain stimulation), neuroethics, optogenetics, novel hardware, adaptive DBS, neuroimaging

INTRODUCTION

The Eighth Annual deep brain stimulation (DBS) Think Tank meeting was held virtually on September 1 and 2, 2020 (Zoom Video Communications) due to restrictions related to the COVID-19 pandemic. The DBS Think Tank presenters pooled data and determined that DBS has expanded in its scope and has been applied to multiple brain disorders. There have now been an estimated 208,000 DBS devices implanted for neurological and neuropsychiatric disorders worldwide. The DBS Think Tank was founded in 2012 and provides a space where clinicians, engineers, clinical-researchers, basic researchers and scientists from both industry and academia engage in discussions on current and emerging DBS technologies as well as tackle logistical and ethical issues facing the field. The DBS Think Tank has an emphasis on cutting edge research and collaboration which is aimed to more rapidly advance the DBS field.

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

(1) optogenetics as a tool for comprehending the neurobiology of diseases and on optogenetically inspired DBS,
(2) the cutting edge of emerging DBS technologies,
(3) ethical issues affecting DBS research and access to care,
(4) neuromodulatory approaches for depression,
(5) advancing novel hardware, software and imaging methodologies,
(6) the use of neurophysiological signals in adaptive neurostimulation,
(7) the use of more advanced technologies to improve DBS clinical outcomes,
(8) the use of novel techniques such as INTRSECT (intronic recombinase sites enabling combinatorial targeting),
(9) an updated survey of 178 attendees which is performed each year to track trends in the field.

These proceedings will summarize the Eighth Annual DBS Think Tank meeting.

OPTOGENTICALLY-INSPIRED DBS

Optogenetics has advanced our comprehension of the pathophysiology and neurobiology of disease, and continues to bring promise to our fundamental comprehension of the role of specific cell types, and even single cells, in the brain. Channelrhodopsins are naturally occurring light-gated ion channels in algae, which have become important in neuroscience research for targeted control of specific circuit elements with optogenetic techniques. Here we discuss how optogenetics as a research tool can be used to uncover underlying circuitry and to motivate new approaches for applying DBS into the human population.

Inner Workings of Channelrhodopsins

It was Francis Crick who first suggested the rather far-fetched idea that light could be a useful tool for the investigation of neural function and that it could be used in a targeted manner. Since then, converging advances in genetics, optics and engineering have collectively shown substantial promise for the investigation of neurological diseases. Current neuromodulation methods (achieved via DBS) tend to stimulate all neurons in a certain volume of tissue, which may include cells not involved in disease and thus likely result in undesirable side-effects. Hence, controlling the activity of specific neurons has significant potential to advance the field of neuromodulation. Cell specific excitation (or inhibition) of neurons can be achieved using light via microbial opsins, which encode all-in-one proteins including ion channels called channelrhodopsins that transduce photons into electrical current (Nagel et al., 2002; Deisseroth and Hegemann, 2017), enabling the first temporally precise control of genetically targeted cells in behaving mammals (Adamantidis et al., 2007). One of the early studies showing the generality of this methodology in an exploration of the role of bed nucleus of the stria terminalis (BNST) circuit elements in modulating anxiety, involved integrating behavior, electrophysiology, respiratory physiology, and optogenetics. It was discovered that three BNST efferent projections—to the lateral hypothalamus, parabrachial nucleus, and ventral tegmental area—each corresponded to a unique aspect of anxiolysis: that is, reduced risk-avoidance, reduced respiratory rate, and positive valence of the state, respectively (Kim et al., 2013). Subsequent studies revealed that optogenetics recruits naturalistic patterns of downstream neuronal population activity (Allen et al., 2019; Jennings et al., 2019). One of these studies (Allen et al., 2019) utilized optogenetics to recruit neurons that were normally activated upon deprivation of water, by providing input to the median preoptic nucleus of the hypothalamus (MnPO), while simultaneously recording from thousands of neurons across the brain using electrophysiology; all during behavior. It was found that targeted optogenetics recruits a naturalistic brain-wide pattern of activity like that elicited by natural thirst and water-seeking behavior (Allen et al., 2019).

Recruitment of opsins to modulate neuronal circuitry at the single cell level in living mammals was initially achieved via two photon activation of neurons (Prakash et al., 2012). This ultimately enabled the first specified-single-cell control of mammalian behavior, via interrogation of orbitofrontal (OFC) neurons during distinct and different behaviors: feeding responses and social interaction (Jennings et al., 2019). Feeding responsive OFC neurons were selected for optogenetic control; it was found that specific modulation of these cells was able to enhance feeding behavior. In order to determine if these behavioral effects associated with stimulation were specific to the feeding cells, OFC cells not involved in feeding behavior (social behavior-responsive cells) were stimulated, and found to instead result in inhibition of feeding. These experiments inform on the role of well-defined OFC networks involved in feeding and social behaviors and demonstrate that mammalian behavior can be specifically controlled via modulation of individual cells within a network, and that optogenetic identification of subnetworks results in elucidation of the dynamics involved in primary motivational drives. The discovery of ChRmine, a fast and highly sensitive red-shifted opsin, has recently facilitated precise control over large ensembles of individually specified single cells in behavior (Marshel et al., 2019), and is suitable for deep transcranial optogenetic modulation of behavior in mouse, as was seen in a later paper addressing multiple specific behaviors including appetitive conditioning (Chen R. et al., 2020). This methodology makes it possible for the exploration of therapeutic interventions wherein the source of light can be distinctly separated from the target cell population. Thus, specific adaptive behavior can be elicited via deep transcranial ChRmine photoactivation, which precludes the need for intracranial surgery. In parallel with the revolution arising from optogenetic approaches, the recent explosion of single-cell transcriptomic data has made clear that cell types can be usefully targeted by more than one genetic feature. INTRSECT (intronic recombinase sites enabling combinatorial targeting) addresses this opportunity by allowing the expression of adeno associated virus (AAV) based payloads by combining synthetic introns, and two recombinases (Cre and Flp) defining cellular populations specified by two features. INTRSECT has been used to identify functional roles for projection patterns of diverse neuronal subtypes (Chuhma et al., 2018; Poulin et al., 2018; Fenno et al., 2020) in physiology and behavior. Further development of this approach has resulted in a triple recombinase dependent gene targeting approach (Triplesect) (Fenno et al., 2020); this technology can achieve superior viral targeting specificity and will likely result in the ability to study the role of cell types that are triply defined genetically and/or anatomically.

ADVANCES IN COMMERCIALLY AVAILABLE NEUROMODULATION TECHNOLOGIES

Over the past years, chronically sensed brain signals have been established as an important new opportunity for advancing the standard of care (SOC) in DBS therapies. Historically,

access to such signals has been available on a limited basis via investigational devices specialized for such recordings, which have collectively allowed constrained exploration of such signals in research contexts. However, these signals were the impetus of significant scientific and technological discoveries in the DBS space. In the research literature, it has been shown that such signals are robust and chronically present over months to years (Abosch et al., 2012; Giannicola et al., 2012; Trager et al., 2016; Neumann et al., 2017), that they often correlate with patient symptoms and additionally can be used with the delivery of therapy (both stimulation and medications) (Kuhn et al., 2006; Quinn et al., 2015; Trager et al., 2016; Neumann et al., 2017), and finally that it is feasible and there may be benefits to applying closed-loop methodologies using these correlations to adapt therapy over time and thereby adjust for fluctuations in symptoms (Velisar et al., 2019; Petrucci et al., 2020). With the first availability of commercial devices (Percept PC^{TM}) to implement chronically sensed brain signals, these opportunities for clinical value have become available more broadly. Very early evidence (Koeglsperger et al., 2020) suggests that the findings of the research community can be replicated in these commercial devices, demonstrating the feasibility of using in-clinic signals during the programming process and at-home signals to understand the real-world characteristics of signals outside the clinic. The next opportunity to be explored is chronic closed-loop or adaptive therapies in naturalistic settings. Medtronic's Percept PC^{TM} is enabled for these types of control algorithms through a software unlock, and these capabilities will be explored via industry-sponsored studies in Parkinson's disease (PD; e.g., ADAPT PD – NCT04547712) beginning early in 2021. The Percept PC^{TM} platform has also been architected to unlock other advanced capabilities with appropriate regulatory approvals for research, including novel stimulation waveforms, network connectivity, and directional sensing with DBS leads bearing segmented electrodes. Research-enabled commercial device platforms such as the Percept PC^{TM} are poised to enable more rapid research translation through faster access to technological innovations and also offer fewer tradeoffs to clinical researchers and to research subjects.

Advancement of DBS device technology has made it possible to have multiple combinations of DBS programming settings in an effort to deliver better outcomes. Device programming on the other hand has only become more complicated. The development of a computer-guided closed-loop based programming algorithm could potentially make DBS programming easier for clinicians. In this context, Boston Scientific Neuromodulation (BSN) is working to improve tools to aid the clinical DBS workflow. These tools broadly include computer-aided programming (using objective outcome measurements), as well as stimulation field modeling with specificity to patient anatomy, which has been pursued through Boston Scientific's CLOVER Study. CLOVER (NCT03037398) is a multi-center study which uses direct and objective symptom measures, such as from PD-validated, commercial finger-worn accelerometers, and integrates these measurements with a BSN-developed search and optimization algorithm. After three starting measurements, this algorithm iteratively suggests the next settings to test, until an optimum setting is found. Such an algorithm could assist both in-clinic and in remote programmers. BSN has recently updated the CLOVER algorithm to support programming of their directional leads. The preliminary results indicate that the new algorithm is able to converge in a single visit on stimulation settings that result in UPDRS motor score reductions (as compared to the baseline scores) that are statistically equivalent to multi-visit SOC programming (as defined by the clinician in the study) (Sasaki et al., 2021).

Programming may also be aided using patient imaging data paired with three-dimensional stimulation models in the Guide XT software, developed in collaboration with BrainLab. When available, the combination of surgical, imaging, and stimulation response (such as aggregated therapy sweet spots) with real-time clinical response may further assist DBS programmers. BSN is working toward tools to enable large scale, group studies to further investigate the relationships between stimulation locations and clinical outcomes, including using population statistics in order to build probabilistic maps of stimulation. The results of these population-based analyses could be used to inform programming software. More research is needed to further explore the predictive value of these maps and their potential use in routine clinical DBS programming practices.

Real-world analyses of claims data have previously shown a higher rate of DBS revision/removal procedures than typically recognized (Rolston et al., 2016). The impact of modern systems, with significant advancements in design and manufacturing, has not been previously studied. Abbott labs presented a study evaluating the impact of a modern DBS system on revision and replacement rates. Medicare fee for service claims were used to identify patients undergoing DBS implantation for PD or Essential Tremor between January 1, 2016–December 31, 2018. Claims records were linked to manufacturer device registration data to identify which patients had been implanted with Abbott Infinity, at the time the only commercially available system in the United States with directional stimulation capability; linked patients were assigned to the Treatment (Directional System) group. A total of 3,271 patients in Omnidirectional and 596 patients in Directional System group met the inclusion/exclusion criterion. Revision or replacement rates in patients implanted with the Infinity directional DBS system were significantly reduced compared to those with traditional omni-directional DBS systems. Further analysis and future studies may elucidate the mechanism of reduced risk. Another study evaluated an investigational software extension that enabled remote programming of previously implanted DBS devices. The paucity of trained neurologists and urban concentration of specialty care centers has contributed to care access burden for patients with DBS and their caregivers, particularly in the context of the COVID-19 pandemic. Remote monitoring[1] and remote support technologies[2] have been established in other Class 3 active implantable technologies. Remote programming of DBS

[1]https://www.cardiovascular.abbott/us/en/patients/living-with-your-device/arrhythmias/remote-monitoring.html

[2]https://www.bostonscientific.com/content/gwc/en-US/products/remote-patient-monitoring/heart-connect-system.html

systems has been enabled by China-based manufacturers but is not yet available in countries requiring CE or FDA approvals (Zhang et al., 2018). Abbott investigated an investigational remote programming feature to enable programmers to directly adjust DBS therapy settings in real-time via a secure video-based mobile platform in patients implanted with an Infinity™ DBS system[3]. The primary endpoint of this study was to determine remote programming safety by evaluating adverse events (AEs) reported by subjects within three weeks of a programming session which was conducted using the remote programming feature. Ten subjects connected with their treating clinician through the secure remote programming feature. No serious AEs were reported in this study and anticipated, non-serious AEs that were reported for 1 subject resolved without sequalae. Evaluation of such remote programming features will likely advance the field towards low-burden therapy options for patients and clinicians in the rapidly emerging digital health realm.

ON TARGET, AND (YET) OFF-LABEL USES OF DBS: ETHICAL CONCERNS, CAVEATS, AND CONSIDERATIONS

With the increased investigation and subsequent use of novel DBS therapies, there has been a simultaneous growth in ethical issues and considerations. One important issue that has been emerging is continued device access after the conclusion of a research study, which is generally considered to be ethically appropriate and desirable. Ascertaining whether researchers and industry sponsors are ethically obligated to facilitate continued access to those participants whose benefit requires a dialogue and engagement of all the relevant stakeholders. Additionally, the potential of DBS technologies for off-label use and the ethics surrounding this, specifically in vulnerable patient populations, must also be developed and subsequently reviewed.

DBS for Less Prevalent Diseases, Continued Access After Trials and the NIH BRAIN Initiative Ethics Updates

The use of various forms of neurotechnologies and techniques to define and model loci for possible interventional neuromodulation is opening new vistas of "on target," and (yet still) off-label uses of DBS (Ramirez-Zamora et al., 2017, 2019) see, for example, this report. As we have noted, such new horizons of possibility must be approached with ethical probity (Giordano, 2015). The novelty of utilizing DBS in such ways mandates explication of current uncertainties about the durability of clinical benefit, future side effects, and sustainability of intervention as contingencies for informed patient consent (Giordano, 2016).

That DBS affords effective clinical benefit can be seen as only an initial component (and hurdle) of successful care. Indeed, there have been—and remain—ethical and policy challenges regarding post-trial management of brain implant devices (Lazaro-Munoz et al., 2018; Sierra-Mercado et al., 2019). Brain implant trials generally do not have provisions to ensure that patients/subjects who gain clinical benefit from the use of DBS will have access to maintenance of the device after completion of the trials.

Patients who participate in these trials have severe and treatment-resistant neuropsychiatric conditions. Axiomatically, patients with "treatment-resistant" disorders who benefit from an experimental DBS intervention during a trial have no other effective treatment alternatives; and guaranteed provision of services and resources to assure maintenance of DBS devices upon completion of such trials is lacking. To be sure, such continued maintenance may incur significant costs. While sustainability of these devices for extant (CPT-code listed) indications *may* be covered by health insurance providers, such coverage is not obligated (and therefore is routinely not provided) for those indications that are experimental (Rossi et al., 2017). The significant burdens (i.e., surgery, multiple clinical visits) incurred by participants in these trials heighten their dependence upon the study teams for access to the only intervention that has afforded them successful clinical outcomes. Thus, we posit that these patients' vulnerability is increased, and in this light, strongly advocate development of a system to ensure (and *insure*) post-trial continuity of clinical care for those patients/subjects for whom therapeutic benefits are achieved. Public and private research sponsors, device manufacturers, researchers—and the institutions in which this research occurs—can, and we believe should, play active roles in facilitating both the discourse as well as the resources required to assure these patients' continued access to successful clinical care.

Of additional interest, particularly for experimental (i.e., off-label) uses of DBS are potential side effects that can occur in either the short, intermediate, or long-term. Provocative questions have arisen whether closed-loop neuromodulation could induce changes to a patients' sense of identity and agency. Ongoing discussions in the literature have been equivocal, noting a paucity of data and arguing that such concerns may be overdrawn (Giordano, 2016). To address the need for empirical investigations, we at UCSF examined constructs and the subjective experience of identity in patients with refractory epilepsy undergoing responsive neurostimulation (RNS)—the first FDA-approved, commercially available closed-loop brain stimulation system. Pre- and post-implantation observations of 12 patients were conducted, in addition to in-depth interviews with both these patients and their respective caregivers. These interviews revealed that patients and caregivers did not attribute any perceived changes in patients' identity or agency to the device's operation, thereby refuting concerns that have been raised in the (conceptual) neuroethics literature. When such changes were noted, they were readily and characteristically described by patients and caregivers as attributable to their disorder, or as side effects of medications. Importantly, these reports indicated that the qualitative techniques used were able to elicit such concerns if and when present.

An unexpected finding was that the ability to view the neural recordings collected by the device was regarded as highly

[3]https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619001660178

meaningful and personally significant to patients and caregivers; in some cases, independent of the device's stimulation algorithm and/or effect(s). Notably, patients reported that neural recordings enabled visual demonstration of the disease process in ways that affected their understanding of the disorder, and themselves. These are the first such empirically obtained findings from clinical populations undergoing closed-loop neuromodulation, which we believe illustrate—and support—how empirical studies can and should inform the conceptual neuroethics literature.

DEPRESSION DBS: WHERE CAN WE GO? LESS VS MORE FOR DBS DEPRESSION

Major depressive disorder (MDD) is a prevalent disease, and one of the leading causes of disability worldwide (Giacobbe et al., 2009). A failure to identify and treat depression can have profound negative public health impacts such as hospitalizations, inter-personal issues, lack of productivity, and suicide. After early randomized controlled trials failed to show improvement, it is now becoming increasingly evident that DBS can be useful for treatment resistant depression, and several studies are showing promise (Holtzheimer et al., 2017; Hitti et al., 2020; van der Wal et al., 2020) Bergfeld, 2020). Stimulation of the subgenual cingulate has been shown to produce clinical benefits in patients with treatment resistant depression (Mayberg et al., 2005). Increased clinical benefits in these trials has stemmed from improvements in neuroimaging, personalized targeting, neurophysiology and stimulation delivery. Neuroimaging has aided in personalized lead targeting by defining critical white matter tracts that may be crucial in the pathology of depression. Furthermore, sites (discussed herein) have been using a network-based approach adopted from epilepsy which entails the temporary implantation of stereo-EEG electrodes either to study the network involved in depression, to choose optimal stimulation settings, or to demonstrate biomarkers that can be used in a closed-loop paradigm. As these neurophysiologic data are collected in both the temporary and long-term settings using devices such as the Summit RC + S, the heterogeneity in response to DBS may be elucidated and more refined symptom-specific biomarkers may be discovered. These advances will ultimately produce optimized DBS paradigms which are specific to each patient's symptoms. Here we describe advances made in the field of DBS for depression across three different centers.

Baylor Preliminary Experience Depression DBS Trial

Deep brain stimulation for severe, treatment-resistant depression (TRD) is an investigational therapy. Previous studies have shown heterogeneous results, with early open-label studies demonstrating promise (Holtzheimer et al., 2012); however, industry-sponsored, blinded randomized trials were stopped at interim analyses points without demonstrating a difference between active and sham stimulation (Holtzheimer et al., 2012). We propose that an important limitation in applying DBS for this indication has been an incomplete understanding of the network of brain regions responsible for the multifactorial dysfunction underlying depression. To address this limitation, we applied an approach borrowed from another challenging and highly individualized disorder: epilepsy. As is done commonly in epilepsy, our study involves intracranial recordings using temporarily placed stereo-EEG (sEEG) electrodes in brain regions hypothesized to be within the TRD networks. We simultaneously place permanent DBS leads in two bilateral regions: the ventral capsule/ventral striatum (VCVS) and sub-callosal cingulate (SCC) regions (**Figure 1**). The patient is kept in the hospital "neurophysiological monitoring unit" (NMU) for 10 days and undergoes a number of recording and stimulation activities to understand brain network neurophysiology across a variety of states (resting/baseline, emotional valence states, cognitive effort states) and in response to stimulation across a variety of stimulation parameters (frequency, pulse width, amplitude, direction). One of the many goals of this intracranial recording phase is to narrow the vast parameter space to a few parameter sets that can be implemented in the chronic outpatient phase of the trial.

We report the results from the first patient in this trial (NCT03437928), which is funded by the NIH BRAIN Initiative (UH3 NS103549; PIs Sheth, Pouratian, Goodman). This trial was approved by the FDA (IDE G180300) and IRB. We gathered a plethora of data during the intracranial phase that helped to create a model of the relationship between imaging, neurophysiology, and behavioral/symptomatic response. We used this information to create three parameter sets, which we tested in the outpatient phase. Implementing these individualized parameter sets across the four DBS leads led to a steady reduction in symptom scores, such that the subject achieved symptom remission by 22 weeks.

We propose that "sEEG-guided DBS" is a useful platform for developing a network understanding of disorders and that this approach will provide sufficient information to optimize neuromodulatory therapies such as DBS. Future challenges include balancing the competing drives of optimizing previously studied DBS targets versus exploring new targets, properly interpreting acute results for chronic use, and translating this paradigm so that in the future, inpatient intracranial recordings will not be needed.

UCSF Preliminary Experience From an Ongoing Depression Trial

MDD is a common and highly disabling disorder worldwide. While the majority of patients respond well to medication and psychotherapy, a substantial number of patients remain refractory to all available treatments. DBS is a highly promising therapy for this subset of patients with treatment resistant disease. However, results from randomized controlled studies of DBS for depression have not been consistent, suggesting that novel strategies in DBS treatment are needed. Three approaches toward DBS optimization in depression are currently underway by groups at Mt. Sinai, Baylor and UCSF. They include enhanced target engagement through tractography

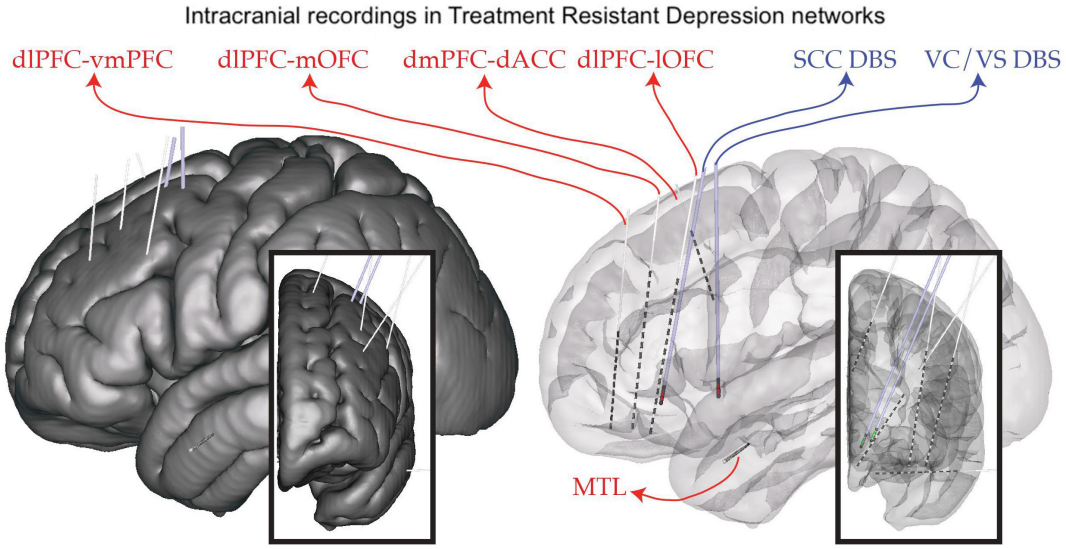

FIGURE 1 | Implant plan. StereoEEG electrodes (red) are placed in a variety of brain regions thought to be part of the depression network (dorsolateral prefrontal cortex, dlPFC; ventrolateral PFC, vlPFC; dorsomedial PFC, dmPFC; medial and lateral orbitofrontal cortex, mOFC, lOFC; dorsal anterior cingulate cortex, dACC; medial temporal lobe, MTL). DBS leads (blue) are placed in the subcallosal cingulate (SCC) and ventral capsule/ventral striatum (VC/VS). Placement is individualized using tractography derived from diffusion MRI.

and biomarker development, DBS parameter optimization through individualized network targeting, and development of a personalized closed-loop paradigm.

At UCSF, we are conducting a 3-stage feasibility study of personalized closed-loop stimulation for treatment resistant MDD. Surgical implantation of 10 intracranial EEG electrodes allows for personalized stimulation site selection and biomarker discovery over 10 days of intensive in-patient monitoring. Intracranial-EEG electrodes are then removed and a chronic DBS device (NeuroPace RNS® System) is implanted in sensing and stimulation targets identified in the discovery stage. An open label period follows where a biomarker-based detection algorithm is developed and integrated into closed-loop therapy and then tested through a randomized controlled study. In this talk, we discuss the rationale behind a closed-loop DBS approach. We discuss the conceptualization of depression in a closed-loop model, implications for patient selection, and a strategy for personalized clinical mapping that integrates clinical responses with functional and structural connectivity mapping. We highlight differences of our approach in comparison to the approaches at Mt. Sinai and Baylor and suggest strategies for integration of the three complementary efforts (**Figure 2**).

Optimizing SCC DBS for TRD Using Chronic Sensing: Less Versus More

It has been 15 years since the first proof-of-principle report of DBS for treatment resistant depression, targeting the subcallosal cingulate (SCC) region (Mayberg et al., 2005). Initial studies were catalyzed by critical clinical need, informed by converging findings from imaging studies of depression pathophysiology and antidepressant treatment, and operationalized using established imaging standards for movement disorder surgery including trial-and-error behavior testing during chronic stimulation at individual contacts on each implanted DBS lead (Kennedy et al., 2011; Holtzheimer et al., 2012). As SCC DBS has evolved and matured, neuroimaging continues to play a crucial role, with implementation of refined multimodal techniques for surgical targeting and long-term studies of treatment mechanisms (Crowell et al., 2019). Most critically, increased precision has been achieved with implementation of an individualized tractography-guided, template-matching lead implantation procedure (**Figure 3**), now successfully deployed in two successive cohorts, with a resulting 6- month response rate of 80% (8 of 11 patients) (Riva-Posse et al., 2018) and 90% (9 of 10 patients) (unpublished), respectively.

This standardized method for reproducible lead implantation and contact selection for chronic stimulation has been further verified by robust and reproducible intraoperative behavioral effects associated with unilateral and bilateral therapeutic stimulation at the predefined targets (Smart et al., 2018; Riva-Posse et al., 2020). With this critical variable of reliable targeting now achieved, current experiments have been focused on outpatient strategies to characterize the unexplained differences in the speed and trajectory of antidepressant effects facilitated by chronic DBS. Such studies have been enabled by device innovations, specifically the Activa PC + S and Summit RC + S systems (Medtronic), that have facilitated ongoing interrogation of DBS mechanisms at the neural level (Veerakumar et al., 2019). To further refine and optimize DBS treatment, neural biomarkers that reliably track the depression state over time and that can discriminate depression relapse from transient fluctuations in negative mood and from arousal are needed. Ideally, these new brain tracking metrics would be derived using

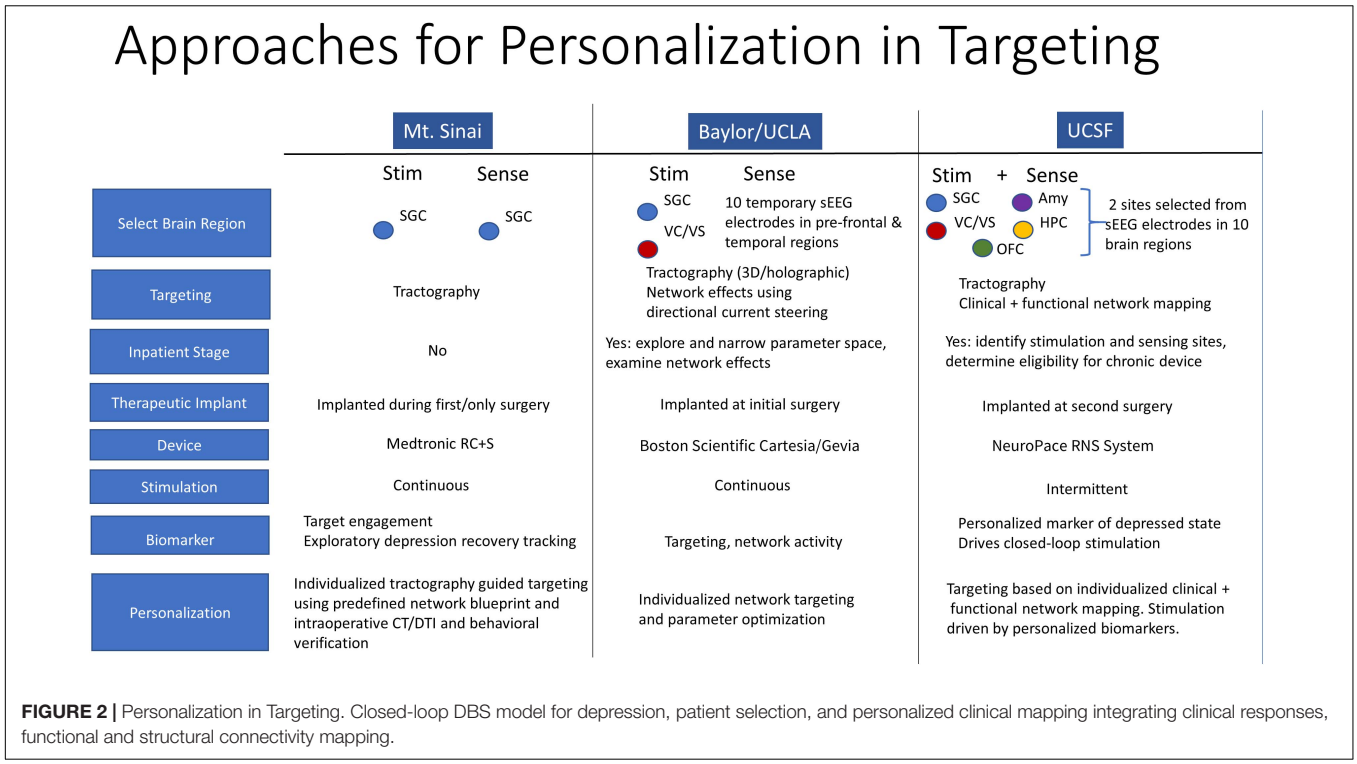

FIGURE 2 | Personalization in Targeting. Closed-loop DBS model for depression, patient selection, and personalized clinical mapping integrating clinical responses, functional and structural connectivity mapping.

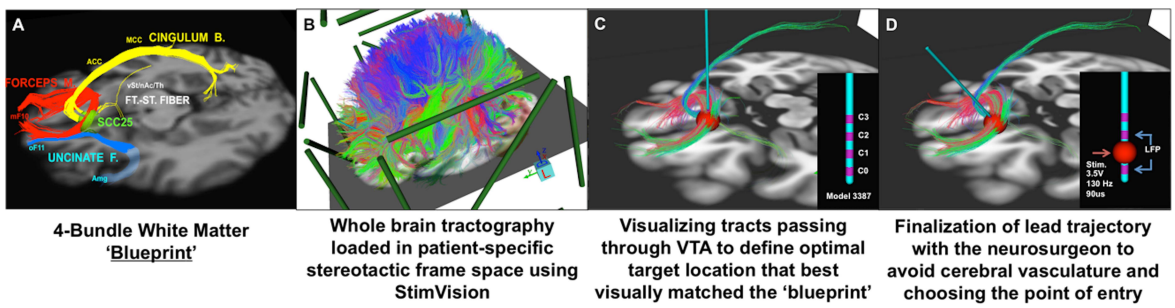

FIGURE 3 | Individualized tractography-guided, template-matching lead implantation procedure for SCC DBS for TRD. **(A)** 4-bundle tractography target template (Riva-Posse et al., 2014). **(B)** Overlap of whole-brain deterministic tractography in patient-specific stereotactic frame space using the "StimVision" toolbox (Noecker et al., 2018). **(C)** Initial placement of electrode within SCC and visualization of WM pathways passing through the VTA. **(D)** Personalized optimal electrode location with the arc and ring angle determination by a neurosurgeon. Estimated VTA with standard stimulation settings (i.e., 3.5V, 130Hz, 90ms) is visualized with local field potential recording from adjacent contacts (sandwiching recording to minimize stimulation artifact). Composite images courtesy of Ki Sueng Choi, Icahn School of Medicine at Mount Sinai.

novel quantitative behavioral assessments that are not totally dependent on patient self-report. While standardized depression rating scales are generally effective in establishing the clinical efficacy of DBS, they may be inadequate to develop neural control policies in order to monitor and to optimize DBS delivery.

To this point, preliminary studies have demonstrated that following 2 months of therapeutic SCC DBS, machine learning models of facial expression and vocal inflection drawn from unstructured patient interviews can reliably predict 6-month outcomes, outperforming classical depression severity rating scales (Harati et al., 2020). However, these methods have not yet fully exploited the richness of the available recorded brain derived datasets. Quantitative analyses of facial, voice, and body dynamics combined with concurrent home and lab recordings of SCC LFPs and self-paced video diaries have been undertaken (in progress) to test this hypothesis, with the goal to further streamline and to optimize SCC DBS for TRD.

NEW HARDWARE/SOFTWARE/IMAGING

Advances in MRI technology has made it feasible to visualize brain networks in a manner previously thought to be impossible. The Human Connectome Project has enabled the generation of publicly available normative connectomes, which has proven invaluable for neuromodulation research (Yeo et al., 2011;

Van Essen et al., 2012; Holmes et al., 2015). Neuroimaging improvements have enabled the identification of pathological circuits responsible for symptom manifestations, thus potentially leading to advances like personalized, connectivity-driven lead targeting. Furthermore, neuroimaging can help aid in the accurate mapping of the patient-specific stimulated area, lending to the understanding of either the improvement/worsening of symptoms or potential off-target side effects. Herein, we discuss recent advances in the use of imaging technology for improving DBS precision and outcomes.

Toward Precision Imaging and Connectomic Surgery

Shortly after publishing their seminal paper about a stereotaxic apparatus for human brain surgery in 1947 (Spiegel et al., 1947). Ernest Spiegel and Henry Wycis published the concept of *ansotomy* for treatment of Parkinsonian tremor (Spiegel and Wycis, 1954) with the aim to cut pallidofugal efferent fibers within the *ansa lenticularis* (Meyers, 1951). Hence, the concept of retuning brain function by modulating brain connectivity is actually a previously explored notion. What is new is our ability to integrate electrode localizations with connectome data non-invasively acquired using advanced MRI technology. Pioneered by multiple groups worldwide (Coenen et al., 2009, 2011; Anderson et al., 2011), this concept has become increasingly powerful in order to understand how the effects of DBS may impact the brain. When mapping DBS electrodes with neuroimaging, it is crucial to attain the highest degree of accuracy possible; since millimeters matter. Specialized neuroimaging pipelines that have this goal in mind include multispectral registration algorithms (Ewert et al., 2019), correction for bias introduced by brain shift (Horn et al., 2019), phantom-validated electrode reconstructions, and correction for detection of directionality in the specific case of segmented leads (Dembek et al., 2019). These tools allow us to precisely register DBS stimulation sites to other datasets, such as histological atlases (Ewert et al., 2018; Ilinsky et al., 2018), postmortem imaging (Edlow et al., 2019), or to normative connectome data aggregated from thousands of subjects (Horn et al., 2017a; Horn and Fox, 2020). In cases where patient-specific connectivity data is unavailable, normative connectome data can be an effective surrogate (Baldermann et al., 2019; Wang et al., 2020) and can potentially add the advantage of higher precision and increased signal-to-noise ratios when including data from the postmortem specimen (Calabrese et al., 2015), histology (Alho et al., 2020), or with integrated anatomical expert knowledge (Petersen et al., 2019; Middlebrooks et al., 2020; **Figure 4**).

A first report that applied this concept calculated a model of optimal connectivity in a cohort of PD patients and used these data to predict clinical improvement in a second cohort from a different center (Horn et al., 2017b). Since this publication, the concept has been applied to essential tremor, dystonia, and epilepsy (Middlebrooks et al., 2018; Al-Fatly et al., 2019; Okromelidze et al., 2020) and has been applied to predict side-effects. Using a related technique termed *tract-filtering*, specific bundles associated with optimal clinical improvement can be identified. This technique was first used in an obsessive compulsive disorder (OCD) cohort (Li et al., 2020).

In the future, a similar methodology could be used to define symptom-specific circuitopathies that may ultimately facilitate personalization of DBS targets to a somatotopic domain and to a symptom-spectrum of individual patients. Furthermore, advanced imaging technology will likely continue to enter the operation room in an effort to integrate surgical targets with a variety of neuroimaging data.

Utilizing Multi-Country Imaging and Clinical Outcomes for Neuromodulation

Tourette syndrome (TS) is a complex neuropsychiatric disorder characterized by tics and often associated with psychiatric comorbidities, such as obsessive-compulsive behavior (OCB). DBS is an effective therapy for select patients with severe, treatment-refractory TS. However, patient responses to DBS are variable and there are currently no reliable predictors of symptom improvement. One contributing factor to the variability in clinical outcomes is the uncertainty into how to optimally target stimulation to improve tics or OCB. Progress toward identifying predictors of symptom improvement and effective neuroanatomical structures for stimulation has been limited by the relative paucity of TS cases implanted at individual centers. The International TS DBS Registry and Database (Deeb et al., 2016) was established to overcome this limitation by aggregating data from multiple international centers, including clinical data, stimulation settings, clinical rating scale scores, and pre- and postoperative imaging.

Using multicenter data from the registry, recent studies have aimed to identify the neuroanatomical structures associated with improvement in tics and comorbid OCB in patients who have undergone DBS for TS. Image-based computational models were constructed based on patient-specific lead locations and on individual stimulation settings to visualize the active contact locations across patients and to identify the structural networks and local fiber pathways modulated by DBS (**Figure 5**). The results highlighted the variability in applied stimulation across patients (Johnson et al., 2019). Structural connectivity of the site of stimulation and activation of specific local fiber pathways were predictive of improvement in tics and comorbid OCB (Johnson et al., 2020). The results could possibly be used to refine stimulation targets and to develop network-based approaches for DBS for TS in order to improve patient outcomes. Collectively, these analyses demonstrate the value of combining data across clinical centers in an effort to investigate DBS for less common indications.

Predicting DBS Outcomes

Deep brain stimulation is an effective treatment for PD, but its efficacy depends heavily on selection of optimal stimulation parameters for each individual patient. DBS programming is frequently time consuming and burdensome for patients, caregivers, and clinicians. We recently conducted a multi-center study (NCT02474459) to test if the integration of the Mobile Application for PD DBS (MAP DBS), a clinical decision support

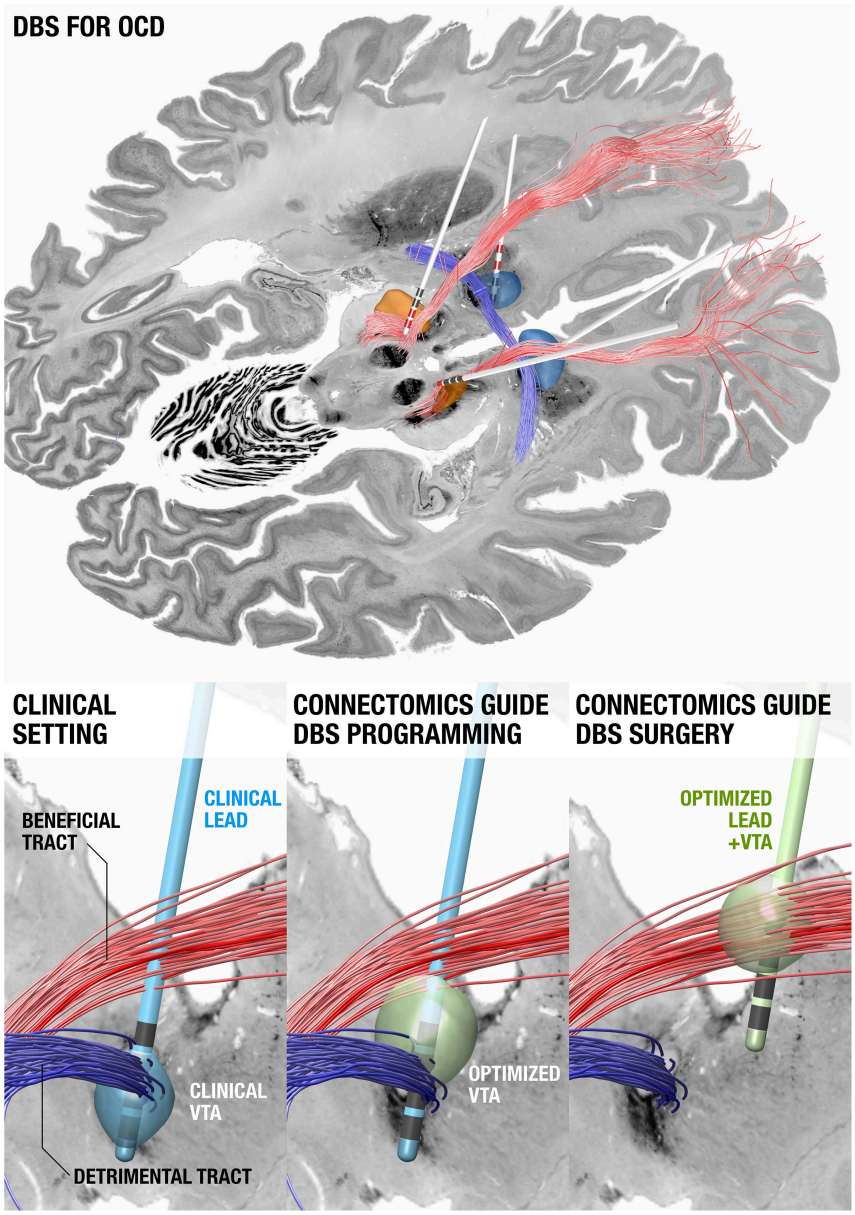

FIGURE 4 | Using connectomics to guide surgery and DBS programming. **(Top)** DBS tract filtering. Four DBS electrodes implanted to the anteromedial subthalamic nucleus and anterior limb of the internal capsule in a patient with obsessive compulsive disorder. Active contacts are marked in red. A tract associated with optimal clinical improvement across 50 patients (limbic hyperdirect pathway within the anterior limb of the internal capsule) is shown in red, one associated with poor improvement (posterior limb of the anterior commissure) in blue. **(Bottom left)** Clinical DBS setting. **(Bottom middle)** Upon further confirmation of results, based on the existing electrode and the connectomic information, the stimulation settings could be optimized. **(Bottom right)** In novel patients, both surgical targeting and DBS programming could potentially be optimized. Data from Li et al. (2020), background slices show the BigBrain dataset (Amunts et al., 2013) after precise co-registration.

system, into the DBS programming process could transform the care model by enabling home health nurses to effectively manage patients at home. We conducted two open-label, 1:1 randomized, controlled, clinical trials. The first trial, which was conducted at six expert DBS centers across the United States, compared 6 months of SOC to 6 months of MAP DBS-aided programming. The primary outcome was the total time spent on DBS programming over all clinical visits during the study period. In the second trial, we compared 6 months of SOC to 6 months of home health postoperative DBS management. The home health postoperative management was conducted by a home health nurse who chose DBS settings with the aid of the MAP DBS system. By design, the home health nurse had no prior experience providing DBS care. The primary outcome was the number of times each patient traveled to the movement disorders clinic during the study period. In both studies, the secondary outcomes

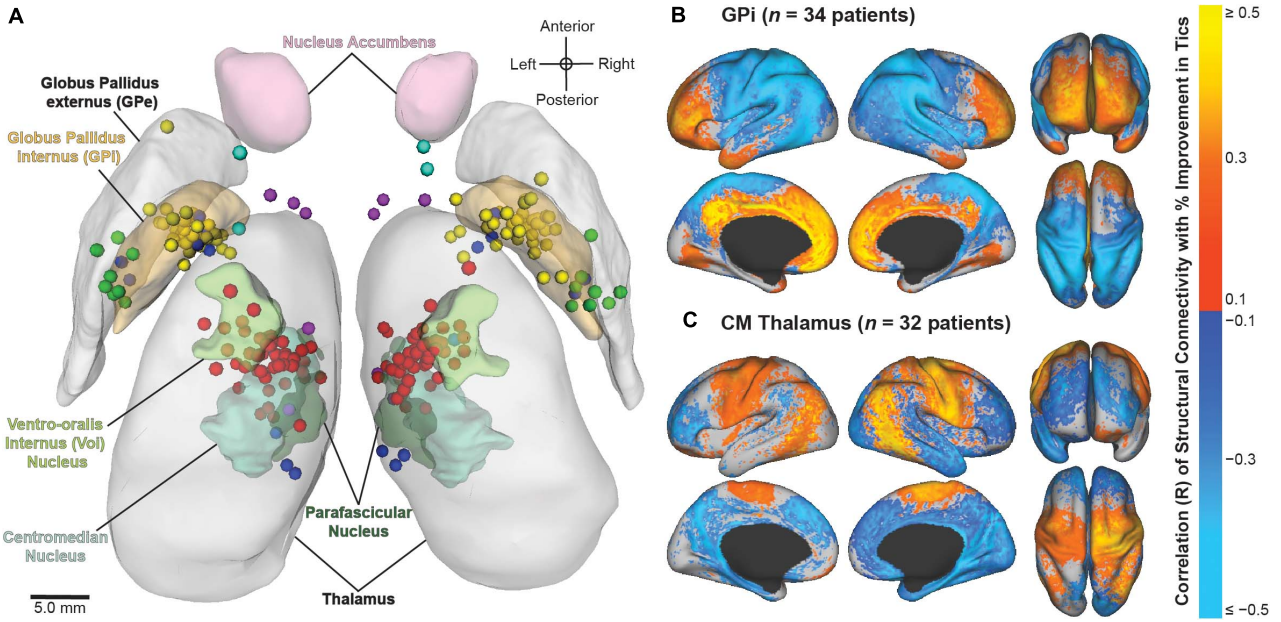

FIGURE 5 | Image-based analyses of multicenter data from the International Tourette Syndrome (TS) Deep Brain Stimulation (DBS) Registry and Database. **(A)** Active contact locations for *N* = 70 patients implanted in the centromedial (CM) thalamus (red); anteromedial globus pallidus internus (GPi) (yellow); posteroventral GPi (green); nucleus accumbens/anterior limb of internal capsule (NA/ALIC) (turquoise); CM thalamus and GPi (blue); or CM thalamus and NA/ALIC (purple). From Johnson et al. (2019). **(B,C)** Stimulation-dependent structural connectivity associated with improvement in tics in patients implanted with DBS in the **(B)** GPi or **(C)** CM thalamus. From Johnson et al. (2020).

were changes in the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor score), the total UPDRS (sum of parts I through IV), the 39-question Parkinson's disease rating scale (PDQ-39), the Multidimensional Caregiver Strain Index (MCSI), and levodopa equivalent daily doses (LEDD) between the baseline and six-month outcomes visit. We analyzed 72 (SOC = 37, MAP DBS = 35) patients in the first trial (Phase I). In the second trial (Phase II: home health nurse management) we analyzed 42 patients (SOC = 19, home health = 23). The study results are in submission but will help us to understand how tools like MAP DBS can be used to enhance the experience of non-expert home health nurses. Additionally, this data will be used to design and pilot a study of home health nurse driven telemedicine in DBS.

CHRONIC BRAIN SENSING AND ADAPTIVE DBS

Seminal papers on adaptive neuromodulation and brain sensing have been primarily demonstrated in clinic or in postoperative settings (Pina-Fuentes et al., 2017). While the next generation device (i.e., Medtronic's Summit RC + S) is being released, which includes chronic neural sensing, long-term home behavioral measurements may now be performed. These findings validate what has been reported in short perioperative settings, such as beta power alterations during DBS. Additionally, chronic sensing allows us to continually analyze pathological biomarkers, both subcortically and cortically, or brain states and how they respond to stimulation, aiding in the design of adaptive deep brain stimulation (aDBS) paradigms. Furthermore, as aDBS expands into real-world scenarios, the importance of defining individual biomarkers and the optimal site for sensing develops along with the utility of stereoelectroencephalography (sEEG) recordings before implantation of the DBS lead placement (Sanger et al., 2018; Shirvalkar et al., 2018). aDBS demonstrates promise in treating complex dynamics in signals (such as beta bursts) (Tinkhauser et al., 2017a,b; Deffains et al., 2018) or in disease states (such as pain or epilepsy).

However, if we want to achieve optimal aDBS outcomes, not only will electrode location and biomarker sensing be key, but also, the type of control algorithm used will ultimately affect the outcome and success of any aDBS paradigm. Previous control algorithms for PD have used a pre-specified threshold on beta (Little et al., 2013; Pina-Fuentes et al., 2017; Arlotti et al., 2018) or gamma (Swann et al., 2018) power, voltage linearly following beta power (Rosa et al., 2015), or dual threshold designs also on beta power (Velisar et al., 2019; Petrucci et al., 2020). Newer designs have focused on temporal dynamics of beta (Tinkhauser et al., 2017a). How complex must aDBS algorithms be to capture the dynamics of pathological biomarkers, especially as other indications arise like chronic pain? Overall, preliminary studies with chronic brain sensing will likely lead the way to a better understanding of neural circuitry under various medication and stimulation states and lead to the development of more sophisticated methods for targeting, individual neural biomarker or symptom identification profiles, and aDBS protocols across neurological disorders.

Chronic Sensing and Closed-Loop Approaches in Parkinson's

Invasive neural recordings in humans have shown promise for understanding physiological signatures or "biomarkers" of specific motor and non-motor signs of PD. Until recently, most recordings were performed for short durations from externalized brain leads in hospital settings. The availability of bidirectional (sense and stimulate) neural interfaces has launched a new approach: chronic invasive brain sensing at home. This approach offers many advantages over brief recordings: validation in the "real world" of biomarkers identified at rest with externalized leads in defined medication states, identification of "personalized" biomarkers based on chronic recordings over many exacerbations and remissions of a specific sign or symptom within a single subject, understanding effects of chronic DBS on neural circuits, and implementation of aDBS. Here, we highlight several uses of chronic brain recordings in PD at UCSF. Using an investigational first-generation bidirectional interface, the Activa PC + S (Medtronic) in four patients, we identified prefrontal cortical beta band activity as a possible signature of anxiety and depression. More recently we have used a second-generation bidirectional interface, Summit RC + S (Medtronic). This device has the capability for high volume wireless data streaming at home over many hours, improved signal to noise ratios, and better management of stimulation artifacts as compared to its precursor device. Five PD patients streamed bilateral 4-channel motor cortex and basal ganglia field potentials at home for over 2,600 h. Recordings were paired with wearable monitors for the neural decoding of motor fluctuations at home (**Figure 6**). We validated personalized neural biomarkers during normal daily activities. We examined the effects of chronic DBS and of sleep on these biomarkers and implemented aDBS at home, using both cortical and subthalamic signals to track motor fluctuations.

Closed-Loop Modulation and Brain State Tracking for Epilepsy

Electrical brain stimulation (EBS) is an effective therapy for neurological and psychiatric diseases. Currently available systems, however, do not provide a bi-directional interface suitable for ambulatory biomarker tracking, patient reporting, or adaptive therapy. While regulatory challenges exist, integrating EBS implants with off-the-body computing devices, like a smart phone, can enable tracking, analyzing, and modulating brain activity in ambulatory subjects while also providing real-time behavioral data via phones and wearable sensors. The bi-directional interface between ambulatory patients, their brain activity, as well as the local and distributed computing environments creates a powerful platform for therapy optimization and neuroscience discovery.

Current FDA approved EBS devices for epilepsy do not utilize adaptive therapy, take years for therapy optimization, and do not track seizures or treat common comorbidities like mood, sleep, and cognition. Here, we describe a Digital Epilepsy Management System for drug resistant epilepsy that integrates a brain stimulation and sensing implant with off-the-body devices and cloud computing enabled ambulatory tracking of seizures, biomarkers, behavior, sleep, cognition, and mood that can all possibly drive adaptive therapy (**Figure 7**).

Pre-clinical work at the Mayo Clinic was completed in research and pet canines with epilepsy using an investigational Medtronic Summit RC + S (bilateral hippocampus and anterior nucleus of the thalamus) sensing and stimulation implantable device integrated with a tablet computer and cloud-based system for streaming data acquisition from the brain and wearable sensors, patient and device triggered tablet annotations, data analytics, and visualization.

The system is currently deployed in a person with epilepsy and 2 pet dogs with epilepsy living with their owners. We have demonstrated automated seizure catalogs, interictal biomarker tracking, sleep staging, and patient mood and cognition testing in the naturalistic settings. The Digital Epilepsy Management System provides an interactive interface between patient and physicians and should be useful for optimizing adaptive EBS therapy in patients with epilepsy.

Closed-Loop DBS for Refractory Chronic Pain

A diverse array of chronic pain syndromes is refractory to almost all treatment modalities; however, they involve pathological activity in similar brain regions. This finding suggests therapeutic potential for DBS to treat pain, but despite early promise, long-term efficacy is lacking. Prior DBS approaches have been limited in anatomical reach, targeting brain regions underlying only single dimensions of pain (such as somatosensation). Further, DBS therapy has been bluntly applied in an open-loop, continuous fashion without regard to underlying physiology. As a result of these shortcomings, DBS for pain is frequently ineffective or shows diminished effect over time. DBS could be significantly improved by seeking individually optimized brain targets or by using neural biomarkers of pain to selectively control stimulation when it is needed (closed-loop DBS). This type of approach may help avert tolerance and may provide prolonged pain relief.

Using personalized neural signatures of acute and chronic pain states over long-time scales (weeks to months), we at UCSF are developing a closed-loop DBS technology to treat chronic pain. In our first cohort of four subjects with chronic pain, we have implanted electrodes in the anterior cingulate and orbitofrontal cortices. Using machine learning methods, we have successfully decoded high versus low pain states and identified personalized biomarkers of clinically relevant chronic pain states. The stimulation of anterior cingulate cortex (ACC) and orbital frontal cortex (OFC) has been variably analgesic with inconsistent results over time. In a newer study, we are using sEEG to perform a temporary stimulation trial of multiple brain targets that underlie the somatosensory, affective, and cognitive dimensions of pain. Based on this trial period, we can identify personalized brain targets for each subject to maximize both stimulation-induced pain relief and pain biomarker detection. These pain biomarkers can then be used as a next step and be embedded into closed-loop DBS control algorithms to provide long term pain relief.

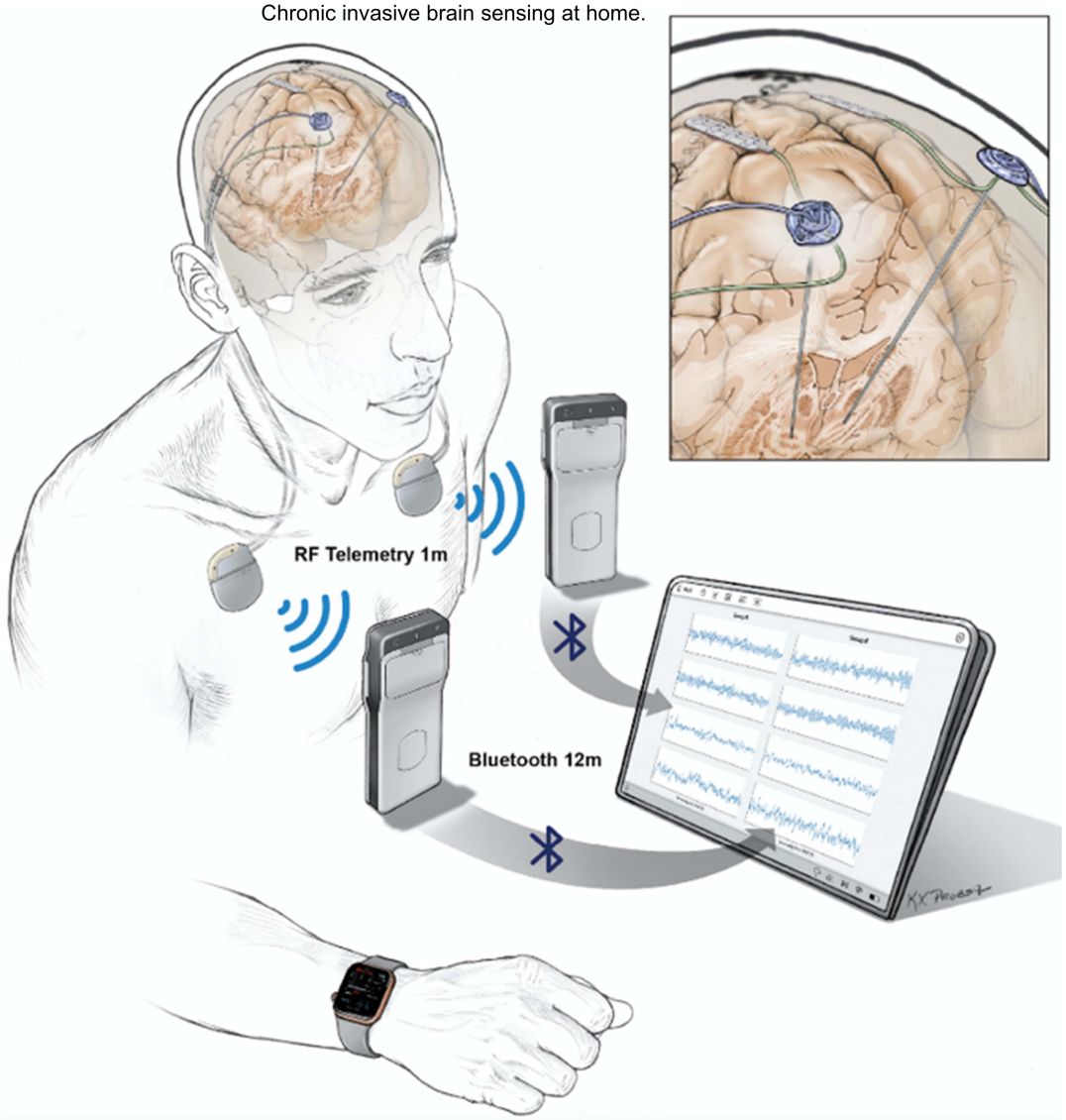

FIGURE 6 | UCSF protocol for data streaming from Summit RC + S. Quadripolar leads were placed bilaterally into the subthalamic nuclei and over the motor cortex. Leads were connected to the ipsilateral Summit RC + S neural interfaces. Each RC + S device wirelessly communicates with a pocket-sized relay device, usually worn on the patient. The relay devices transmit by Bluetooth to a single small Windows-based tablet at a distance of up to 12 m, allowing sensing of local field potentials from up to four bipolar electrode pairs for up to 30 h per device, before recharge is needed. Data from a wristwatch-style actigraphy monitor (Parkinson's Kinetograph, Global Kinetics) are synchronized off-line with neural recordings to facilitate brain-behavior correlations.

IMPULSIVITY AND NEUROPSYCHIATRIC ASPECTS OF DBS

As DBS has proven successful in well-selected patients for the treatment of movement disorders, such as PD and essential tremor, its indications are expanding to include intractable or severe neuropsychiatric conditions such as post-traumatic stress disorder (PTSD; Larkin et al., 2020), OCD (Goodman et al., 2020), and impulsive behavior (Wu et al., 2020). As DBS expands into neuropsychiatry, several questions and opportunities for development arise. These include optimal targets or targeting, either anatomical or functional-based, individualistic biomarkers of pathology, which can aid in the development of aDBS paradigms, identifying circuitries involved in psychiatric disorders, patient selection and ideal stimulation paradigms (i.e., open- vs. closed-loop strategy).

Intracranial Neurophysiological Biomarkers of Hypervigilance and Fear in Humans

The ability to detect and subsequently remember threats is critical for survival. However, extreme, or life-threatening situations, can produce long-standing changes in fear-processing circuitry

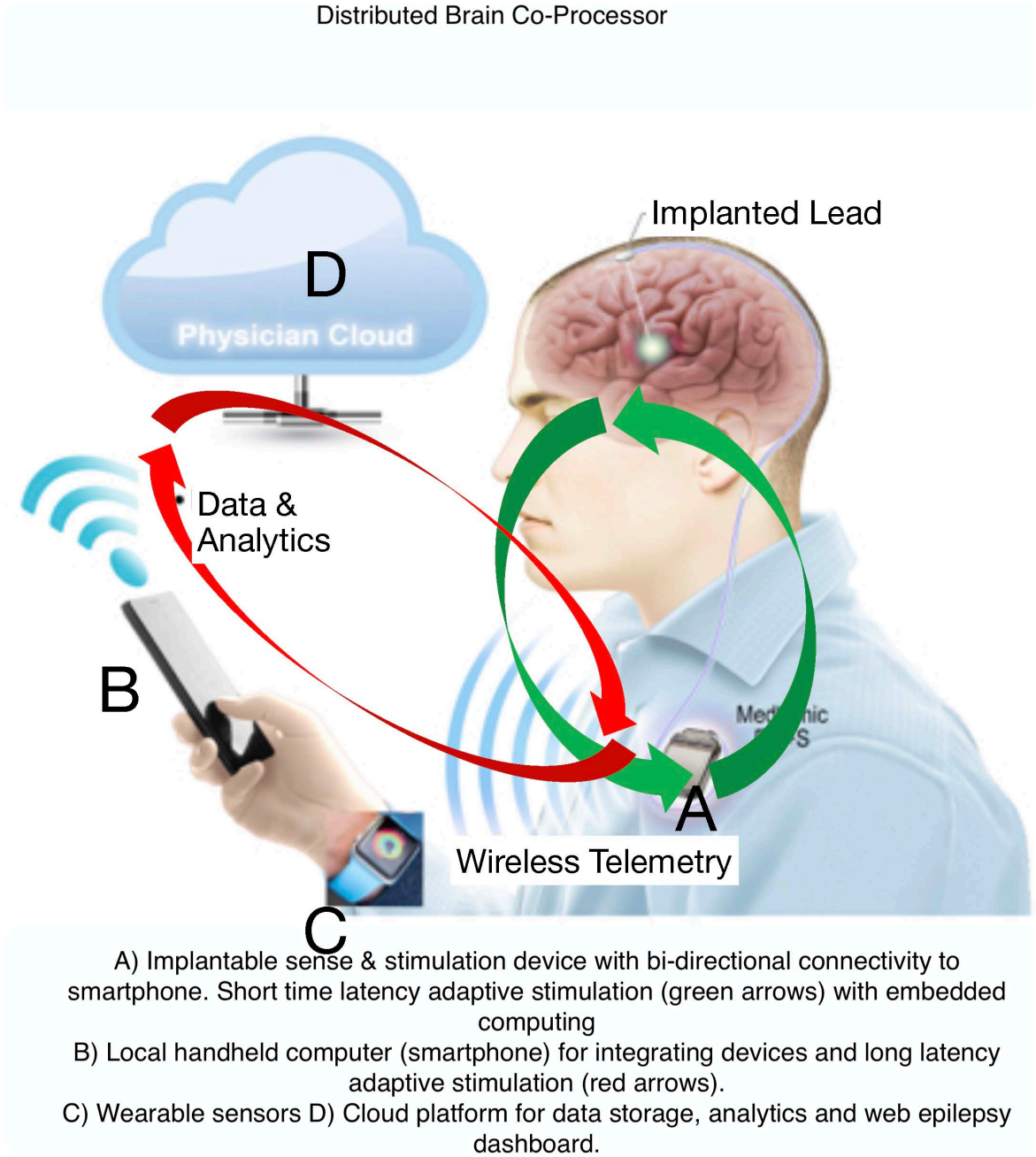

FIGURE 7 | Digital Platform for Neurological and Psychiatric Disease. Integration of brain implants, smart phones, wearable sensors, and computing environments that provide data analytics synchronized with biomarker or user triggered interactions that can enable new therapy paradigms.

and these can lead to anxiety disorders such as PTSD. Through a collaboration between Jean-Philippe Langevin, members of the Suthana laboratory, and colleagues at the Veteran's Administration Greater Los Angeles Healthcare System, we were able to record intracranial electroencephalographic (iEEG) activity in veteran participants with implanted electrodes placed within amygdala, hippocampal, and prefrontal regions. Participants included those with an implanted RNS® System (NeuroPace, Inc.), sEEG electrodes for seizure evaluation, or intra-operative recording electrodes implanted prior to DBS placement in a patient with PTSD. A subset of the participants was diagnosed with PTSD and/or generalized anxiety disorder (GAD). Results yielded low and high frequency oscillatory biomarkers that were and will be used to trigger responsive neurostimulation in PTSD patients as part of an ongoing NIH UH3 funded clinical trial. Future studies will focus on characterizing amygdala-hippocampal-prefrontal circuit mechanisms underlying fear-related memory and improve the

ecological validity of laboratory-based tasks using virtual reality, simultaneous physiological (e.g., heart rate, skin conductance, and pupillometry) and iEEG activity combined with intracranial electrical stimulation [for methods see (Topalovic et al., 2020)].

Development of Adaptive DBS for OCD

Ventral striatum (VS) DBS for treatment of intractable OCD benefits approximately 50–60% of cases, leaving room for improvement in both clinical outcomes and reduction of DBS-induced behavioral side effects, notably hypomania. An adaptive DBS (aDBS) system may improve efficacy of DBS for OCD by facilitating the titration of stimulation parameters in response to neural biomarkers of hypomania and in response to OCD-related distress. In an NIH UH3 (NS100549; PI Goodman) for aDBS in OCD, five participants underwent DBS surgery; two with the Medtronic Activa PC + S, and three with the Medtronic Summit RC + S. Participants returned to clinic for DBS programming and to conduct neural recordings [local field potentials (LFPs) and scalp EEG], video and heart rate monitoring, as well as behavioral tasks, all measured on a bi-weekly to monthly basis. Early evidence from one participant suggested an increase in the left vs delta-band power over a timeline of weeks since the DBS ON condition. This increase in power preceded symptom improvement, which occurred after an increase in pulse width from 90 to 120 μs that elicited a mirthful response. In addition to in-clinic data collection, we captured data in the participants' home environments. The Summit RC + S device enabled streaming of neural data at home during natural fluctuations in OCD symptom intensity and hypomania, as well as during exposure response therapy. There were 228 h of neural data streamed from one Summit RC + S participant during a range of behavioral states and tasks. The majority of LFP data was collected during active DBS therapy. To better understand underlying neural activity, we developed a novel stimulation artifact removal paradigm, termed Period-based Artifact Reconstruction and Removal Method (PARRM). PARRM is applicable to various neurostimulation paradigms beyond DBS, is superior in signal recovery, low complexity, and requires minimal onboard storage. Next, we plan to examine behavioral and neural data collected across various behavioral states to identify biomarkers that can be deployed in an effort to enable aDBS for OCD.

Closing the Loop on Impulsivity With Deep Responsive Neurostimulation: Past, Present, and Future of BITES

Loss of control (LOC) is a pervasive feature of eating disorders and contributes significantly to the epidemic of obesity. Responsive DBS that is guided by low-frequency changes in the nucleus accumbens (NAc), was previously observed to block binge-eating behavior in mice (Halpern et al., 2013). Following novel preclinical work and a human case study which demonstrated an association between the delta-band (1–4 Hz) and reward anticipation, an Investigational Device Exemption for a first-in-human trial was approved by the US FDA (Brain Intervention Therapy for Eating Suppression, the BITES study). BITES is a single site (Stanford University), early feasibility trial with a randomized, single-blinded, staggered-onset design. Six participants will undergo bilateral DBS of the NAc for LOC eating using the RNS® System (NeuroPace, Inc.). Eligible participants must have treatment-refractory obesity with a body mass index (BMI) 40–60 kg/m^2.

There are three participants currently enrolled. Electrophysiological signals of LOC will be characterized in humans using ambulatory recording capabilities and controlled, in-clinic behavioral tasks. We have developed novel behavioral tasks and we will utilize virtual reality and eye-tracking to capture anticipatory signals for LOC eating during intraoperative testing and in the laboratory. Using eye-tracking and remote telemetry communication, we captured real-time electrophysiological signals during naturalistic eating behaviors in the clinic. We assess LOC eating in the clinic by introducing participants to a validated multi-item buffet task where they are given a standard breakfast and lunch (500 kcal/meal), and following a brief LOC priming period with mood provocation, participants are presented a buffet of preferred, high fat-caloric food (∼5,000 kcal). Further, we utilize ambulatory data collection via magnet swiping which is paired with ecological momentary surveys, food diaries, and wearables to capture real-world LOC cravings and eating episodes. Initial piloting of these tasks and assessments were used for feasibility in the initial pilot study and analysis for a LOC-responsive biomarker study. Collectively, these preliminary results demonstrate the usefulness of long-term, objective neural recordings in naturalistic environments and the potential of individualized biomarkers of pathology or symptoms for the potential successful employment of aDBS.

EMERGING TECHNIQUES FOR DBS

New techniques for the application of DBS have emerged with the advent of imaging, which has resulted in a paradigm shift toward targeted modulation of a particular network (Gonzalez-Escamilla et al., 2019, 2020; Horn et al., 2019). Another emerging and as yet unresolved area is how beta oscillatory activity in the basal ganglia is affected by DBS and how this is associated with symptom improvement (Lofredi et al., 2019; Petersson et al., 2020). Studies demonstrating suppression of beta activity by DBS revealed that this was associated with amelioration of symptoms, and also with an attenuation of this effect after continuous stimulation (Chen Y. et al., 2020). This section summarizes the latest information on device technology, structural/functional aspects, and biomarkers for improved DBS programming.

Update on Emerging Technologies and Deep Brain Stimulation

Initially, DBS was thought to mimic the effect of lesioning through neuromodulation of neuronal activity within the area surrounding the stimulating electrode. However, current physiological concepts imply, that DBS has multiple, time-dependent effects on the cellular, local neuronal circuitry and also at the large-scale network level. These changes may influence the dysfunctional activity within symptom specific neural circuits.

Axons originating or terminating within the stimulation volume or bypassing it are the key elements potentially mediating multiple clinical responses (Kuhn and Volkmann, 2017; Lozano et al., 2019). Therefore, ideal neurostimulation technology.

- should be flexible in stimulating only a small volume of interest,
- should preferentially stimulate axons mediating benefit,
- should avoid stimulation of axons or other excitable elements resulting in adverse effects,
- should eliminate the neuronal signal mediating a network dysfunction (e.g., oscillopathy),
- should not interfere with normal (physiological) network function.

Recent methodological advances addressing these needs include segmented electrode designs and an expanded pulse parameter space (e.g., shorter pulse durations, anodic stimulation) for more precise delineation of the stimulation volume and for selective stimulation of particular fiber pathways of interest. Another advance includes sensing capability using either brain signals or peripheral kinematic sensors to adapt stimulation to fluctuating symptom severity and to the underlying dynamics of neural circuits. Finally, future advances include the rapidly advancing field of digital innovations for clinical response prediction which may inform and substantially shorten programming times for DBS.

Several open source and commercial software have facilitated visualization of the volume of tissue activated (VTA) based on axon cable models in patient specific anatomical models (derived from MRI and CT imaging). Aggregated data from large patient cohorts have facilitated the creation of probabilistic maps of clinical responses, which in turn can be used to train machine learning algorithms for predicting a clinical (individual) response with a given electrode location and a particular stimulation setting (Reich et al., 2019). We hope, that resulting "expert systems" will help to better manage DBS patients in a more reliable and consistent way across centers and will reduce the need for high-level individual expertise in DBS programming. A clinical trial (site: University of Würzburg, Germany) comparing machine based and best clinical programming in dystonia has recently received funding from the German Ministry of Research and Technology and will be initiated in 2021 (DIPS: Dystonia Image-based Programming of Stimulation: A prospective, randomized, double-blind crossover trial).

Structural and Functional Network Characterization for Prediction of DBS Patients

Despite the vital role of brain network studies to predict disease trajectories in patients with movement disorders, their analysis and modeling are often difficult to interpret due to complexity, uniqueness, test-retest issues and group or single subject validity of the data. Of distinct importance for the comprehension of the analytical framework is to note, that network interactions occur at specific spatial locations within regions (space) over distinct time dimensions (state). With this in mind, we hypothesize that brain networks have instantaneous state and space properties at each level. Proper identification and association of features (within and between brain regions) from these critical variables at different time scales can be modeled by newly proposed computational approaches (Gonzalez-Escamilla et al., 2020; Muthuraman et al., 2020) that can then have the potential to predict individual responses to DBS.

In a recent review, we comprehensively describe the causal interrogations and modulations of network states using neuroimaging and electrophysiology (Gonzalez-Escamilla et al., 2020). Using structural magnetic resonance imaging (sMRI), we were further able to show in the pre-operative MRI the cortical thickness (CT) in the frontal lobe predicted the clinical improvement after STN-DBS (Muthuraman et al., 2017) and cortical atrophy in sensorimotor areas in dystonia patients (Gonzalez-Escamilla et al., 2019). In the same direction, frontal lobe network proxies can predict postoperative clinical response to STN-DBS using diffusion tensor imaging (DTI; Koirala et al., 2018). By using functional state recordings and analyses from electroencephalography (EEG) and electromyography (EMG) we were able to show the topography of oscillatory coherent sources in the cerebellum and sensory-motor cortex could robustly separate patients with different tremor syndromes and act as variables for closed-loop approaches (Muthuraman et al., 2018). Moreover, in advanced network analyses using a similar analytical framework with high-density EEG we described cross frequency coupling as a marker for clinically effective DBS of the STN-DBS, that modifies fine-tuned gamma oscillations for the optimal clinical response (Muthuraman et al., 2020). After identifying these network proxies (**Figure 8**), the aim is for rapid translation of scientific knowledge to clinical practice. There is a clear need for testing of this proposed state- and space framework in the clinical setting.

Local Field Potentials as Biomarkers for DBS Control and Programming

Over the last decade, we and others have used the access to deep brain nuclei in patients undergoing DBS not only for treatment of motor symptoms, but also to record neuronal activity in order to understand the underlying pathophysiology of movement disorders. We could show that the temporal pattern of neuronal output is highly important to understanding network disorders. The oscillatory activity pattern is different in bradykinetic and hyperkinetic disorders, i.e., dynamic changes in the network related to a specific motor state of the patient. Best known is the increased subthalamic oscillatory beta (13–35 Hz) band activity which has been shown to be a potential electrophysiological signature of bradykinetic motor signs in patients with PD (Silberstein et al., 2003). Dopaminergic medication has been associated with a decrease of this pathologically enhanced activity, specifically in the low beta sub-band (13–20 Hz) (Kuhn et al., 2006, 2008).

In several studies, a significant correlation between parkinsonian symptom severity and beta synchronization has been reported (Kuhn et al., 2006, 2008), even months after neurostimulator implantation (Neumann et al., 2017).

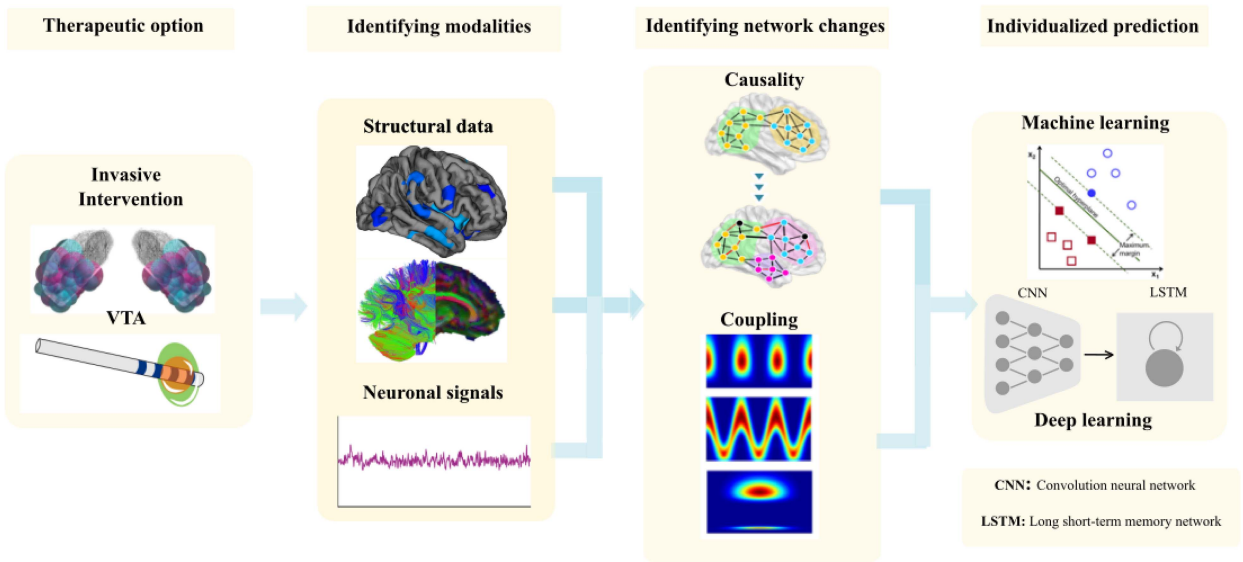

FIGURE 8 | The methodological framework to entangle network proxies for prediction of the outcome of the DBS patients from volume of tissue activated (VTA) modeling to identifying the correct modalities to identify the network changes and use it for individual prediction using matching learning algorithms.

Moreover, beta band activity has been shown to be suppressed by neuromodulation (Kuhn et al., 2008; Eusebio et al., 2011). Research has focused on the improvement of DBS and there has been movement toward more patient-tailored, adaptive stimulation (aDBS). The idea of aDBS has been to switch stimulation ON/OFF or to modulate the stimulation amplitude in response to the real-time analysis of a potential biomarker, e.g., beta band activity in PD (Little et al., 2013). A recent technical development has facilitated chronic sensing using the PERCEPT (Medtronic) pulse generator. This new technical advancement will help to define the biomarker as a feedback signal for future adaptive DBS.

Our first experience with PERCEPT has revealed that a stepwise increase of stimulation amplitude was mirrored in the sequential decrease of beta oscillatory activity, which occurred in parallel with the improvement in bradykinesia. Mean beta band (13–20 Hz) activity correlated significantly with the UPDRS scores during DBS. Further studies using chronic sensing will likely reveal circadian fluctuations in oscillatory patterns. This will also likely be useful for application to aDBS in real life situations. This finding may also be important to future clinical development.

NEUROTECHNOLOGY AND NEUROENGINEERING IN DBS RESEARCH

This section describes the advances in the field of neurotechnology as applicable to DBS research. This includes real-time neural recordings, remote DBS programming, optimization of electrode configurations, and model-based algorithms, which can all be developed to further incorporate physiological signals in the optimization process. Finally, we address issues surrounding chronic implantation and utilization of neural micro-devices, which have the potential to provide sensory information feedback, and how to mitigate these issues.

Real Time Recording of EEG and ECG Using DBS Electrodes

With sensing-enabled deep brain stimulators, chronically monitoring neural activities in the deep brain has become a reality. This capability could play a key role in clinical neuroscience and neuromodulation technology. We developed a DBS system with the capability of chronic recording (Qian et al., 2016). We investigated artifact removal methodologies (Qian et al., 2017a,b) and we built a software platform to improve signal recording and signal processing. Based on this technology, we conducted longitudinal clinical recordings to observe chronic LFPs and the effects of DBS on neuromodulation (Qian et al., 2016). The results have revealed that there may be a chronic change in the beta suppression of DBS in the subthalamic nucleus of PD patients.

In addition to this change we also observed combinations of alpha, beta and gamma bands which could be used as chronic biomarkers for the classification of different sleep stages (Chen et al., 2019). The results have guided the development of a closed-loop DBS approach. Recently, this sensing-enabled device has been improved by employing Bluetooth communication, facilitating the potential for the application of implantable brain-machine interfaces. The latest advance has been the first Bluetooth DBS device which was implanted in China. The device could directly connect to a mobile device by Bluetooth and was capable of transmitting up to eight channels of LFPs, one channel of ECG as well as 3-D acceleration signals (**Figure 9**).

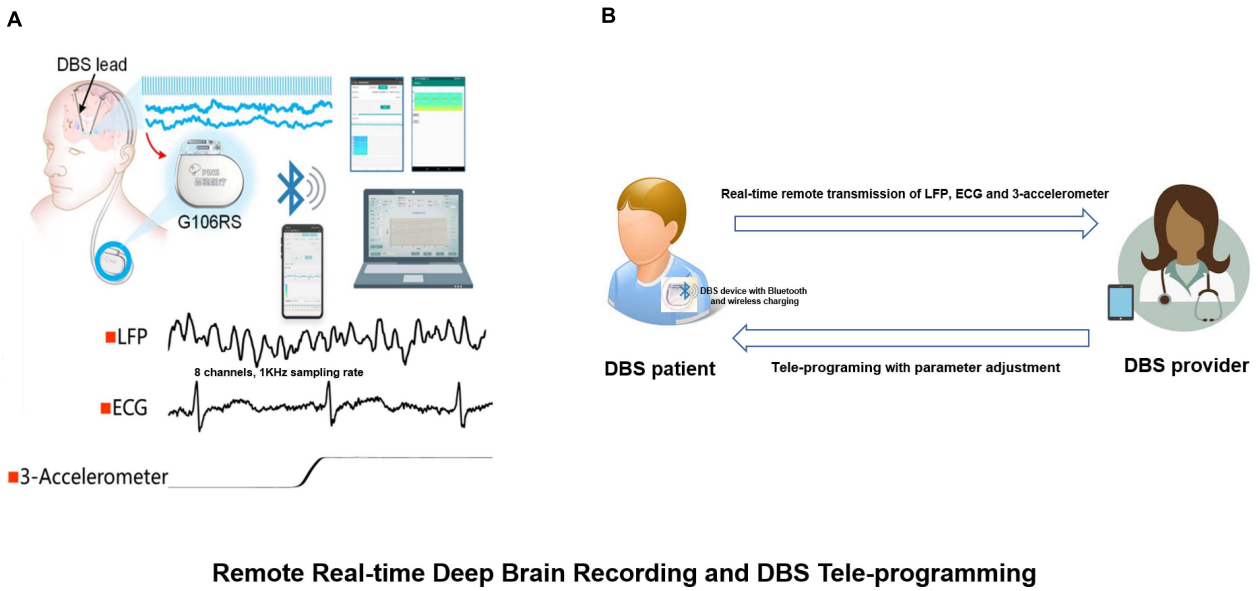

FIGURE 9 | Remote real-time deep brain recording and DBS tele-programming. **(A)** The G106RS system, a sensing-enabled DBS with Bluetooth connection, can monitor deep brain rhythms remotely. Specifically, it was capable of transmitting up to eight channels of local field potentials (LFPs) with 1,000 Hz sampling rate, one channel of electrocardiogram (ECG) and 3-D accelerometer signals; **(B)** DBS patient equipped with G106RS device with Bluetooth connection and wireless charging. A tele-programming DBS system can remotely adjust parameters via Bluetooth technology by the provider. The LFP, ECG and 3-D accelerometer signals can be transmitted remotely from the G106RS device to a data receiver accessed by the provider.

Remote DBS Programming During COVID-19 Pandemic

In the past five years, remote programming technology has been widely expanding in large medical centers specifically in an effort to improve access, and particularly for those residing in remote locations. At the beginning of the COVID-19 pandemic, many patients were secluded from standard medical services due to social distancing, quarantine, and lockdowns. For patients with PD, efficient programming could be safely achieved by a remote tele-programming system. We have developed a DBS programming technology using a Bluetooth communication interface. We reported the application of the device during the pandemic, particularly for PD patients with freezing of gait (FOG) who were able to be programmed with a complex variable frequency stimulation (VFS; Jia et al., 2018) paradigm (Zhang et al., 2020). This technology could potentially be shared among multiple medical centers when paired with the implementation of adequate privacy protections.

Our remote programming system provides a promising approach for the control of a wide range of implantable medical devices. We anticipate that telemedicine for remote DBS programming will be an important trend in future DBS management.

Model-Based Algorithms for Optimizing DBS Therapy

Computational models of DBS have provided significant insight into the regions and pathways involved in treatment and side effect induction with DBS therapy. To date much of the research has focused on retrospective analysis in which previously collected clinical outcomes are matched with model predictions of the regions or pathways activated by clinically optimized or suboptimal stimulation settings that may or may not induce side effects. As we continue to pursue these retrospective studies, the knowledge gained provides an opportunity to build data-driven algorithms for identifying therapeutic electrode configurations prospectively and on an individual subject basis.

Several targeting algorithms have been developed in recent years including neural network classification based on VTA morphologies (Chaturvedi et al., 2013), convex optimization for targeting several (Xiao et al., 2016), or a broader range (Anderson et al., 2018) of axonal pathways, orientation-selective stimulation (Lehto et al., 2017; Slopsema et al., 2018, 2020) and particle swarm optimization that can incorporate single (Pena et al., 2017) or multiple (Pena et al., 2018) objective functions. While these studies have focused primarily on optimizing electrode configurations, including monopolar and multipolar stimulation, and stimulation amplitude, model-based algorithms have also shown utility for optimizing the pattern of stimulation (Brocker et al., 2017; Cassar et al., 2017) and the shape and size of DBS (Howell et al., 2015) electrodes (Teplitzky et al., 2016).

Model-based algorithms can also be extended to incorporate physiological signals in the optimization process. Examples of these approaches include adaptive closed-loop strategies that integrate a response surface model to intelligently guide and update stimulation parameters. One recent example is the development of Bayesian adaptive dual control that balances exploitation of DBS settings that are known to be therapeutic with the exploration of settings that may yield a better outcome

(Grado et al., 2018; **Figure 10**). As telehealth becomes more mainstream for DBS programming and in cases in which the clinical effects of DBS have long wash-in and wash-out time constants, model-based optimization algorithms are poised to make a significant future impact.

Engineering the Neuronal Response to Electrical Microstimulation

The loss of sensorimotor function has devastating consequences on quality of life. One approach to restoring lost sensorimotor abilities is to supply patients with implants that provide a direct interface with the central nervous system. For an amputee or tetraplegic patient, this interfacing could allow a patient's desired limb movement to be executed by a prosthetic limb, and to convey to the patient, sensory information about the consequences of these movements. Highly sophisticated robotic limbs have been developed, as have algorithms to decode motor commands from the brain. However, somatosensory feedback is critically important in activities of daily living. Furthermore, touch is important in emotional communication and in embodiment of our limbs. Without touch, the dexterity of the prostheses will be limited, as will the degree to which they are incorporated into the self-image. Given the importance of touch, upper limb neuroprostheses may not be clinically viable until these devices provide informative tactile feedback.

Direct interfacing of micro-devices with the brain has the potential to provide sensory information feedback. However, chronic implantation and utilization of neural micro-devices can result in a reactive tissue response that both functionally isolates the device from the tissue as well as triggers neuronal apoptosis or migration. The goal of our research is to understand and to mitigate this limited functionality. Our research seeks to determine the interdependent effects of device design, electrophysiological recording, electrical stimulation, and the reactive tissue response on the efficacy of neural interfaces. We: (1) conduct psychophysical experiments using multi-channel cortical implants in the cortex, (2) collect longitudinal electrochemical and electrophysiological recordings, (3) investigate mitigation strategies, and (4) use advanced histological approaches to evaluate the device-tissue interface. Our lab studies these various approaches and their implications for reliable chronic neural interfacing via micro-devices. We expect that these data will enable further neuroprosthetic development for many neural interfaces' potential applications.

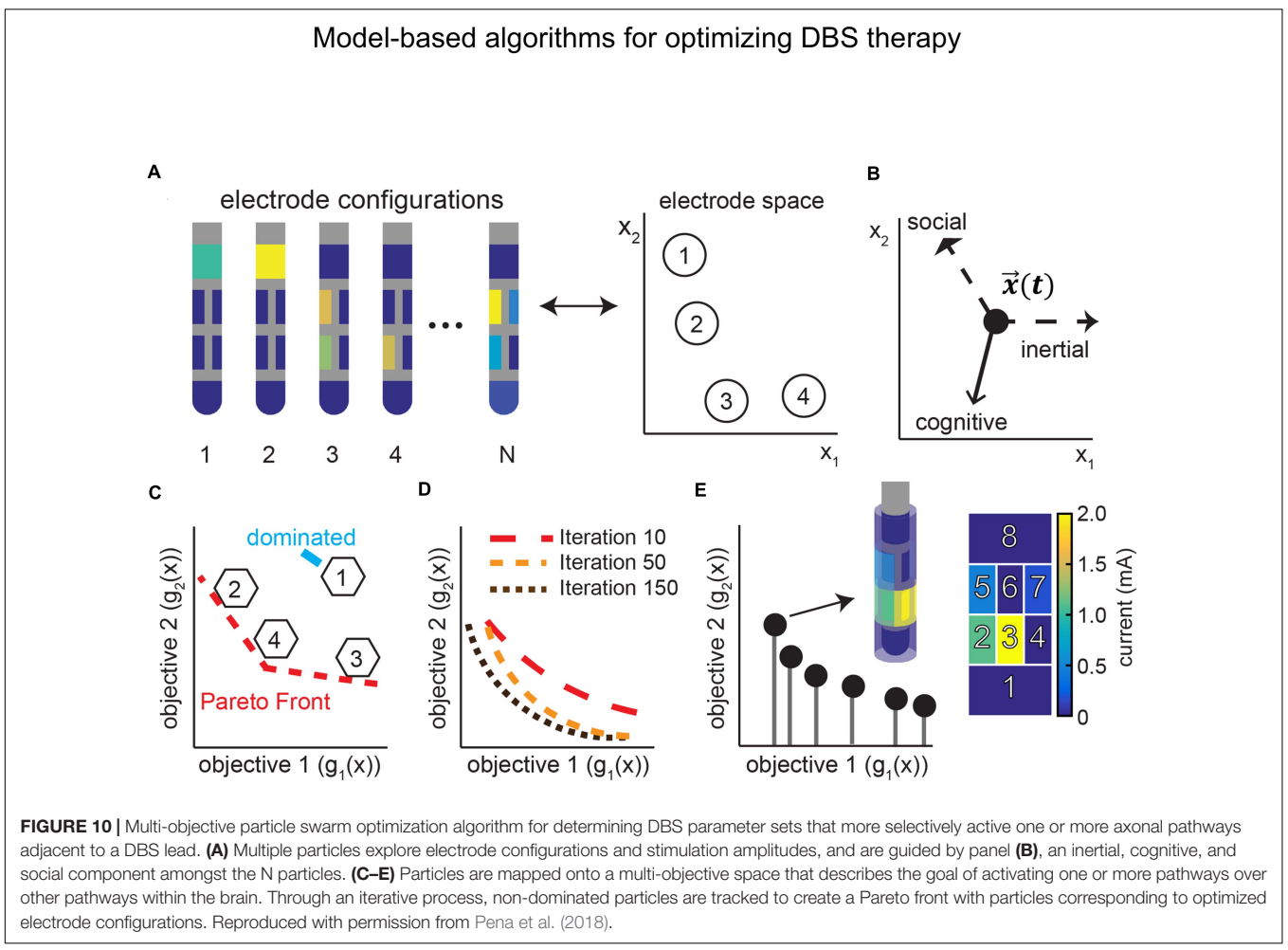

FIGURE 10 | Multi-objective particle swarm optimization algorithm for determining DBS parameter sets that more selectively active one or more axonal pathways adjacent to a DBS lead. **(A)** Multiple particles explore electrode configurations and stimulation amplitudes, and are guided by panel **(B)**, an inertial, cognitive, and social component amongst the N particles. **(C–E)** Particles are mapped onto a multi-objective space that describes the goal of activating one or more pathways over other pathways within the brain. Through an iterative process, non-dominated particles are tracked to create a Pareto front with particles corresponding to optimized electrode configurations. Reproduced with permission from Pena et al. (2018).

SUMMARY AND CONCLUSION

The Eighth Annual DBS Think Tank meeting provided scientific insight into the most current commercially available technologies and also facilitated important dialogue as to how clinical outcomes may be influenced The topics included (1) closed-loop and adaptive DBS for the treatment of multiple emerging indications, (2) improved imaging techniques which could expand our understanding of brain circuitry and improve DBS outcomes by offering more personalized targeting, (3) optogenetics to elucidate the fundamental roles of various cell types in the neurobiology of disease and could lead to a better understanding of pathological brain circuitries, and (4) the use of chronic neural recordings to define symptom-specific, individualized biomarkers. The Think Tank also addressed a multitude of emerging ethical issues arising from research and from the application of these aforementioned technologies, especially when DBS is successfully applied for off-label uses. We discussed the ethical implications of post-trial management. Furthermore, attendees of the DBS Think Tank completed a questionnaire and 178 participants responded. The participants were primarily scientists or clinicians at academic institutions/universities. The weighted-mean experience in the field of neurotechnology of the participants was 12.3 years. Within the last year, DBS for essential tremor and PD remain at the slope of enlightenment, with mean scores of 5.38 and 5.36, respectively. Additionally, cochlear implants have joined the slope of enlightenment this year. Optogenetics for clinical neural interfaces remains as a technology trigger. Several DBS indications (PTSD, obesity, traumatic brain injury, addition, Alzheimer's) have moved from technology trigger to peak of inflated expectations, corresponding to the expanding research and clinical trials. Results indicated that some uses and techniques of DBS remained on the trough of disillusionment (intraoperative physiology, imaging post DBS implant, DBS for epilepsy, DBS for Tourette) or moved to the trough of disillusionment (DBS for OCD, DBS for chronic pain, closed-loop DBS).

These proceedings present the latest advances in the field of neuromodulation and emerging challenges that will require international collaboration to more rapidly advance DBS 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 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 fulfilled authorship criteria by substantial contributions to the conception of the work, providing data for the work, revisiting it critically for important intellectual content, approving the final version, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Corrigendum: Proceedings of the Eighth Annual Deep Brain Stimulation Think Tank: Advances in Optogenetics, Ethical Issues Affecting DBS Research, Neuromodulatory Approaches for Depression, Adaptive Neurostimulation, and Emerging DBS Technologies

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A Corrigendum on

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Wei Hu was not included as an author in the published article.

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A correction has been made to the Conflict of Interest Statement, with the following sentence added:

"Research devices for Dr. Goodman's NIH funded study were donated by Medtronic."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Safety and Tolerability of Burst-Cycling Deep Brain Stimulation for Freezing of Gait in Parkinson's Disease

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Background: Freezing of gait (FOG) is a common symptom in Parkinson's disease (PD) and can be difficult to treat with dopaminergic medications or with deep brain stimulation (DBS). Novel stimulation paradigms have been proposed to address suboptimal responses to conventional DBS programming methods. Burst-cycling deep brain stimulation (BCDBS) delivers current in various frequencies of bursts (e.g., 4, 10, or 15 Hz), while maintaining an intra-burst frequency identical to conventional DBS.

Objective: To evaluate the safety and tolerability of BCDBS in PD patients with FOG.

Methods: Ten PD subjects with STN or GPi DBS and complaints of FOG were recruited for this single center, single blinded within-subject crossover study. For each subject, we compared 4, 10, and 15 Hz BCDBS to conventional DBS during the PD medication-OFF state.

Results: There were no serious adverse events with BCDBS. It was feasible and straightforward to program BCDBS in the clinic setting. The benefit was comparable to conventional DBS in measures of FOG, functional mobility and in PD motor symptoms. BCDBS had lower battery consumption when compared to conventional DBS.

Conclusions: BCDBS was feasible, safe and well tolerated and it has potential to be a viable future DBS programming strategy.

Keywords: deep brain stimulation, freezing of gait, Parkinson's disease, burst cycling, GPi, STN, globus pallidum interna, subthalamic nucleus

INTRODUCTION

Freezing of gait (FOG) is a common symptom in Parkinson's disease (PD) and tends to increase in prevalence with disease duration (Giladi et al., 2001). Although the underlying mechanism is not well understood, FOG has a complex pathophysiology that can be provoked by a variety of internal and external stimuli (Gilat et al., 2018). Historically, FOG can be dopamine responsive or "dopamine-resistant" and has been challenging to address (Okuma, 2014). FOG therefore can be a disabling manifestation of PD and can severely impact quality of life. Although deep brain stimulation (DBS) has emerged as a reliable treatment option for motor fluctuations, dyskinesia, and tremor, there has been mixed success when applied to FOG (Weaver, 2009). The subthalamic nucleus (STN), globus pallidus internus (GPi), and pedunculopontine nucleus (PPN) have all been trialed for FOG (Nilsson et al., 2009; Rocchi et al., 2012; Schrader et al., 2013; Vercruysse et al., 2014; Welter et al., 2015; Kim et al., 2019). Exploratory studies have observed that axial symptoms such as FOG are less responsive to conventional high-frequency DBS (>100 Hz; Gervais-Bernard et al., 2009; Fasano et al., 2010, 2015). However, several small studies have found that low-frequency stimulation (<100 Hz) can improve gait in PD (Moreau et al., 2008; Xie et al., 2016). Additionally, physiology studies have shown a dynamic temporal relationship between intrinsic basal ganglia oscillations and the various components of gait (Fischer et al., 2018, 2020). Novel stimulation paradigms have been proposed as a possible alternatives to conventional DBS that may improve the suboptimal responses to classic DBS approaches (Akbar et al., 2016). Several previous studies by our group have demonstrated that firmware updates of DBS pulse shapes and patterns can be safe and well-tolerated (Almeida et al., 2017; De Jesus et al., 2018). We conducted a safety and tolerability trial of a temporally focused pattern of stimulation called burst-cycling DBS (BCDBS) applied to PD subjects with chronically implanted unilateral or bilateral STN or GPi DBS.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board (IRB201602593) at the University of Florida (UF). Ten PD subjects with complaints of FOG interviewed by a movement-disorders neurologist in clinic setting were recruited for this study. The primary outcome measure of the study was the safety of BCDBS as determined *via* first hand observation by the examiner. Poor tolerability was defined as the occurrence of any stimulation induced side effects that required cessation of BCDBS programming. Secondary outcome measures included assessment of BCDBS on FOG, gait metrics, and motor symptom severity *via* the Unified PD Rating Scale (UPDRS).

Inclusion criteria for this study were: (1) a diagnosis of PD as defined by UK Brain Bank Criteria; (2) complaints of FOG at home; (3) chronic and optimized DBS; and (4) Medtronic DBS lead (model 3387) and implantable pulse generator (IPG) that is either Activa SC, PC, or RC (Medtronic, Minneapolis, MN, USA; Gelb et al., 1999). "Chronic and optimized" DBS in this study is defined as having the same DBS settings for a duration of at least 6 months. Exclusion criteria in this study were: (1) any other previous neurological surgery; (2) DBS hardware other than the Medtronic system; (3) baseline utilization of complex DBS programming settings such as interleaving stimulation; and (4) suspicion of other neurologic diagnoses such as Parkinsonism, Atypical parkinsonism, or Alzheimer's disease.

The study was conducted during a 1-day office visit. The study visit lasted approximately 6 h and included clinical testing under five different DBS programming conditions. Specifically, the subjects in this study presented to the clinic in the medication-OFF state after a 12-h overnight withdrawal of dopaminergic medications. Upon arrival, the patient IPG was interrogated using the standard Medtronic clinician programmer. The interrogation was used to verify hardware integrity. The IPG was then flashed to a Medtronic research firmware using the Medtronic Neuro Research Programmer (NRP) tool (Akbar et al., 2016). The NRP tool was then used to program the IPG to the baseline home settings for each subject (i.e., active contacts, voltage, pulse width, and frequency). Each subject was then tested in a single blinded fashion under five different programming conditions: (1) baseline home settings; (2) 30 min after turning the DBS off (i.e., a 30-min "wash-out" period; (3) 4-Hz burst-cycling stimulation; (4) 10-Hz burst-cycling stimulation; and (5) 15-Hz burst-cycling stimulation. There was a 10-min wash-in period between the different burst-cycle settings where the patients were instructed to rest while receiving BCDBS. During BCDBS, the voltage and pulse width were kept at baseline settings. The testing protocol can be seen in **Figure 1**. A visual explanation of BCDBS and comparison to other stimulation paradigms is shown in **Figure 2**. The BCDBS paradigm can be applied to the common programming frequencies conventionally available in the Medtronic clinician programmer.

For each testing condition, the subject was assessed for the following: e modified video UPDRS part III, 3-m timed up and go, freezing during clinic walking path, and a Zeno Walkway gait analysis (i.e., ProtoKinetics LLC, Havertown, PA). The clinic walking path was approximately a 100-foot path that included a wide hallway, a narrow hallway, one right turn and one left turn. During the Zeno Walkway gait analysis, patients were instructed to walk down a 26-foot-long by 2-foot-wide pressure sensing mat at their usual preferred pace, turn around and walk back to the starting position. Stimulation induced side effects were assessed for at the beginning and end of each testing condition interval. A checklist of common stimulation induced side effects as well as open-ended questioning was used to assess for side effects during BCDBS. Motor and gait assessments were videotaped and independently evaluated by two blinded movement-disorders neurologists. During the clinic walk, the movement-disorders neurologists were instructed to identify and count the number of definite freezing episodes observed during the video. For each of the three burst-cycling stimulation programs, clinical assessments were conducted after allowing for a 10-min stimulation wash-in period. At the end of the study, the

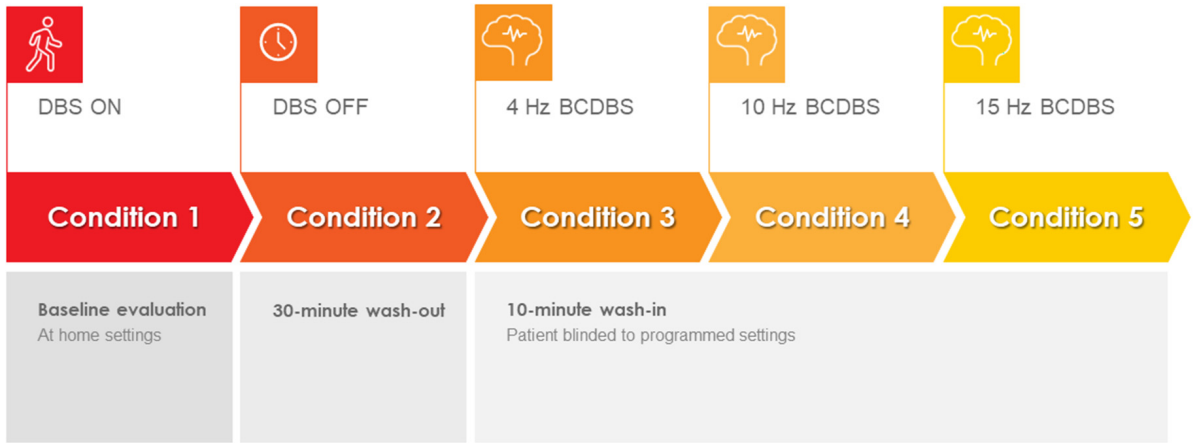

FIGURE 1 | Burst cycling deep brain stimulation (BCDBS) testing protocol: subjects were tested under five sequential conditions: (1) baseline, (2) 30 min after turning the DBS OFF, (3) 10 min after initiating 4-Hz BCDBS, (4) 10 min after initiating 10-Hz BCDBS, and (5) 10 min after initiating 15-Hz BCDBS.

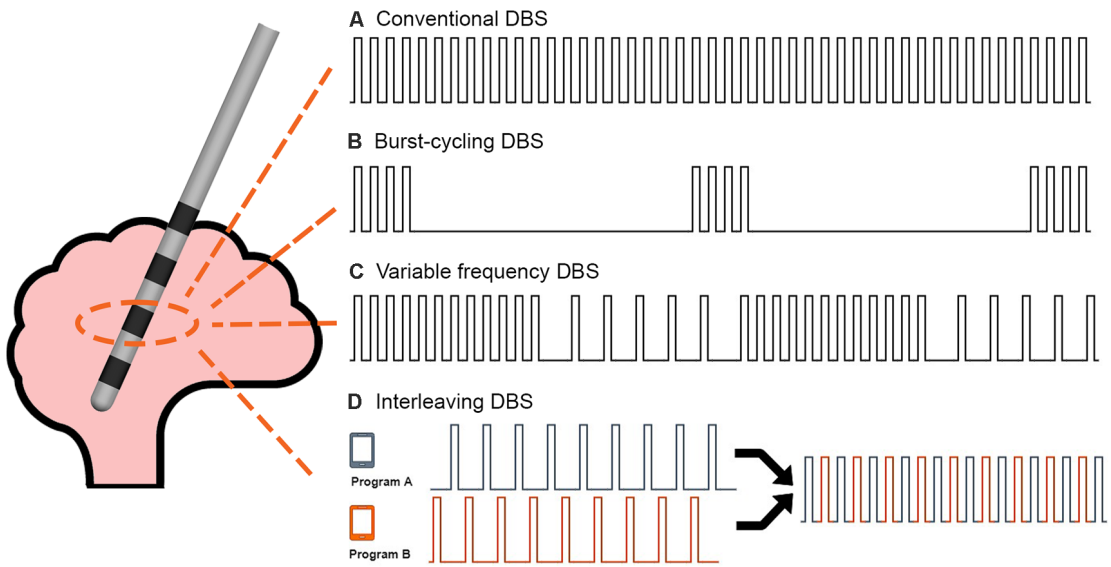

FIGURE 2 | DBS stimulation paradigms: a comparison of the stimulation delivery patterns between **(A)** Conventional DBS, **(B)** Burst-cycling DBS, **(C)** Variable frequency DBS, and **(D)** Interleaving DBS is shown. Burst-cycling DBS delivers four pulses at the same intra-burst frequency as conventional DBS but with an inter-burst frequency of 4, 10, or 15 Hz. The illustrated example shows 4-Hz burst-cycling DBS.

NRP tool was used to unload the research firmware and restore the factory default settings. The standard Medtronic clinician programmer was then used to restore baseline home settings for each subject.

Given the low sample size and the fact that this was a safety and tolerability study, we assumed a non-parametric distribution of data. Each of the clinical metrics were organized by the five testing conditions and were imported into SPSS (version 25; SPSS, Inc., Chicago, IL, USA) for analysis. The five conditions were tested for differences using a non-parametric analysis of variance (Kruskal–Wallis test) using a $p = 0.05$ as the threshold for statistical significance. Wilcoxon's signed rank test was similarly used for non-parametric comparisons of dependent measurements.

RESULTS

Ten PD subjects (eight men, two women) were recruited for the study. The median (IQR) age was 66 (64–75) years. The median (IQR) disease duration was 11 (9–16) years and time since DBS surgery was 19 (11–51) months. The median (IQR) UPDRS part II Freezing when Walking (Item 14) and Walking (Item 15) scores were 2 (2–3) and 2 (0.75–2.3), respectively. The median (IQR) Hoehn and Yahr scale and Dementia Rating Scale (2nd

Edition) were 2.8 (2.4–3) and 135 (133–139), respectively (Jurica et al., 2001). Five subjects had unilateral GPi DBS, four subjects had bilateral GPi DBS, and one subject had bilateral STN DBS. All subjects were implanted with a Medtronic 3387 DBS lead and either an Activa SC, PC or RC IPG. All subjects complained of FOG before they received DBS surgery.

Response to Stimulation

As part of the post-operative DBS programming protocol at UF, patients are assessed in the medication-OFF, DBS-OFF, and then DBS-ON state at the end of the 6-month optimization period. We analyzed this data to confirm that the subjects in this study were responsive to DBS to eliminate possible confounding factors. The mean (± SD) UPDRS part III motor scores in the medication-OFF/DBS-OFF vs. medication-OFF/DBS-ON state were 36.3 (± 11.9) and 25.2 (± 9.7), respectively (p = 0.001). The mean improvement from the DBS-OFF to the DBS-ON state was 52%.

Safety and Tolerability

The BCDBS stimulation paradigm was safe and well tolerated by PD patients. Two subjects withdrew early from the study as they were unable to tolerate the OFF-medication time required for physical testing, however no adverse events from stimulation were experienced during the time they were participating in the study. There were technical difficulties with uploading the research firmware in one subject and we were unable to complete the testing protocol for that subject. However, the baseline programming settings were restored without difficulty. Expected stimulation induced side effects have been summarized in **Table 1**. The transient side effects all occurred immediately after turning the DBS ON from the DBS OFF state or immediately after modifying programming settings from one test condition to the next. One subject reported a persistent sensation of worsening balance with BCDBS, but this resolved with the return to their baseline settings. There were no permanent adverse effects or severe stimulation induced side effects that prevented participation in this trial. The biggest obstacle was limitation of physical activity in the medication-OFF state.

Clinical Outcomes

A comparison of all five conditions for FOG is illustrated in **Figure 3**. Blinded video analysis of FOG episodes during the clinic walking trial and Zeno Walkway gait path revealed no significant difference among all testing conditions (p = 0.7480 and p = 0.9580 respectively). Single-leg-support percentage and double-leg-support percentage measured in the left and right leg using the Zeno Walkway gait analysis system identified no significant differences among all stimulation conditions (left single support p = 0.9820, left double support p = 0.9956; right single support p = 0.9115, and right double support p = 0.9942). Zeno Walkway assessment of temporal and spatial gait metrics showed no significant difference among all testing conditions for gait velocity and gait cadence (p = 0.9359 and p = 0.6854). Lastly, there was no difference detected among the testing conditions for the modified UPDRS part III motor scale and the timed up and go test (p = 0.9541 and p = 0.8984). The motor and gait outcomes are summarized in **Supplementary Figures 1, 2**.

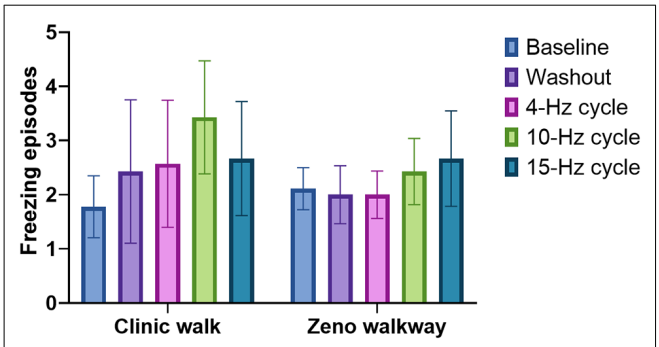

FIGURE 3 | The effect of BCDBS on freezing of gait (FOG): the number of freezing episodes during two different walking tasks are shown for all five test conditions. There were no significant differences among all five groups.

TABLE 1 | Stimulation induced side effects during burst-cycling deep brain stimulation (BCDBS).

Side effects	4-Hz BCDBS (*n*)	10-Hz BCDBS (*n*)	15-Hz BCDBS (*n*)
Transient paresthesias	2	2	2
Transient concentration change	0	1	0
Persistent worsening balance[1]	1	1	1

[1]*Worsening of balance resolved upon reverting back to conventional deep brain stimulation (DBS).*

DISCUSSION

FOG can be a debilitating symptom in PD and a challenge to treat *via* medication or neuromodulation (Huang et al., 2018). Given the associated increased risk of falls, FOG can have a significant impact on quality of life. In this study, we focused on evaluating the safety and feasibility of applying BCDBS for FOG in the setting of PD. We observed that BCDBS was safe and well tolerated. Stimulation induced side effects were transient, however one subject experienced a persistent sensation of worsening balance with BCDBS that resolved upon reverting back to conventional DBS. The most common feedback received during the testing protocol was difficulty engaging in physical activity in the medication-OFF state. There were no issues encountered with patient recruitment nor were there challenges with carrying out the testing protocol. The one instance of firmware technical difficulty was resolved by restoring the IPG back to manufacturer default settings. The observations from this study revealed that BCDBS could be safely applied in the clinic setting for future and potentially larger trials.

This study observed that BCDBS was non-inferior to conventional DBS for FOG, gait metrics, and motor symptoms in an acute setting. At the same time, BCDBS requires 88% less (at 4 Hz) to 54% (at 15 Hz) less battery consumption compared to conventional DBS at 130 Hz. As our collective understanding of neuromodulation expands along with evolving hardware

and software capabilities, non-conventional DBS stimulation paradigms will likely continue to emerge. New paradigms could provide alternative solutions for DBS optimization in the context of sub-optimally placed leads, waning efficacy with disease progression, or difficult to treat symptoms (i.e., FOG).

It will be important to concurrently study the effects of new patterns of BCDBS at a brain-network level. Based on the stimulation-delivery paradigm, we hypothesized that BCDBS may confer electrophysiologic effects comparable to coordinated reset neuromodulation, variable frequency DBS or Temporally Optimized Patterned Stimulation (TOPS) DBS (Tass, 2003; Tass et al., 2012; Wilson and Moehlis, 2015; Jia et al., 2017). In this model, brief high-frequency pulses unlink the pathologic neuronal synchronization that is characteristic of the PD disease state (Tass et al., 2012). Other studies investigating the frequency-dependent effects of DBS have proposed that there is enhancement of inhibitory synaptic plasticity and frequency-dependent neuronal depression (Milosevic et al., 2018; Horn et al., 2020). Milosevic et al. (2018) observed a complex and dynamic temporal relationship with frequency-dependent stimulation. This suggests that there may be an optimal inhibitory plasticity state induced by neuromodulation and that advanced programming strategies may be able to achieve this.

Concurrent electrophysiology recordings enabled by new advances in hardware may also elucidate BCDBS effects on beta-band bursts and modulation (Adamchic et al., 2014). Future computational modeling studies could also investigate the effect of frequency for changes in whole brain connectomics. Popovych et al. (2017) demonstrated one such model utilizing a "pulsatile feedback stimulation" paradigm for a closed loop DBS system. Combining neuronal biophysical models with whole brain tractography may provide insight into specific pathways or targets that might most benefit from non-conventional DBS.

We acknowledge several limitations with this study. First, as this study was designed as a safety and tolerability study, a small patient cohort was evaluated in a within-subject crossover testing paradigm that was not counterbalanced. This introduces error into our clinical outcomes in the form of testing fatigue and prolonged medication-OFF time. Although there were no statistical differences among all testing conditions, trends that suggest 10-Hz and 15-Hz BCDBS had overall worse outcomes. This may be attributed to fatigue as 10-Hz and 15-Hz conditions were the last tests performed. Future studies utilizing a counterbalanced design in which the burst-cycling frequencies are tested in a randomized nonsequential order are needed to further explore this observation. Additionally, midway through the study our institution moved to a new facility. As a result, 3 out of 10 subjects were tested in a different clinic environment. This can affect the frequency of freezing episodes and gait metrics appreciated during the study. Furthermore, this study evaluated BCDBS in an acute setting. Observation of BCDBS in a chronic setting may be needed to elucidate any therapeutic effect. Lastly, this study was not designed to compare target-specific differential effects of BCDBS. A future prospective trial is needed to adequately evaluate if there are unique responses to BCDBS across the commonly used targets for FOG DBS.

In conclusion, BCDBS can be a safe and well tolerated novel stimulation paradigm. Future larger prospective studies will be needed to investigate the effectiveness of BCDBS and to understand the brain-network effects underpinning changes induced by this paradigm.

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 human participants were reviewed and approved by University of Florida Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW, RB, and LA: study conception and design. JW, WH, RB, JLo, PT, ZJ, AW, and LA: acquisition of data. JW, KM, JLe, AW, and TT: analysis and interpretation of data. JW and WH: drafting of manuscript. JW, WH, RB, JLo, JJ, RR, TT, MO, and LA: critical revision. All authors contributed to the article and approved the submitted version.

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JW's research was supported by NIH R25NS108939. WH, RB, JLo, KM, JLe, PT, ZJ and AW declare no competing interests. TT was supported by a research fellowship program of the Uehara Memorial Foundation. RR is a paid employee of Medtronic Neuromodulation Global Research and provides technical support but did not contribute to the analysis of clinical results. JJ has received research grants from the Michael J. Fox Foundation. 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 principal investigator (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 works as a consultant and participates in advisory boards for Boston Scientific and Medtronic, and has received honoraria for these services.

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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.2021.651168/full#supplementary-material.

SUPPLEMENTARY FIGURE 1 | Motor outcomes from burst-cycling deep brain stimulation (BCDBS): the mean duration and standard error of the **(A)** Timed Up and Go Test and **(B)** modified video Unified Parkinson's Disease Rating Scale (UPDRS) part III are plotted for all five conditions in the medication-OFF state. There were no significant differences among all five conditions.

SUPPLEMENTARY FIGURE 2 | Gait metrics from BCDBS: the mean and standard error of the **(A)** gait cadence, **(B)** gait velocity, and **(C)** single support/double support % for both legs are shown for all five conditions in the medication-OFF state. Gait metrics were recording using the Zeno walkway gait-analysis system. There were no significant differences among all five conditions. LSS, left single support; LDS, left double support; RSS, right single support; RDS, right double support.

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MR Tractography-Based Targeting and Physiological Identification of the Cuneiform Nucleus for Directional DBS in a Parkinson's Disease Patient With Levodopa-Resistant Freezing of Gait

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Background: Freezing of gait (FOG) is a debilitating motor deficit in a subset of Parkinson's Disease (PD) patients that is poorly responsive to levodopa or deep brain stimulation (DBS) of established PD targets. The proposal of a DBS target in the midbrain, known as the pedunculopontine nucleus (PPN), to address FOG was based on its observed neuropathology in PD and its hypothesized involvement in locomotor control as a part of the mesencephalic locomotor region (MLR). Initial reports of PPN DBS were met with enthusiasm; however, subsequent studies reported mixed results. A closer review of the MLR basic science literature, suggests that the closely related cuneiform nucleus (CnF), dorsal to the PPN, may be a superior site to promote gait. Although suspected to have a conserved role in the control of gait in humans, deliberate stimulation of a homolog to the CnF in humans using directional DBS electrodes has not been attempted.

Methods: As part of an open-label Phase 1 clinical study, one PD patient with predominantly axial symptoms and severe FOG refractory to levodopa therapy was implanted with directional DBS electrodes (Boston Science Vercise Cartesia™) targeting the CnF bilaterally. Since the CnF is a poorly defined reticular nucleus, targeting was guided both by diffusion tensor imaging (DTI) tractography and anatomical landmarks. Intraoperative stimulation and microelectrode recordings were performed near the targets with leg EMG surface recordings in the subject.

Results: Post-operative imaging revealed accurate targeting of both leads to the designated CnF. Intraoperative stimulation near the target at low thresholds in the awake patient evoked involuntary electromyography (EMG) oscillations in the legs with a peak power at the stimulation frequency, similar to observations with CnF DBS in animals.

Oscillopsia was the primary side effect evoked at higher currents, especially when directed posterolaterally. Directional DBS could mitigate oscillopsia.

Conclusion: DTI-based targeting and intraoperative stimulation to evoke limb EMG activity may be useful methods to help target the CnF accurately and safely in patients. Long term follow-up and detailed gait testing of patients undergoing CnF stimulation will be necessary to confirm the effects on FOG.

Clinical Trial Registration: Clinicaltrials.gov identifier: NCT04218526.

Keywords: freezing of gait, gait dysfunction, Parkinson's Disease, mesencephalic locomotor region, cuneiform nucleus, pedunculopontine nucleus

INTRODUCTION

Gait disturbances feature prominently in Parkinson's disease (PD) and contribute significantly to patient disability, a decreased quality of life, and increased morbidity through risk of falls (Kerr et al., 2010; Allen et al., 2013). Freezing of gait (FOG) is one of the most debilitating of these deficits, and is described as the sudden and paroxysmal inability to generate effective stepping, despite the intention to do so (Giladi and Nieuwboer, 2008). It is a poorly understood phenomenon without a single unifying pathology and may represent a heterogeneous collection of circuitopathies affecting nodes along the locomotor control network (Rahimpour et al., 2020). Perhaps consequently, the management of FOG is complicated by its variable response to dopaminergic therapy—while some patients improve with medication, others have freezing that is refractory to levodopa (Nonnekes et al., 2015). Further still, in a small subset of patients, FOG appears to be induced or exacerbated by dopaminergic treatments (Espay et al., 2012). Patients with FOG that does not improve with levodopa are considered poor candidates for deep brain stimulation (DBS) surgery targeting the usual subthalamic nucleus (STN) or globus pallidus interna (GPi) targets (Thevathasan et al., 2018), leaving this population with few viable treatment options.

The mesencephalic locomotor region (MLR) has been identified as an important locomotor control center in the midbrain of multiple vertebrate species (Shik et al., 1966; Eidelberg et al., 1981; Skinner and Garcia-Rill, 1984; Cabelguen et al., 2003; Takakusaki et al., 2003). Functional imaging studies suggest that a homologous entity also exists in humans (Jahn et al., 2008), and clinicians have pursued this region as a potential DBS target to ameliorate gait dysfunction and FOG over the past 15 years with mixed reported outcomes (Mazzone et al., 2005; Plaha and Gill, 2005; Ferraye et al., 2010; Yeh et al., 2010; Thevathasan et al., 2011; Welter et al., 2015; Mestre et al., 2016). While animal studies have long distinguished between the pedunculopontine nucleus (PPN) and the slightly dorsally positioned cuneiform nucleus (CnF) in debates over the exact structural correlate to the MLR [(see Ferreira-Pinto et al. (2018) for a review], with many suggesting the CnF may be more efficacious for gait (Shik et al., 1966; Eidelberg et al., 1981; Takakusaki et al., 2016; Opris et al., 2019; Chang et al., 2021; **Figure 1**), neurosurgeons have exclusively targeted the PPN. This raises the possibility that target optimization in this region, including with the use of new directional DBS electrodes, could improve outcomes (Chang et al., 2020b).

Recently, several optogenetic studies targeting the MLR in mice have functionally characterized and distinguished neuronal populations within the MLR by neurochemistry and anatomy, suggesting that glutamatergic CnF neurons are the principal group within the MLR involved in initiating and controlling locomotion (Caggiano et al., 2018; Josset et al., 2018; Dautan et al., 2020). Supported by a recent anatomical-clinical study (Goetz et al., 2019), we hypothesized that targeting the CnF could lead to improved outcomes for PD patients with FOG and devised a pilot feasibility study. In this paper, we report our method of targeting the CnF using pre-operative DTI along with intraoperative physiology and preliminary post-surgical assessments of the effects of CnF DBS on gait in our first patient.

MATERIALS AND METHODS

The subject was recruited for this study from the Movement Disorders Clinic at the University of Miami Hospital. This study was approved by the University of Miami Human Subject Research Office (UM HSRO; IRB #20190702) and the United States Food and Drug Administration with an Investigational Device Exemption (G190164) as a phase I clinical trial. The trial is registered in ClinicalTrials.gov (NCT04218526), and the full study protocol is described elsewhere (Chang et al., 2020a). As part of the study protocol, the subject underwent a thorough multi-disciplinary evaluation, including psychological assessment and evaluation by multiple movement disorder specialists and a neurosurgeon, to determine surgical candidacy.

Pre-operative Imaging and Planning

The subject underwent pre-operative imaging as an outpatient 1 week prior to DBS surgery, including multi-planar, multi-echo 3T MRI sequences with and without contrast, as well as diffusion tensor imaging (DTI) using a Siemens Magneton Vida 3T with a standard Siemens 32 channel head coil (Siemens, Erlangen, Germany). T1 imaging was acquired with the following sequence parameters: repetition time (TR) = 1,900 ms; echo time (TE) = 4.9 ms, matrix = 256 × 206; field of view (FOV) = 200 mm × 250 mm; slice thickness = 1.30 mm; scan time 11 min, 24 s. T2 imaging was acquired with the

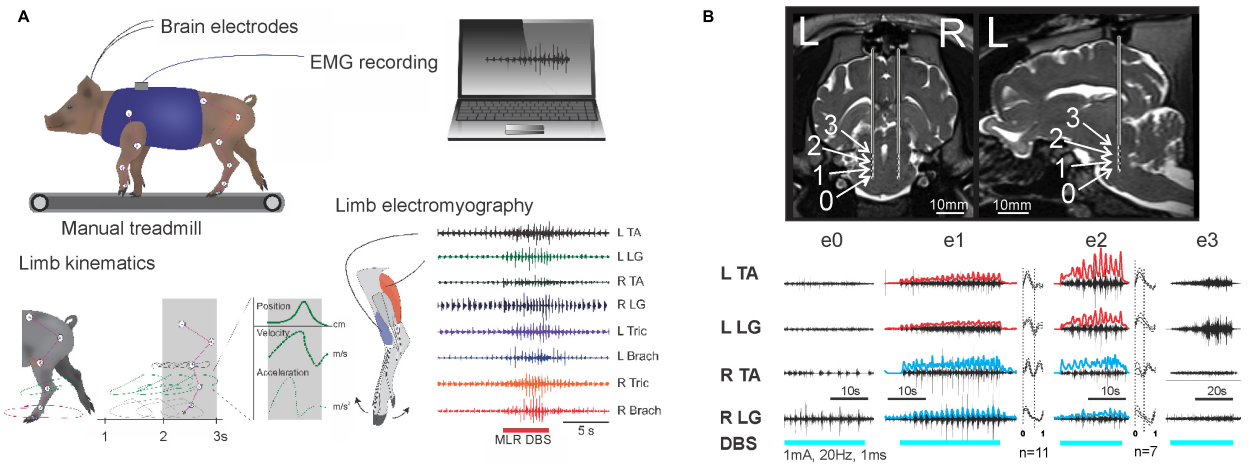

FIGURE 1 | Electrical mapping of the MLR in a large animal model. **(A)** Experimental schematic in the micropig model. **(B)** Intraoperative stimulation of the MLR. Top: Coronal and sagittal views showing calculated positions of electrodes 0–3. Bottom: EMG responses to cathodic biphasic stimulation of electrode 0–3 on left side (1 mA, 20 Hz, and 1 ms). Rectified and high pass filtered traces of individual EMG traces from e1 and e2 are overlaid in red (left) and blue (right). Step cycle averages for e1 and e2 are shown on right of each muscle, with the number of step cycles averaged indicated. Best locomotor-like response is observed with e1 and e2 stimulation, located within the cuneiform and adjacent subcuneiform region. Adapted from Noga et al. (2020), with permission.

following sequence parameters: TR = 4,780 ms; TE = 79 ms; matrix = 256 × 256; FOV = 250 mm × 250 mm; slice thickness = 2.00 mm; scan time = 3 min, 49 s. The DTI was acquired with the following sequence parameters: TR = 5,300 ms, TE = 75 ms; matrix 128 × 128; FOV = 250 mm × 250 mm; slice thickness = 4.00 mm; scan time 8 min, 19 s. The DTI was non-linearly transformed to the structural T1 MRI to correct for susceptibility-induced and eddy current-induced distortions using the Brainlab cranial distortion correction algorithm and then used to estimate the tractography of the superior cerebellar peduncle [SCP; seeds = dentate nucleus, red nucleus; fractional anisotropy (FA) = 0.15; minimum length = 80 mm; maximum angle = 20°], the medial lemniscus (ML; seeds = posterior to medullary pyramids, ventroposterolateral nucleus of thalamus; FA = 0.15; minimum length = 80 mm; maximum angle = 20°), and the central tegmental tract (CTT; seeds = red nucleus, inferior olivary nucleus; FA = 0.08; minimum length = 54 mm; maximum angle = 20°) using Brianlab Elements Fibertracking (Brainlab AG, Munich, Germany), based on fiber assignment by continuous tracking. Since the cuneiform nucleus is not visible on MRI, three-dimensional reconstructions of these tracts were superimposed onto the T1 MRI to guide our targeting of the CnF based on its known relationships to these tracts (**Figure 2**).

At the level of the pontomesencephalic junction, starting with brainstem normalized coordinates (0.66, 0.4, 0), the target was adjusted posteriorly to accommodate a point that was posteromedial to the ML and posterolateral to the CTT and SCP [see (Goetz et al., 2019) for a review of the brainstem normalized coordinate system]. Once the tractography-guided target had been selected, the images were imported into the Medtronic Stealth Planning Station (Medtronic, Minneapolis, MN, United States) to calculate AC-PC coordinates for the targets (Right: Lateral +2.79 mm, AP −20.71 mm, dorsoventral −13.95 mm, with AC-PC distance of 28.1 mm; Left: −2.47 mm, AP −20.08 mm, dorsoventral −13.94 mm) and to create appropriate electrode trajectories avoiding cortical sulci, vessels, and ventricles. Additionally, the trajectories were planned to place the six directional contacts of each lead (contacts 2–7) at the estimated CnF target.

Surgical Implantation and Intraoperative Physiology

Surgery was performed similarly to standard DBS cases reported previously (Okun et al., 2012; Cordeiro et al., 2020; Vitek et al., 2020). Local infiltration and light sedation were used to fix the Cosman–Roberts–Wells (CRW) head frame (Integra Life Sciences, Plainsboro, NJ, United States) to the subject's skull, and a CT scan was performed to co-register the frame to the pre-operative imaging. In addition to the standard intraoperative monitoring for DBS implantation, differential surface electromyography (EMG) electrodes were placed over the subject's *rectus femoris* (RF), *medial gastrocnemius* (MG), *biceps femoris* (BF), and *tibialis anterior* (TA) bilaterally. This was done to detect if stimulation near the predicted CnF would elicit limb EMG activity, as has been reported in animal studies. A video camera was used to record leg movements.

With the subject awake, off medication, and under tight blood pressure control (targeting a systolic blood pressure of 100–120 mmHg), microelectrode recordings (MERs) were performed along the planned trajectory using a single microelectrode in the Ben-Gun array (NeuroNav, Alpha Omega Co., Alpharetta, GA, United States). Beginning at +3 mm from the planned target, stimulation was performed along the trajectory while recording leg EMGs and observing for off-target effects (stimulation parameters: frequency, 20 Hz; pulse width, 100 μs; current amplitude, 0.1–2 mA). Involuntary leg EMG oscillations were observed with stimulation near our target at currents between

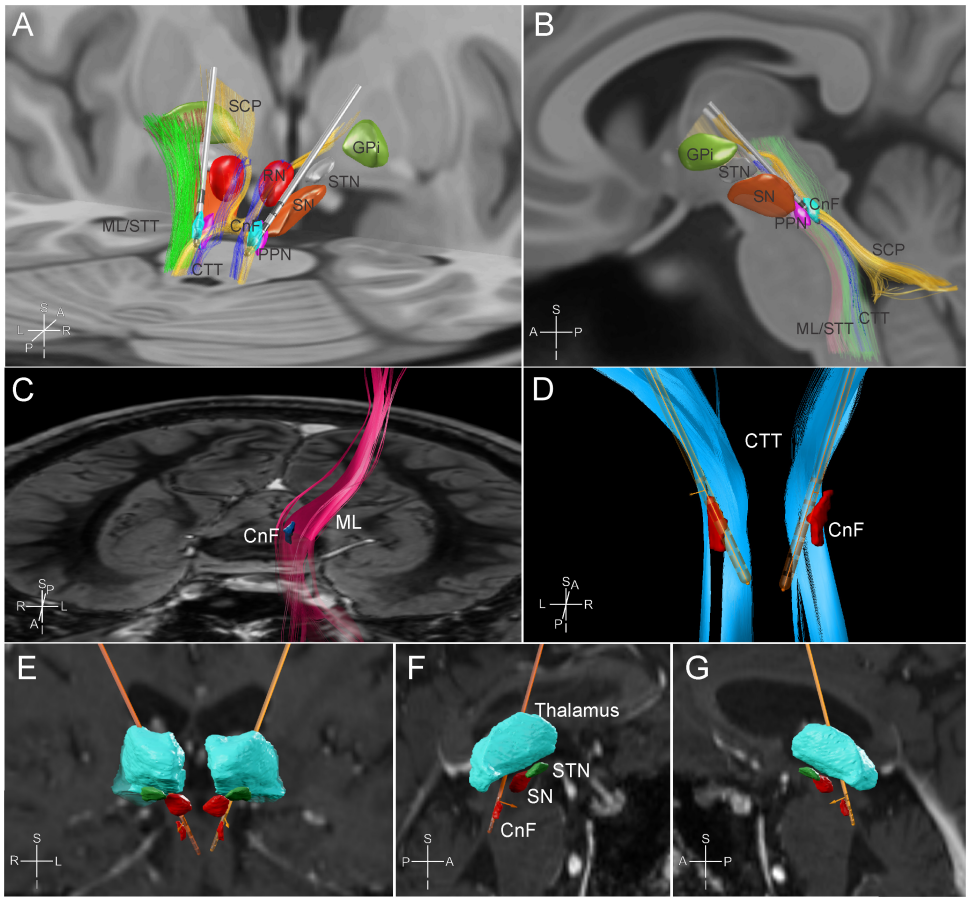

FIGURE 2 | MR tractography-based targeting of the cuneiform nucleus. Posterior oblique **(A)** and sagittal **(B)** views of a three-dimensional reconstruction of the regional anatomy and tractography based on available template atlases in Lead DBS (Horn and Kühn, 2015; Ewert et al., 2018; Yeh et al., 2018). A model of the Boston Scientific Vercise Cartesia™ directional electrode is placed in the field targeting the cuneiform nucleus bilaterally for demonstration. CnF, cuneiform nucleus; CTT, central tegmental tract; GPi, globus pallidus internus; ML, medial lemniscus; PPN, pedunculopontine nucleus; RN, red nucleus; SCP, superior cerebellar peduncle tracts; SN, substantia nigra; STN, subthalamic nucleus; STT, spinothalamic tract. **(C–G)** Subject specific tractography-based targeting, visualized in Brainlab Elements software (Brainlab AG, Munich, Germany). **(C)** Frontal view from above of subject's left medial lemniscus reconstruction (fuchsia) in relation to a preplanned estimate of the CnF target (blue) against a pons level axial slice of the brain. **(D)** Posterior view of the final electrode positions in relation to the estimated CnF target (red) and the subject's reconstructed central tegmental tracts (light blue). **(E)** Frontal and **(F,G)** sagittal views of the final electrode positions in relation to the thalamus, substantia nigra (SN), subthalamic nuclei (STN), and CnF (red).

0.6–2 mA. The most common side effect of stimulation reported by the subject was oscillopsia, occurring reproducibly in this region at 1.5–2.0 mA. Based on our intraoperative physiology, an octopolar directional DBS electrode (Vercise Cartesia™, Boston Scientific) was implanted to center the directional electrodes at the region that best elicited leg EMG oscillations. The same procedure was repeated for the left side, again with careful monitoring and control of blood pressure. After implantation of both electrodes, the patient was placed under general anesthesia, and the sub-clavicular generator and extension cables were placed to connect to the implanted leads.

Post-operative Management

The subject received a post-operative CT scan (1 mm slices) to identify electrode positions and to rule out hemorrhage. Systolic blood pressure control was relaxed to 140 mmHg and the subject was admitted overnight for monitoring. The subject was discharged the following day and scheduled for a clinic follow up visit 2 weeks after surgery for DBS programming by CL, IH, BN, and SC.

LFP Signal Processing

Local field potential (LFP) data captured using the NeuroSmart system (Alpha Omega Co., Alpharetta, GA, United States) were processed using MATLAB 9.9 R2020b (The Mathworks, Natwick, MA, United States) with custom written scripts. LFP data was sampled at 760 Hz and band-pass filtered between 1 and 250 Hz. Spectrograms were calculated using a short-time Fourier transform with 300 ms Kaiser windows and 50% overlap (Matlab function spectrogram) for each depth recorded near the target while the patient was at rest.

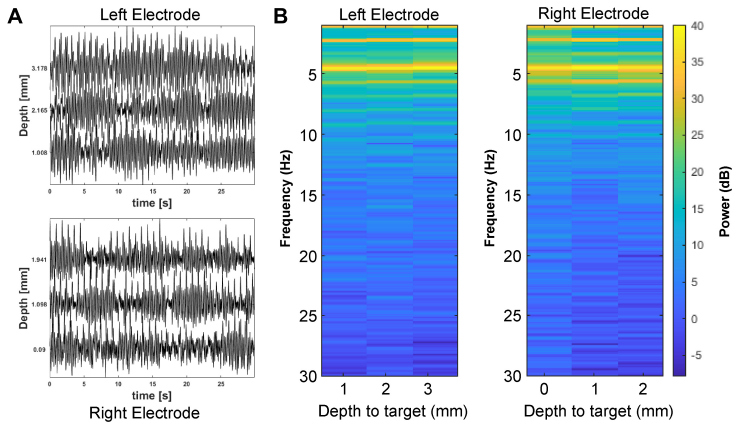

FIGURE 3 | Local field potential (LFP) recordings near the cuneiform nucleus. **(A)** Baseline LFP recordings from the left and right brainstem are shown for several depths approaching the planned electrode tip target. **(B)** LFP spectrograms are plotted for the left and right electrodes by distance to the planned electrode tip target.

Spectral-depth maps were created by first computing the power spectral density from 1 to 30 Hz using the multi-taper method using slepian tapers (Matlab pmtm function) at each recorded depth. The spectral densities were then aggregated into a matrix (with one column for each depth recorded) and data used to construct an image (Matlab imagesc function).

EMG Preprocessing and Feature Extraction

Surface EMGs were collected intraoperatively as European Data Format (.edf) files sampled at 256 Hz and pre-processed with a high-pass filter above 10 Hz using a 7th order Chebyshev filter in EDFbrowser (De Luca, 2003). These signals were then loaded into MATLAB 9.9 R2020b (The Mathworks, Inc., Natick, MA, United States) for feature extraction and analysis (Too et al., 2019). EMG characteristics analyzed included measures of amplitude (mean absolute value, enhanced mean absolute value, root-mean-square) and frequency (zero crossing, slope sign change SSC). The right *rectus femoris* was analyzed as a representative muscle in this preliminary study. An EMG spectral-depth map was created using the same method described for the LFPs, but for frequencies between 0 and 50 Hz.

Gait Assessments

For the Timed up and go test, the total time required for the subject to stand up from a chair, walk forward 3 m, turn around, walk back to the chair, and sit down, was recorded. For the turning tests, the patient made a complete 360° turn on the spot in either the clockwise or counterclockwise direction. The total time and the number of steps were recorded. For calculation of gait parameters, a 2-min walk test with turns was performed by the subject wearing Opal inertial measurement unit sensors (APDM Inc., Portland, OR, United States). Gait parameters were calculated using the Opal software (APDM, Inc., Portland, OR, United States) and include stride length and velocity, gait cycle time and cadence, percent of step cycle spent in swing vs. stance, arm and shank range of movement, turning time and the number of steps per turn, and the phase coordination index—a measure of bilateral coordination (Plotnik et al., 2007). Measures of gait variability were calculated from the individual gait cycle times and cadences.

Data Analysis

For all tests, an α threshold of 0.05 was set to determine statistical significance. RStudio was used to perform statistical analyses. Differences between the DBS ON and DBS OFF state were compared using a paired *t*-test.

RESULTS

As the nuclei comprising the MLR are reticular structures not easily visible with available MR sequences, surgeons have relied on the use of coordinate systems and anatomical landmarks to target these regions. Some surgeons have thus resorted to using a brainstem normalized coordinate system to account for individual differences in anatomy that might affect accurate targeting of this area (Goetz et al., 2019). Diffusion weighted imaging performed in our subject allowed us to estimate the tractography of known tracts in this region to adjust our initial target coordinates for this specific subject (**Figure 2**). Post-operative imaging revealed accurate positioning of leads at the designated targets.

Intraoperative LFP Recordings Near the Cuneiform Nucleus

Local field potential recordings were made with electrodes on each side at multiple depths approaching the cuneiform nucleus target. **Figure 3** shows the LFP recordings made with the microelectrode on each side during its advance to the planned electrode tip target, spanning the estimated location of the cuneiform nucleus. Recordings from this region with the subject at rest showed spectral power peaks in the theta

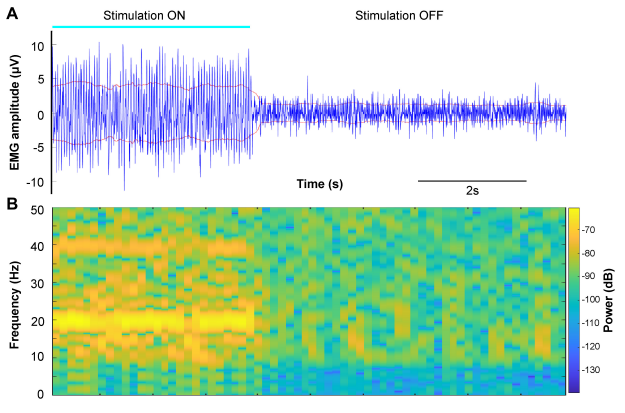

FIGURE 4 | Example of surface EMG changes during DBS of the cuneiform nucleus target. **(A)** Right rectus femoris surface EMG (blue) during and after cessation of stimulation (1 mA, 20 Hz, and 0.2 ms) near the cuneiform nucleus target. The root-mean-square envelope for the signal is shown in red. **(B)** Spectrogram of the EMG signal in panel **(A)**.

TABLE 1 | Changes in EMG features during intraoperative stimulation of the cuneiform nucleus.

EMG feature	Stimulation OFF (mean ± SD)	Stimulation ON (mean ± SD)	*P*-value
Mean absolute value	0.96 ± 0.04	3.68 ± 0.29	0.0033
Enhanced mean absolute value	0.90 ± 0.02	2.21 ± 0.11	0.0017
Root-mean-square	1.24 ± 0.06	4.56 ± 0.37	0.0037
Zero crossing	553.7 ± 21.1	325.3 ± 8.3	0.0019
Slope sign change	583.0 ± 19.0	509.3 ± 37.4	0.032

SD, standard deviation

range (4–8 Hz) bilaterally, common oscillatory frequencies that have been reported in association with the FOG phenomenon (Shimamoto et al., 2010; Chen et al., 2019; Marquez et al., 2020). Similar peaks in the beta (15–25 Hz) range were not observed.

Leg EMG Changes With Stimulation Near the Cuneiform Nucleus

In animal models, intraoperative electrical stimulation of the cuneiform nucleus elicits EMG activity and sometimes even visible limb movements, which can be used as a physiological biomarker for targeting this area (Takakusaki et al., 2016; Opris et al., 2019). Thus, we sought to see if similar responses could be elicited with electrical stimulation of this area in our subject (**Figure 4**). Stimulation of our estimated targets on both sides evoked involuntary EMG activity that was observed in each of the leg muscles recorded for the duration of stimulation, without gross leg movements. Spectral analysis demonstrated the presence of a strong peak at 20 Hz and multiples, the stimulation frequency (**Figure 4B**). This peak did not appear at lower amplitude stimulation, potentially suggesting a motor thresholding effect (**Supplementary Figure 1**). **Table 1** shows that the analyzed EMG features extracted from multiple DBS-ON and DBS-OFF epochs were significantly changed during intraoperative DBS of this target.

Stimulation-Induced Side Effects

Stimulation at higher current amplitudes induced side effects intraoperatively and in the clinic. The most significant and least tolerable side effect was oscillopsia, where the subject reported seeing objects in his entire visual field shaking. This was reliably reproduced with stimulation above certain thresholds and did not appear to dissipate over time; no gross movement of the eyes was perceptible. Notably, directing stimulation anteriorly reduced this side effect and increased the current threshold for evoking it by almost double, while posteriorly directed stimulation enhanced this phenomenon. Decreasing stimulation pulse width from 0.2 to 0.1 ms also alleviated this side effect, allowing significant increases to the current amplitude before it was encountered again. Other side effects described included a feeling of nasopharyngeal or ear fullness, headache, and nausea, each of which was better tolerated by the subject and which partially resolved over time.

Preliminary Results of Cuneiform Nucleus DBS in Freezing of Gait

The subject (male, 66 years old at surgery) was diagnosed with PD 6 years prior to surgery, with initial complaints of difficulty writing due to right-hand stiffness, which progressed to gait difficulties the following year. While he initially responded to levodopa therapy, his gait problems worsened to severe FOG resulting in falls and became refractory to levodopa medication. The subject's issues are primarily axial in nature.

Implantation of DBS leads was uneventful and without surgical complications. Although the subject did continue to

TABLE 2 | Preliminary gait testing results.

Gait test	Baseline (mean ± SD)	DBS ON (4 weeks) (mean ± SD)	*P*-value
Timed up and go	27.6 ± 2.2 s	15.6 ± 1.7 s	0.026
CW 360° turn (time)	27.1 ± 4.1 s	7.9 ± 1.2 s	0.024
CW 360° turn (steps)	21.0 ± 4.4	7.7 ± 1.2	0.046
CCW 360° turn (time)	47.4 ± 18.0 s	12.5 ± 4.4 s	0.069
CCW 360° turn (steps)	37.7 ± 11.4	11.0 ± 1.7	0.041
Gait parameters			
Stride length (m)	1.04 ± 0.20	1.24 ± 0.05	1.2×10^{-9}
Stride velocity (m/s)	0.685 ± 0.153	0.925 ± 0.079	1.5×10^{-14}
Gait cycle time (s)	1.53 ± 0.24	1.35 ± 0.11	1.6×10^{-6}
Gait cycle time variability	0.155	0.082	
Cadence (steps/min)	80.6 ± 16.3	89.5 ± 7.0	0.0002
Cadence variability	0.202	0.078	
Swing (%)	27.0 ± 3.9	32.7 ± 1.4	4.2×10^{-14}
Stance (%)	73.0 ± 3.9	67.3 ± 1.4	4.2×10^{-14}
Arm RoM (degrees)	19.1 ± 4.9	29.6 ± 6.8	$<2.2 \times 10^{-16}$
Shank RoM (degrees)	58.9 ± 10.4	66.8 ± 2.4	$<2.2 \times 10^{-16}$
Turning time (s)	9.4 ± 3.5	3.3 ± 0.5	0.0006
Steps per turn	12.3 ± 4.2	5.6 ± 0.7	0.001
Phase Coordination Index (%)	14.9	7.95	

CW, clockwise; CCW, counterclockwise; RoM, range of movement; SD, standard deviation.

experience falls after surgery, neither he nor his family members considered these to be above his prior baseline. **Table 2** compares the subject's baseline gait and turning to his 6-week post-operative visit (after 4 weeks of DBS ON). Significant improvements were seen in the timed up and go and turning tests, except for counterclockwise turn time, which showed a trend toward improvement. Gait and turning parameters during the 2-min walk test with DBS showed significant improvements in stride length and velocity, with reductions in gait variability (as measured by gait cycle time and cadence) and phase coordination index (better bilateral coordination). Notably, turning time and the steps per turn decreased significantly (**Supplementary Video 1**).

DISCUSSION

Although numerous studies have targeted the MLR in PD patients over the past 15 years as a potential site for neuromodulation to alleviate gait deficits, few have looked to optimize target selection or electrode positions to maximize this effect. Furthermore, no other groups have used the more recently available directional electrode technology in this region, where the ability to steer current in specific directions could be helpful in minimizing the activation of unrelated fiber tracts passing through the region. Based on many electrical mapping studies (Shik et al., 1966; Eidelberg et al., 1981; Takakusaki et al., 2016; Opris et al., 2019; Chang et al., 2021), as well as more recent optogenetic studies of the MLR (Caggiano et al., 2018; Josset et al., 2018; Dautan et al., 2020), we proposed to target the cuneiform nucleus, rather than the traditionally targeted PPN.

We used the subject's regional DTI tractography to refine our pre-determined brainstem normalized coordinates for this target, since this region does not have clear boundaries on T1- or T2-weighted MR imaging (Zrinzo et al., 2008; Shimamoto et al., 2010; Cong et al., 2018). LFP recordings near our target during rest demonstrated an obvious peak in the theta range, consistent with some prior literature in PD patients with gait freezing in the PPN (Shimamoto et al., 2010) and in the STN (Chen et al., 2019). We did not observe a peak in the beta range, as has been reported in some electrophysiological studies of the PPN (Weinberger et al., 2008; Shimamoto et al., 2010), although at least one PPN study did not find LFP peaks in the beta range (Androulidakis et al., 2008), with no clearly accepted physiological markers of the PPN during MER mapping (Molina et al., 2020). Taking a cue from animal studies of CnF stimulation, we recorded limb EMGs during stimulation of our target. In these studies, it has been demonstrated that MLR stimulation frequency controls locomotor speed and frequency of locomotor movements (Sirota et al., 2000; Cabelguen et al., 2003; Chang et al., 2021). The ability to evoke involuntary EMG oscillations in the subject's legs with a power peak at the stimulation frequency was encouraging as a potential biomarker for the target and has not previously described in humans. Mechanistically, this may involve the activation of descending reticulospinal and monoaminergic pathways that are classically described as being controlled by the MLR in cats (Noga et al., 2003, 2017).

Stimulation near our predicted cuneiform target also elicited side effects at higher currents, with oscillopsia being the most prominent. Notably, this side effect has been described previously with PPN DBS (Ferraye et al., 2009; Jenkinson et al., 2012), with stimulation of the oculomotor nerve (Ferraye et al., 2009), the superior cerebellar peduncle and cerebellar uncinate fasciculus (Jenkinson et al., 2012), and the medial longitudinal fasciculus proposed as potential causes (Fournier-Gosselin et al., 2013). Based on our finding using directional electrodes that posteriorly directed stimulation enhanced this effect while anteromedially directed stimulation ameliorated it, involvement of the trochlear nerve as it courses posteriorly and laterally around the inferior colliculus appears to fit best with the regional anatomy, rather than the oculomotor nerve (superomedial), the superior cerebellar peduncle (medial), or the medial longitudinal fasciculus (medial). Our subject's reported feeling of nasopharyngeal or ear fullness may relate to stimulation of the nearby mesencephalic nucleus of the trigeminal nerve, which is known to receive proprioceptive afferent input from the nose, palate, and teeth (Linden, 1978).

There are important limitations to our study. Due to the COVID-19 pandemic, we have currently implanted only one subject in our study, with only preliminary gait data. We also did not stimulate points outside of the CnF to definitively rule out DBS artifact in the EMG recordings, though stimulation at lower amplitudes suggested a motor threshold. Future subjects will help us determine if this is a true biomarker of the region or a DBS artifact. Furthermore, while our subject's improvements in gait and turning parameters after DBS are promising, our pilot study is primarily designed to demonstrate safety and feasibility. Future, larger studies based on this one may be able to confirm efficacy in improving gait dysfunction associated with conditions such as PD, spinal cord injury, or stroke. Interestingly, our subject is able to reliably detect when stimulation is turned on, stating that his legs feel like they "want to go." This unfortunately makes it difficult to blind the subject to DBS during gait testing to control for potential placebo effects, a known challenge in designing effective neuromodulation studies (Boakye et al., 2021).

CONCLUSION

We describe the first implantation of directional electrodes in the human MLR and the first deliberate targeting of the more posteriorly located cuneiform nucleus in a subject with PD and refractory FOG, as part of a pilot study. Targeting was guided by the subject's regional DTI tractography and intraoperative physiology suggested similarities to observations in animal studies of the cuneiform nucleus. Our study provides evidence that a functional homolog to the cuneiform nucleus exists in humans and can be safely targeted for DBS.

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 human participants were reviewed and approved by University of Miami Human Subject Research Office. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JJ is the principal investigator and performed surgery. SC drafted the manuscript and created the Figures. SC, IC, and CL collected the data. SC and IC analyzed the data. All authors were involved in the conception and design of the study as well as the reviewing and editing of the manuscript and read and approved the final manuscript.

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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.2021.676755/full#supplementary-material

Supplementary Figure 1 | (A) EMG spectrogram from same representative muscle in **Figure 4** during stimulation at 0.2 mA, 20 Hz, and 0.2 ms with no obvious power peak. **(B)** EMG spectrogram from the same muscle during stimulation at 0.4 mA, 20 Hz, and 0.2 ms, beginning to show a power peak at 20 Hz.

Supplementary Video | 360° turn at pre-operative baseline and after surgery with and without CnF DBS.

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Globus Pallidus Internus Deep Brain Stimulation for Dystonic Opisthotonus in Adult-Onset Dystonia: A Personalized Approach

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Introduction: Dystonic opisthotonus is defined as a backward arching of the neck and trunk, which ranges in severity from mild backward jerks to life-threatening prolonged severe muscular spasms. It can be associated with generalized dystonic syndromes or, rarely, present as a form of axial truncal dystonia. The etiologies vary from idiopathic, genetic, tardive, hereditary-degenerative, or associated with parkinsonism. We report clinical cases of dystonic opisthotonus associated with adult-onset dystonic syndromes, that benefitted from globus pallidus internus (GPi) deep brain stimulation (DBS).

Methods: Clinical data from patients with dystonic syndromes who underwent comprehensive medical review, multidisciplinary assessment, and tailored medical and neurosurgical managements were prospectively analyzed. Quantification of dystonia severity pre- and postoperatively was performed using the Burke-Fahn-Marsden Dystonia Rating Scale and quantification of overall pain severity was performed using the Visual Analog Scale.

Results: Three male patients, with age of onset of the dystonic symptoms ranging from 32 to 51 years old, were included. Tardive dystonia, adult-onset dystonia-parkinsonism and adult-onset idiopathic axial dystonia were the etiologies identified. Clinical investigation and management were tailored according to the complexity of the individual presentations. Although they shared common clinical features of adult-onset dystonia, disabling dystonic opisthotonus, refractory to medical management, was the main indication for GPi-DBS in all patients presented. The severity of axial dystonia ranged from disturbance of daily function to life-threatening truncal distortion. All three patients underwent bilateral GPi DBS at a mean age of 52 years (range 48–55 years), after mean duration of symptoms prior to DBS of 10.7 years (range 4–16 years). All patients showed a rapid and sustained clinical improvement of their symptoms, notably of the dystonic opisthotonos, at postoperative follow-up ranging from 20 to 175 months. In some, the ability to resume activities of daily living and reintegration into the society was remarkable.

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Conclusion: Adult-onset dystonic syndromes predominantly presenting with dystonic opisthotonus are relatively rare. The specific nature of dystonic opisthotonus remains a treatment challenge, and thorough investigation of this highly disabling condition with varying etiologies is often necessary. Although patients may be refractory to medical management and botulinum toxin injection, Globus pallidus stimulation timed and tailored provided symptomatic control in this cohort and may be considered in other carefully selected cases.

Keywords: axial dystonia, movement disorders, globus pallidus internus, deep brain stimulation, opisthotonus

INTRODUCTION

Adult-onset truncal dystonia (ATD) is more frequently reported in the context of severe segmental and generalized dystonic syndromes, and rarely as an isolated presentation of dystonia (Bhatia et al., 1997; Benecke and Dressler, 2007; Albanese et al., 2013; Lizarraga and Fasano, 2019). It accounts for about 10% of segmental dystonia and affects predominantly the trunk, including the paraspinal and abdominal wall muscles, with sparing or minimal involvement of the limbs and occasional contiguous spread to the cranio-cervical junction (Jabbari et al., 1992; Bhatia et al., 1997; Albanese et al., 2013; Shaikh et al., 2014). ATD is a major source of disability, occurring in either anteroflexion, retroflexion, lateroflexion or combined, and usually worsens with action or voluntary movement (Lizarraga and Fasano, 2019). A non-fixed forward bending of the trunk (>45 degrees) caused by hyperactivation of the rectus abdominis muscles is defined as camptocormia, which is the most common presentation of idiopathic ATD (Bhatia et al., 1997; Ehrlich and Frucht, 2016), although also described in association with Parkinson's disease (Azher and Jankovic, 2005). Another form of ATD is the dystonic opisthotonus, which is characterized by a backward arching of the trunk and neck due to overactivation of the paraspinal extensor muscles (Bhatia et al., 1997; Benecke and Dressler, 2007; Ehrlich and Frucht, 2016). A less common presentation of ATD is the reversible lateral bending of the trunk, with a tendency to lean to one side, sometimes described as Pisa syndrome (Bhatia et al., 1997; Barone et al., 2016; Ehrlich and Frucht, 2016; Lizarraga and Fasano, 2019).

In terms of etiology, ATD is highly heterogeneous (Jabbari et al., 1992; Bhatia et al., 1997; Benecke and Dressler, 2007; Shaikh et al., 2014; Selikhova et al., 2015). It has been observed in genetic, idiopathic and acquired dystonic syndromes (Jabbari et al., 1992; Bhatia et al., 1997; Shaikh et al., 2014; Selikhova et al., 2015; Lizarraga and Fasano, 2019), and can have central and peripheral etiologies. It may be associated with parkinsonism and neuromuscular disorders (Stamelou et al., 2013; Lizarraga and Fasano, 2019) as well as with neuroleptic-induced acute and tardive dystonia (Bhatia et al., 1997; Benecke and Dressler, 2007; Barone et al., 2016).

Although botulinum toxin injections are generally the treatment of choice for adult-onset focal and segmental dystonia, the response of ATD to medical treatment, including botulinum toxin, is often limited due to the large number of muscles involved and consequently high total toxin dose required to produce the relevant clinical benefit (Bhatia et al., 1997; Benecke and Dressler, 2007; Zittel et al., 2009; Cloud et al., 2014; Shaikh et al., 2014; Mehta et al., 2020). Deep brain stimulation (DBS) in the treatment of generalized and segmental dystonia is now supported by robust evidence (Fox and Alterman, 2015). Nevertheless only few reports have specifically addressed the potential role of DBS in the management of dystonic opisthotonus in the context of truncal predominant adult-onset dystonia (Lizarraga and Fasano, 2019). Here we describe three cases of medically refractory ATD, where disabling dystonic opisthotonus was the main indication for bilateral globus pallidus internus (GPi) DBS.

MATERIALS AND METHODS

All three patients underwent comprehensive pre-operative multidisciplinary assessment prior to DBS intervention. Quantification of dystonia severity was performed using the Burke-Fahn-Marsden dystonia rating scale (BFMDRS; Burke et al., 1985). Quantification of overall pain severity was performed using the Visual Analog Scale (VAS). Quadripolar Medtronic 3389 DBS electrodes (Medtronic Inc., Minneapolis, MN, United States) were implanted in the GPi under general anesthesia as previously described (O'Gorman et al., 2011). The standard procedure consisted of preoperative stereotactic magnetic resonance imaging (MRI), using a 1.5 T General Electric (GE) MRI scanner (GE Healthcare, Chicago, IL, United States) or a 1.5 T Siemens MRI scanner (Siemens, Erlangen, Germany) on the day of surgery. MRI sequences for surgical planning and acquisition of the stereotactic coordinates consisted of volumetric T1-weighted and proton density-weighted scan for optimal visualization of the GPi, using a repetition time (TR) of 5,630 ms, an echo time (TE) of 15 ms, a slice thickness of 2 mm, field of view (FoV) of 250 mm, flip angle of 250 degrees, base resolution of 256 mm, and a voxel size of 0.5 mm × 0.5 mm × 2 mm. Stereotactic planning was based on the direct visualization of the targeted structure on the proton density sequence, where the posterior one-third of the ventral GPi was targeted for electrode placement. Microelectrode recording was not used in these cases. Surgery was performed in two stages, i.e., insertion of the intracranial leads (3389 electrodes, Medtronic Inc., United States) using the Leksell G frame (Elekta, Sweden), followed by placement of extensions and an implantable pulse generator (Medtronic Inc., United States)

on the same day. Verification of the final position of the electrodes was performed with a postoperative high-definition computed tomography imaging of the head using an Optima 660 CT scanner (GE Healthcare, Chicago, IL, United States). Image processing and segmentation of the DBS leads were performed on LEAD-DBS software (Horn and Kühn, 2015; Edlow et al., 2019). Patients were assessed on a regular basis post-operatively in the multidisciplinary DBS clinic.

This study was approved by our institution's Research Advisory Group and written informed consent was obtained from all patients. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients gave consent to be videoed for publication both in print and online.

RESULTS

Three male patients with medically refractory ATD and severe dystonic opisthotonus, who had undergone GPi-DBS, were studied. The age at diagnosis ranged from 32 to 51 years and the mean duration of symptoms prior to surgery was 10.7 + 5.7 years (range 4–16 years). At the time of surgical treatment patients were 48 to 55 years old. The follow-up period ranged from 20 to 175 months. **Table 1** summarizes the baseline characteristics, pharmacotherapy, stimulation settings, and outcomes. **Figure 1** demonstrates the final position of the electrodes within the bilateral posteroventral GPi.

Case 1

This 67-year-old man was diagnosed with severe tardive dystonia at the age of 43 years, following 9 years of neuroleptic treatment for schizophrenia. His psychiatric disorder had been fully controlled for many years. Over the subsequent 12 years, blepharospasm, facial grimacing and limb dyskinesia were mild, but he had much more severe and disabling dystonic opisthotonus. He could only mobilize with a *geste antagoniste* by voluntarily flexing his trunk forward to 90 degrees. Neuroradiological and biochemical work-up were unremarkable. Preoperative BFMDRS-M score was 34.

Attempts to treat him with clozapine and quetiapine were unhelpful due to sleepiness. Low dose Olanzapine could not be withdrawn as this led to persecutory ideas returning. After further follow-up by both neurologists and psychiatrists, and no evidence of active psychiatric symptoms, bilateral GPi DBS was carefully discussed in our MDT. The patient was 55 years old when surgery was performed. Dramatic improvements of his symptoms were noted upon electrical stimulation starting from the next day (**Supplementary Video 1**, segments 1 and 2). Over the next few months, his quality of life improved to the extent that he was able to participate in social activities, including for the first time in many years going to restaurants, and to spectate at family, school and sports fixtures. During the first 2 years the stimulations settings had to be adjusted at times, until stable and satisfactory response was finally achieved. The stimulation settings have been stable for the last 7 years. At the last follow up appointment (144 months), he had minimal evidence of retrocollis or abnormal truncal movements. Improvements of 77.9% in BFMDRS-M and 100% in VAS scores were noted. Detailed pre- and postoperative outcome scores, including BFMDRS subscores for trunk and neck are presented in **Table 1**.

Case 2

This 56-year-old man developed progressive trunk hyperextension, with backward spasms and lateral flexion over a period of 6 months. The onset of his symptoms was at the age of 51 years, without any prior medical history. He also had intermittent chin tuck while sitting and, mild tongue protrusion and involuntary backwards jerking of his neck. Truncal retroflexion was significantly aggravated on walking, and only modestly relieved by *geste antagoniste*, such as by touching the back of his head or leaning against the wall. Extensive investigations for structural and inflammatory causes did not confirm a diagnosis. Botulinum toxin to the posterior neck muscles was helpful for neck spasms, but the arching back was felt to be too extensive to treat with botulinum injections.

Combinations of medical treatment were unhelpful. A short trial of low dose olanzapine was successful in suppressing his truncal retroflexion, but he quickly developed new parkinsonian side effects of limb bradykinesia, rigidity and jaw tremor. Stopping olanzapine resolved parkinsonism but at the expense of return of original truncal retroflexion. A DaT-scan showed bilateral nigrostriatal dysfunction, which we did not feel was attributable to his medications, nor was this a typical initial presentation of parkinsonism – dystonia.

Genetic tests including for ATP1A3 (DYT12), PANK2, PLA2G6, Wilson's and a further search for the possibility of hitherto undisclosed intake of dopaminergic antagonists were not helpful. No Philippines ancestry was noted. On the rare possibility that the DaT-scan was an erroneous false positive, it was repeated and again showed bilaterally reduced uptake in the striatum. Consideration to adult-onset dopamine transporter deficiency syndrome was given, despite his age. CSF analysis for HVA/5HIAA and neurotransmitters was normal. A minor abnormality in CSF folate metabolism was discounted as relevant because a trial period of Folinic acid supplementation was unhelpful. SLC6A3 and whole genome sequencing were negative. Muscle biopsy was negative for mitochondrial disease. Levodopa had little benefit and a trial of dopamine agonist significantly exacerbated the dystonia. We cannot formally diagnose this disorder, so it is presently pragmatically labeled as adult-onset dystonia-parkinsonism. Preoperative BFMDRS-M score was 26.

Bilateral GPi DBS was carried out at the age of 55 years. The patient presented a remarkable improvement of his symptoms on the first postoperative day, likely due to microlesioning effect, which lasted around 3 weeks (**Supplementary Video 1**, segments 3 and 4). In the monopolar review he presented marked bilateral akinesia or worsening of the truncal dystonia with higher stimulation amplitudes. Nevertheless, further adjustments of the stimulation settings during the following 12 months led to complete resolution of the retrocollis and

TABLE 1 | Patient features, stimulation settings, and outcome.

	Case 1	Case 2	Case 3
Diagnosis	Neuroleptic induced tardive dyskinesia and dystonia	Adult-onset dystonia parkinsonism	Primary adult-onset axial dystonia
Age at diagnosis (years)/Gender	43/Male	51/Male	32/Male
Age at surgery (years)	55	55	48
Disease duration (years)	12	4	16
Medications pre-DBS (total daily dose)	Baclofen 70 mg, clonazepam 1,500 μg, olanzapine 7.5 mg	Baclofen 60 mg, procyclidine 15 mg, co-careldopa 625 mg, lorazepam 4 mg	Zopiclone 30 mg, tramadol 400 mg, benzhexol 2 mg, baclofen 20 mg, tetrabenazine 25 mg, oxazepam 120 mg
Medications post-DBS at last follow-up (total daily dose)	Baclofen 50 mg, clonazepam 1,000 μg, olanzapine 7.5 mg	Baclofen 60 mg, procyclidine 15 mg, co-careldopa 625 mg, Lorazepam 4 mg	Tramadol 400 mg, zopiclone 30 mg
Time to last follow-up (months)	144	20	175
Stereotactic coordinates (tip of the electrode verified postoperatively; mm)	AC-PC length = 24.34	AC-PC length = 24.70	AC-PC length = 27.41
	Left: $x = -22.7$; $y = 3.1$; $z = -4.4$	Left: $x = -19.2$; $y = -0.4$; $z = -4.0$	Left: $x = -21.9$; $y = -0.2$; $z = -4.0$
	Right: $x = 21.9$; $y = 1.2$; $z = -2.8$	Right: $x = 22.2$; $y = -2.1$; $z = -3.0$	Right: $x = 20.3$; $y = -0.4$; $z = -3.0$
Initial Stimulation settings	Left: C + 1-; 1.5 V, 60 ms, 130 Hz	Left: C + 2-; 0.5 V, 450 ms, 130 Hz	Left: C + 2-; 1.0 V, 450 ms, 130 Hz
	Right: C + 5-, 1.5 V, 60 ms, 130 Hz	Right: C + 10-, 0.5 V, 450 ms, 130 Hz	Right: C + 6-, 1.0 V, 450 ms, 130 Hz
Stimulation settings at 1-year follow-up	Left: C + 1-; 2.5 V, 60 ms, 130 Hz	Left: C + 1–2-; 0.5 V, 360 ms, 130 Hz	Left: C + 1–2-; 2.0 V, 450 ms, 140 Hz
	Right: C + 5-, 2.5 V, 60 ms, 130 Hz	Right: C + 10– 9-, 0.5 V, 360 ms, 130 Hz	Right: C + 5– 6-, 2.0 V, 450 ms, 140 Hz
Stimulation settings at last follow-up	Left: C + 1-; 3.5 V, 90 ms, 130 Hz	Left: C + 1–2-; 0.5 V, 360 ms, 130 Hz	Left: C + 0–1–2-; 1.8 V, 450 ms, 140 Hz
	Right: C + 5-, 3.5 V, 90 ms, 130 Hz	Right: C + 5-, 0.5 V, 360 ms, 130 Hz	Right: C + 4–5– 6-, 1.7 V, 450 ms, 140 Hz
	IPG Kinetra (eventually replaced by Activa PC)	IPG Activa PC	IPG Kinetra (eventually replaced by Activa PC)
Preoperative BFMDRS-M	Preoperative: 34	Preoperative: 26	Preoperative: 36
Postoperative BFMDRS-M (1-yr FU)	Postoperative: 9.5	Postoperative: 7.5	Postoperative: 10
% improvement BFMDRS-M (1-yr FU)	Improvement: 72	Improvement: 71.2	Improvement: 72.2
Postoperative BFMDRS-M (last FU)	Postoperative: 7.5	Postoperative 7.5	Postoperative: 4
% improvement BFMDRS-M (last FU)	Improvement: 77.9	Improvement 71.2	Improvement: 88.9
Preoperative BFMDRS-D	Preoperative: 9	Preoperative: 5	Preoperative: 13
Postoperative BFMDRS-D (1-yr FU)	Postoperative: 4	Postoperative: 2	Postoperative: 5
% improvement BFMDRS-D (1-yr FU)	Improvement: 55.6	Improvement: 60	Improvement: 61.5
Postoperative BFMDRS-D (last FU)	Postoperative: 4	Postoperative: 2	Postoperative: 4
% improvement BFMDRS-D (last FU)	Improvement: 55.6	Improvement: 60	Improvement: 69.2
Preoperative Subscores for neck	Preoperative: 8	Preoperative: 8	Preoperative: 8
Postop. subscores for neck (1-yr FU)	Postoperative: 2	Postoperative: 2	Postoperative: 1
% improvement subscore (1-yr FU)	Improvement: 75	Improvement: 75	Improvement: 87.5
Postop. subscores for neck (last FU)	Postoperative: 0	Postoperative: 2	Postoperative: 1
% improvement subscore (last FU)	Improvement: 100	Improvement: 75	Improvement: 87.5
Preoperative Subscores for trunk	Preoperative: 16	Preoperative: 12	Preoperative: 16
Postop. subscores for trunk (1-yr FU)	Postoperative: 2	Postoperative: 3	Postoperative: 6
% improvement subscore (1-yr FU)	Improvement: 87.5	Improvement: 75	Improvement: 62.5
Postop. subscores for trunk (last FU)	Postoperative: 0	Postoperative: 3	Postoperative: 1
% improvement subscore (last FU)	Improvement: 100	Improvement: 75	Improvement: 93.7
Preoperative VAS	Preoperative: 8/10	Preoperative: 8/10	Preoperative: 8/10
Postoperative VAS	Postoperative: 0/10	Postoperative: 4/10	Postoperative: 3/10
% improvement VAS (last FU)	Improvement: 100	Improvement: 50	Improvement: 62.5

DBS, deep brain stimulation; BFMDRS-M, motor component of Burke-Fahn-Marsden Dystonia Rating scale; BFMDRS-D, disability component of Burke-Fahn-Marsden Dystonia Rating Scale; VAS, visual analog scale for pain; 1-yr FU, outcome at 1-year follow-up; and last-FU, outcome at last follow-up appointment.

about 65% improvement of his truncal hyperextension. At last postoperative follow-up (20 months), the dystonic opisthotonus and lateral bending were satisfactorily controlled, allowing independent mobility with near abolition of the involuntary neck and back jerks. An improvement of 71.2% in BFMDRS-M and 50% in VAS scores were noted. Detailed BFMDRS subscores for neck and trunk are presented in **Table 1**.

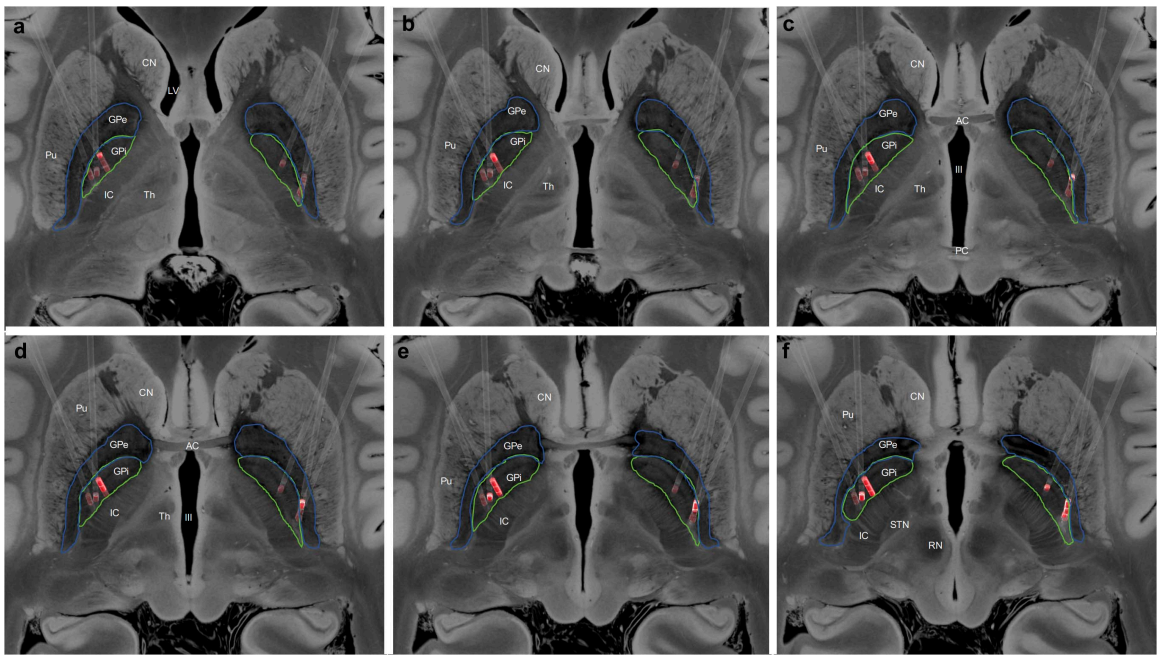

FIGURE 1 | (a–f) Localization of the deep brain stimulation (DBS) electrodes, in standard space, for all patients. The Globus pallidus internus (GPi, green) and Globus pallidus externus (GPe, blue) have been manually segmented, and the active electrode contacts highlighted in red. CN, Caudate Nucleus; LV, Lateral Ventricle; Pu, Putamen; IC, Internal Capsule; Th, Thalamus; AC, Anterior Commissure; PC, Posterior Commissure; III, Third Ventricle; STN, Subthalamic Nucleus; and RN, Red Nucleus.

Case 3

This 62-year-old man was diagnosed with idiopathic adult-onset axial dystonia at the age of 32 years. Initial symptoms were blepharospasm, minor swallowing symptoms and torticollis, which responded to Botulinum toxin injections. Within 16 years, his dystonia progressed to profound axial trunk dystonia with worsening balance, falling backwards and requiring a wheelchair to mobilize because of the severe dystonic opisthotonus. When standing, he could only walk with his trunk flexed and hands on his knees, and he transferred by crawling. Multiple investigations for etiologies were negative and medical therapies were largely ineffective for his truncal retroflexion. Levodopa worsened his symptoms. Genetic testing did not identify a diagnosis. Preoperative BFMDRS-M score was 36.

Bilateral GPi DBS was implanted at 48 years of age. Immediate blepharospasm improvement and gradual resolution of back jerks were noted with therapy initiation. Over the next few months, axial dystonia control was achieved, allowing him to sit, walk straighter and for longer distances (**Supplementary Video 1**, segments 5 and 6). He was able to perform daily activities as well as return to driving. Following surgery, the optimization phase of DBS settings took around 12 months to reach stable settings and good control of dystonic symptoms. However, following a DBS battery change at 7 years follow-up, he presented with worsening of the retrocollis, which resolved after further adjustments of the stimulation parameters. Investigation with neuroimaging did not reveal any sings of electrode displacement. The DBS settings have been stable since then. At last follow-up (175 months), his dystonic symptoms were well controlled with an 88.9% improvement in the BFMDRS-M and 62.5% in the VAS scores.

DISCUSSION

Dystonia is one of the most disabling movement disorders, having a significant impact on the patient's quality of life (Fox and Alterman, 2015; Rodrigues et al., 2019). Rehabilitation and medical management along with local botulinum toxin injections are the treatment of choice in focal dystonia (Albanese and Lalli, 2012; Ehrlich and Frucht, 2016). Since segmental and generalized forms of dystonia may not respond well to pharmacological therapies, there has been growing interest and expansion in the application of bilateral neuromodulation of deep brain structures in the management of these challenging conditions (Zittel et al., 2009; Martínez et al., 2014; Shaikh et al., 2014; Fox and Alterman, 2015; Tambirajoo et al., 2020; Furlanetti et al., 2021). ATD is more frequently reported in the context of severe segmental and generalized dystonic syndromes, and rarely as an isolated presentation of dystonia (Bhatia et al., 1997; Benecke and Dressler, 2007; Albanese et al., 2013; Lizarraga and Fasano, 2019).

Adult-onset dystonic opisthotonus as a main feature is rare and has been described as a "red-flag" sign for drug-induced dystonia, neurometabolic disorders (Wilson Disease, Lesch-Nyhan Syndrome, Maple syrup urine disease) and neurodegeneration with brain iron accumulation (NBIA; Stamelou et al., 2013). The clinical management of ATD, including forms presenting predominantly with trunk and neck

hyperextension is challenging as it often fails to respond to toxin injection (Benecke and Dressler, 2007). Bhatia el al reported a historical cohort of 18 patients with axial adult-onset primary dystonia, where 55% of patients had trunk anteroflexion, 22% trunk hyperextension, and 5.6% lateral bending. The overall response to medical treatment was poor, where only 16.6% had moderate and 22% had pronounced improvement (Bhatia et al., 1997). In line with this, Comella et al. reported their experience in the management of dystonic opisthotonus with botulinum toxin in 5 patients. The mean overall improvement in truncal dystonia subscore was 37%, which was also associated with reduction of pain (Comella et al., 1998).

Deep brain stimulation is now well established as an effective treatment in primary generalized, segmental and cervical dystonia (Eltahawy et al., 2004; Andrews et al., 2010; Koy et al., 2013; Vidailhet et al., 2013; Fox and Alterman, 2015; Moro et al., 2017; Lizarraga and Fasano, 2019; Rodrigues et al., 2019). There is, however, little literature on its effectiveness on medically refractory ATD (Nandi et al., 2002; Sakas et al., 2010; Capelle et al., 2011; Shaikh et al., 2014; Lizarraga and Fasano, 2019; Mohd Fauzi et al., 2019; Rodrigues et al., 2019).

Our clinical study aimed to evaluate the role of bilateral GPi-DBS in the management of adult-onset dystonic opisthotonus in the context of trunk predominant dystonia. Although our patients presented with generalized dystonic symptoms, affecting not only the trunk but to a minor extent also the cranio-cervical and brachial regions, the dystonic opisthotonus was the main disabling problem, and therefore the indication for surgical treatment. The exemplary clinical cases presented cover a range of etiologies, which demanded varying degrees of investigation. The first patient had clear diagnosis of a tardive dystonic syndrome, whereas the etiologies for the remaining two cases could not be determined, despite of extensive neuroradiological and genetic testing. Additionally, we describe the impact of severe dystonic symptoms on each individual patient, including social functioning, as well as difficulties encountered in overall clinical and surgical managements.

Tardive dystonia is a complication of the chronic exposure to dopamine receptor blocking agents (Truong and Frei, 2019). The more common stereotypical movements occur in 15–20% of patients on neuroleptics and dystonic movements occur in 1–4% (Raja, 1995; Adityanjee et al., 1999). The remission rate is less than 15% and occurs on average 2.6 years after discontinuation of the causative agent (Cloud et al., 2014). It is associated with a high incidence of morbidity and mortality (Youssef and Waddington, 1987). GPi DBS has been reported to improve tardive dystonia by more than 90% (Trottenberg et al., 2005; Cohen et al., 2007; Gruber et al., 2009; Shaikh et al., 2015). Our case adds to previous evidence, emphasizing the need for meticulous neurological and psychiatric evaluation before, during and after DBS.

Dystonia is also reported to occur in 30% of patients with Parkinson's disease (PD; Kidron and Melamed, 1987). It is commonly observed in young onset PD and autosomal recessive genetic parkinsonism (LeWitt et al., 1986; Shetty et al., 2019). The underlying pathophysiological mechanism is poorly understood. The dystonia may be a presenting symptom of PD and can precede the typical clinical symptoms of PD by up to a decade (Tolosa and Compta, 2006). Response to dopamine replacement therapy in early dystonia is variable (LeWitt et al., 1986). Additionally, levodopa therapy in itself can cause dystonia (Monville et al., 2009; Shetty et al., 2019). GPi DBS is usually an effective treatment for both dystonia and parkinsonism in Parkinson's patients (Lizarraga and Fasano, 2019; Shetty et al., 2019). Despite extensive investigations, the diagnosis in case 2 described here remains uncertain. The abnormal DaT-scan and certain clinical features emerging later suggest parkinsonism but to the best of our knowledge, dystonic opisthotonus as an isolated initial symptom of PD is rare (Lizarraga and Fasano, 2019).

Despite of initial poor response to medical management, toxin injection and rehabilitation therapies, all patients showed rapid and long-lasting responses to bilateral GPi-DBS. The overall percentage improvement in the BFMRDS at 1-year ranged from 63.8 to 66.8%, improving to 66.7–79% in the long-term follow-up (**Table 1**). Furthermore, all patients had considerable improvement with respect to dystonic pain at the long-term follow-up (VAS% improvement, range 50–100%, **Table 1**). Given that the overall BFMDRS may not accurately reflect the impact of the GPi-DBS on the axial symptoms, we further analyzed the BFMDRS sub-scores for neck and trunk, showing an even greater impact of DBS at the last follow-up, with 75–100% improvement.

These findings are in line with previous reports of ATD successfully treated with DBS (Nandi et al., 2002; Sakas et al., 2010; Capelle et al., 2011; Shaikh et al., 2014; Lizarraga and Fasano, 2019; Mohd Fauzi et al., 2019). In a single case report of a patient with flexion and lateral flexion subtypes, Zittel et al. (2009) showed alleviation of the axial dystonia by GPi DBS. In another series of 4 patients with both flexion and extension subtypes, BFMDRS scores improved by 30% in the first month and over 80% at 2 years (Shaikh et al., 2014). The authors noted that a higher voltage and longer pulse width correlated with better outcomes (Zittel et al., 2009; Shaikh et al., 2014). In their systemic review, Lizarraga et al. recently highlighted varied response rates of trunk postural deformities to DBS. Thus, improvement was noted as 59% in Parkinsonian camptocormia, 50–100% in dystonic camptocormia and 33–66.7% in Parkinsonian Pisa syndrome (Lizarraga and Fasano, 2019). Interestingly, only 2 cases of truncal and neck hyperextension were identified, both in patients with onset of dystonia during childhood, underpinning the rarity of ATD with predominant dystonic opisthotonus (Sakas et al., 2010; Mohd Fauzi et al., 2019). Mohd Fauzi et al. (2019) described a 25-year-old patient with generalized dystonia and predominantly severe neck and trunk hyperextension associated with NBIA, who underwent bilateral GPi-DBS, obtaining a rapid response and 83.3% improvement in BFMDRS trunk subscores, at 2-year-follow-up. Sakas et al. (2010) reported a 29-year-old male with previous history of perinatal hypoxia, confined to bed since the age of 9 years, due to severe dystonic opisthotonus. The patient underwent bilateral GPi-DBS with 61.5% overall improvement in BFMDRS. Due to his long-standing severe dystonic syndrome and some degree of skeletal deformities, the fixed component of dystonia did not improve completely after DBS, as also previously reported (Jankovic, 2008; Lozano et al., 2009; Albanese et al., 2013). Nevertheless, GPi neuromodulation allowed the patient to walk again and climb stairs unaided (Sakas et al., 2010). This was consistent with the findings in 2 of our patients (cases 1 and 3),

who had extraordinary improvement of the mobile component of their axial dystonia following GPi-DBS but did remain with a degree of fixed truncal deformity (**Supplementary Video 1**).

Overall, our series shows that the patients garnered significant control of their dystonic symptoms, with remarkable improvement of the dystonic opisthotonos following DBS, allowing them to reintegrate into their personalized environment and society, aiming toward a normal life. Dystonic symptoms re-emerged rapidly when DBS battery were near or completely depleted. Benefits were reinstated upon battery revision and were maintained in the long-term with no associated morbidity.

CONCLUSION

Adult-onset dystonic syndromes predominantly presenting with dystonic opisthotonus are relatively rare. The specific nature of dystonic opisthotonus remains a treatment challenge, and thorough investigation of this highly disabling condition with varying etiologies is often necessary. Although patients may be refractory to medical management and botulinum toxin injection, Globus pallidus stimulation timed and tailored provided symptomatic control in this cohort and may be considered in other carefully selected cases.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by King's College Hospital NHS Foundation Trust Research Advisory Group. 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

KT and LF organized, executed, wrote, and reviewed the study. MS and KA conceived, organized, supported and reviewed the study, and contributed equally as senior authors. All authors have seen and approved the final version of manuscript being submitted.

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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.2021.683545/full#supplementary-material

Supplementary Video 1 | *Case 1*: preoperative examination standing/walking (segment 1); first postoperative day (segment 2); *Case 2*: preoperative neurological examination in sitting position and standing/walking (segment 3); first postoperative day (segment 4); and *Case 3:* preoperative examination standing/walking (segment 5); postoperative evaluation (segment 6).

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Analysis-rcs-data: Open-Source Toolbox for the Ingestion, Time-Alignment, and Visualization of Sense and Stimulation Data From the Medtronic Summit RC+S System

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Closed-loop neurostimulation is a promising therapy being tested and clinically implemented in a growing number of neurological and psychiatric indications. This therapy is enabled by chronically implanted, bidirectional devices including the Medtronic Summit RC+S system. In order to successfully optimize therapy for patients implanted with these devices, analyses must be conducted offline on the recorded neural data, in order to inform optimal sense and stimulation parameters. The file format, volume, and complexity of raw data from these devices necessitate conversion, parsing, and time reconstruction ahead of time-frequency analyses and modeling common to standard neuroscientific analyses. Here, we provide an open-source toolbox written in Matlab which takes raw files from the Summit RC+S and transforms these data into a standardized format amenable to conventional analyses. Furthermore, we provide a plotting tool which can aid in the visualization of multiple data streams and sense, stimulation, and therapy settings. Finally, we describe an analysis module which replicates RC+S on-board power computations, a functionality which can accelerate biomarker discovery. This toolbox aims to accelerate the research and clinical advances made possible by longitudinal neural recordings and adaptive neurostimulation in people with neurological and psychiatric illnesses.

Keywords: DBS, open-source software, Summit RC+S, bidirectional device, adaptive stimulation, closed-loop stimulation

INTRODUCTION

Bidirectional, chronically implanted, neural interfaces provide an unprecedented window into human neural activity during daily living and across a range of disease and symptom states. In addition, these devices can deliver therapeutic stimulation in response to real-time changes in neural activity features, driven by symptom biomarkers (Lo and Widge, 2017; Bouthour et al., 2019; Velisar et al., 2019). Compared to traditional deep-brain stimulation (DBS) paradigms, this adaptive stimulation approach may provide more nuanced therapy, avoiding side effects and maximizing potential benefit (Herron et al., 2016; Little et al., 2016; Swann et al., 2018; Huang et al., 2019; Velisar et al., 2019). Furthermore, the neural sensing capability of bidirectional devices opens new possibilities for understanding disease mechanisms and functional brain networks

(Swann et al., 2017). The Summit RC+S from Medtronic (Stanslaski et al., 2018), a device available under Investigational Device Exemption, is currently employed in the study of a wide range of clinical indications (**Table 1**). It is a leading example of advanced bidirectional neuromodulation technology that heralds a new era of longitudinal, high-volume brain sensing and neuromodulation in human patients (Gilron et al., 2021). The advanced sense and stimulation capabilities of this device system provide great user flexibility, but also challenges for data handling. Data handling challenges include the need for critical software for reading, handling, processing, or analyzing RC+S data streams.

In order to prevent multiple individual research teams from needing to engineer piecemeal solutions specific to each use-case simply to access the data, we here provide a freely available, comprehensive software toolbox written in Matlab and tested on Mac and Windows[1]. We describe the implementation of this functionality in three parts, with example patient and benchtop data: (1) A data translation tool to ingest raw data from the Summit RC+S and transform those data into a user-friendly, human-readable, conventional analysis-ready format with data streams on a common time base, with consistent inter sample intervals; (2) A plotting tool that dynamically displays multiple raw data streams and associated metadata; and (3) An analysis module that mimics on-board power calculations conducted by the device and plugs in to the constructed human-readable data. Together, these tools can be used to support wide ranging analyses of RC+S data or modeling developed by the end-user.

[1]https://github.com/openmind-consortium/Analysis-rcs-data

TABLE 1 | Clinical trials using the Medtronic Summit RC+S system.

Sponsor/main site	Registration number	Indication	Enrollment target
Baylor College of Medicine	NCT04806516	OCD	5
Baylor College of Medicine	NCT04281134	OCD	3
Duke University	NCT03815656	PD	6
Duke University	NCT03270657	PD (intraop*)	5
Icahn School of Medicine at Mount Sinai	NCT04106466	TRD	10
Johns Hopkins University	NCT04576650	Locked-in Syndrome	5
Mayo Clinic	NCT03946618	Epilepsy	10
Stanford University	NCT04043403	PD	14
University of California, San Francisco	NCT03582891	PD	25
University of California, San Francisco	NCT04675398	PD	10
University of California, San Francisco	NCT04144972	Chronic Pain	6
University of Florida	NCT02649166	ET	20
University of Florida	NCT02712515	ET (intraop*)	50
xUniversity of Nebraska	NCT04620551	PD/Sleep fragmentation	20

*OCD, obsessive compulsive disorder; PD, Parkinson's disease; TRD, treatment resistant depression; ET, essential tremor; *intraop, intraoperative study only (no chronic implant).*

MEDTRONIC SUMMIT RC+S

The Summit RC+S system consists of two surface or depth leads that are implanted in the brain and a neurostimulator (INS) implanted in the chest. The system is capable of sensing neural activity, performing on-board computations, and delivering open-loop or adaptive stimulation based on user-programmed parameters. The device can stream myriad metadata (device and battery status; sensing, stimulation, and adaptive configurations; enabled electrode contacts, etc.) in addition to user-defined selections of time series data [referred to here as "data streams," including: time domain local field potentials, band-pass power, fast Fourier transform (FFT), accelerometry, and adaptive algorithm settings; **Table 2**] to an external tablet.

The richness and completeness of the data that are streamed also present a number of challenges. The device employs User Datagram Protocol (UDP) to transmit packets of data from the implanted INS to an external tablet. However, this transmission protocol does not perform receipt verification, meaning that some data packets may be lost in transmission (e.g., if the patient walks out of range) and/or may be received out of order. Each of the packets contains a variable number of samples, and timing information is only present for the last sample in each packet (**Figures 1A,C**). These data packets are stored in 11 JSON files, such that 11 raw data files are present for each recording (**Figure 1D**). Packets are individually created, sent, and received for the different JSON files, meaning that packets across different data streams have different timing information, and missing packets across data streams may not align. The JSON files contain a combination of meta data and time series information with much of the metadata coded in hex or binary necessitating translation into human-readable values (**Figures 1A,B**). Lastly, information is needed from multiple JSON files simultaneously to provide users with information of interest (e.g., multiple JSON files are needed to recreate the labels of electrode contacts which were being used for stimulation and the parameters for stimulation) (**Figures 1C,D**). The quantity and variety of data from this device far surpass any previous bidirectional neuromodulation system, but this strength has also proven to be a notable barrier to implementation for research and clinical teams. The first and second parts of the presented toolbox seek to address this challenge by providing data parsing

TABLE 2 | Summit RC+S configurable data streams.

Time Domain	Continuous time domain data from up to four channels sampled at 250 or 500 Hz, or from up to two channels sampled at 1,000 Hz.
Accelerometry	Continuous onboard 3-axis accelerometry data sampled at ~4–64 Hz
FFT	Single-sided fast Fourier transform derived by the on-device FFT engine according to user-defined FFT parameters
Power Domain	Continuous power data from the on-board FFT engine in configurable power bands. Up to eight power domain channels can be streamed simultaneously.
Adaptive	Setting and stimulation state information from the adaptive detector.

A One packet from RawDataTD.json

"Header": {"dataSize": 200,"dataType": 1,"dataTypeSequence": 194,"globalSequence": 150,
"info": 6,"systemTick": 52010,"timestamp": {"seconds": 658955632},"user1": 1, "user2": 15},
"PacketGenTime": 1610849882974,"PacketRxUnixTime": 1610849883003,"ChannelSamples": [{
"Key": 0, "Value": [-0.107155, -0.102166, -0.124617, -0.127545, -0.107047, -0.108565, -0.13004,
-0.127545, -0.106396, -0.112036, -0.133076, -0.122881, -0.10401, -0.11594, -0.133185, -0.118543,
-0.101624, -0.119519, -0.136113, -0.116157, -0.105637, -0.126677, -0.134269, -0.111277, -0.105311]
}, {"Key": 1,"Value": [-0.123532, -0.117784, -0.137957, -0.141753, -0.121363, -0.123207, -0.14544,
-0.141861, -0.120062, -0.126244, -0.148477, -0.138174, -0.11876, -0.128087, -0.146417, -0.135137,
-0.118869, -0.134161, -0.149128, -0.132317, -0.120062, -0.13774, -0.149887, -0.128521, -0.120387]
}, {"Key": 2,"Value": [-0.108415, -0.114542, -0.114979, -0.119027, -0.120996, -0.119793, -0.12023,
-0.121215, -0.120121, -0.109837, -0.10032, -0.101195, -0.100648, -0.096162, -0.088614, -0.092443,
-0.096491, -0.095397, -0.094631, -0.096272, -0.09835, -0.097256, -0.097913, -0.103602, -0.104149]
}, {"Key": 3,"Value": [-0.142837, -0.14338, -0.135571, -0.134269, -0.136764, -0.133185, -0.11876,
-0.122014, -0.129931, -0.128196, -0.122122, -0.126786, -0.13351, -0.123207, -0.111927, -0.117567,
-0.127003,-0.12581, -0.119628, -0.120712, -0.119302, -0.106288, -0.099021, -0.10542, -0.107047]}],
"DebugInfo": 6,"EvokedMarker": [],"IncludedChannels": 15,"SampleRate": 1,"Units": "millivolts"

B Subset of time domain channel settings from DeviceSettings.json

"timeDomainChannels": [{"currentMode": 1,"evokedMode": 0,
"gain": 2,"hpf": 0,"lpf1": 18,"lpf2": 9,"minusInput": 1,"outputMode": 1,
"plusInput": 4,"sampleRate": 1}, {"currentMode": 1,"evokedMode": 0,
"gain": 2,"hpf": 0,"lpf1": 18,"lpf2": 9,"minusInput": 1,"outputMode": 1,
"plusInput": 4,"sampleRate": 1}, {"currentMode": 1,"evokedMode": 0,
"gain": 2,"hpf": 0,"lpf1": 9,"lpf2": 14,"minusInput": 1,"outputMode": 1,
"plusInput": 4,"sampleRate": 1}, {"currentMode": 1,"evokedMode": 0,
"gain": 2,"hpf": 0,"lpf1": 9,"lpf2": 14,"minusInput": 2,"outputMode": 1,
"plusInput": 8,"sampleRate": 1}

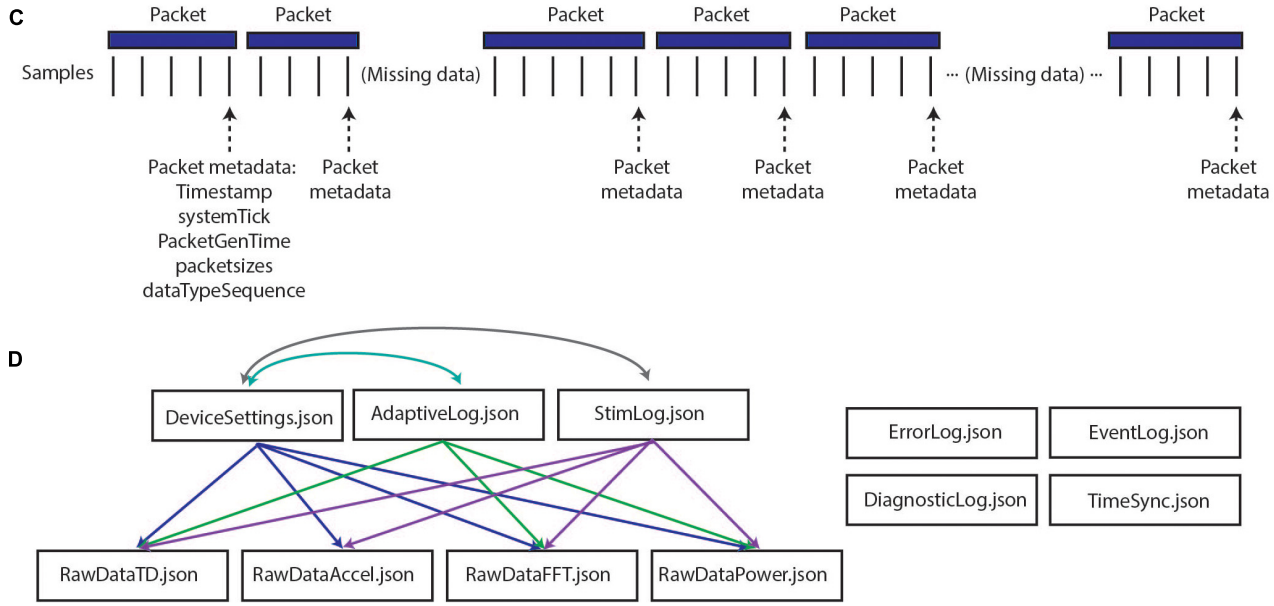

FIGURE 1 | Summit RC+S raw data structure. **(A)** One packet of data from RawDataTD.json; each packet contains one set of timing values and a variable number of time domain samples from each streamed channel; values such as SampleRate must be converted to interpretable values (e.g., Hz). **(B)** One section of values from DeviceSettings.json which provides information on time domain channel settings; mode, gain values, high pass and low pass filter settings, and contacts must be decoded to interpretable values. **(C)** Each time series stream transmits data from the INS in packets of variable sizes using UDP; receipt verification is not performed, so packets may not be received or may be received out of order. Each packet contains one value of timing information per variable, aligned to the last sample in the packet. Each data stream transmits packets separately, with non-aligned timing information. **(D)** The present toolbox is compatible with raw RC+S data which are acquired in 11 JSON files. This relationship diagram depicts that information from multiple files is required to interpret the recordings. For example, interpretation of RawDataTD.json may require all other JSON files which are connected to it *via* arrows. Colors are used to aid visualization.

and time alignment across the data streams and streamlined data visualization.

A key mode of operation for the Summit RC+S uses an "embedded" algorithm to control adaptive stimulation, which is also complex to implement. A typical workflow for programming of this mode includes identifying neural activity which is correlated with or predictive of symptoms (i.e., a biomarker), programming the device to calculate the biomarker, and setting the device detector with threshold values such that when the biomarker moves between predefined states, stimulation delivery and/or stimulation parameters are adjusted (Provenza et al., 2019). Specifically, the Summit RC+S includes on-board computational capability to calculate FFT, band-pass power, and execute linear discriminant analysis (LDA) to control the administration of adaptive stimulation. Effectively programming the device and managing patients using adaptive stimulation can be challenging because the biomarker characteristics (e.g., frequency band limits, dynamic range) must be known, and parameters of the on-board computation of the FFT and power (e.g., interval, size, Hann window) can change values going into the LDA. Exhaustively testing these parameters in patients is time consuming and not feasible. Therefore, the third part of our toolbox is to provide a power calculation module which allows for off-device power computation using streamed time domain data. This tool can be set to use the same parameters as the Summit RC+S, allowing for the optimization of settings to

increase detector performance without creating undue burden on the patient. A key feature differentiating the power computations in our toolbox from standard offline power calculations is that the magnitude, update rate, and range of power values will be comparable to those calculated by the device; these values can directly inform optimal programming of adaptive stimulation.

METHOD AND RESULTS

Part 1: Data Parsing and Time Alignment

Conventional neurophysiological analyses are greatly simplified by the use of a standardized timebase across data streams and a consistent sampling rate (i.e., inter-sample interval). This facilitates time-frequency decomposition and supports downstream modeling of disease biomarkers, analysis of stimulation impact, and parameter selection for adaptive stimulation. Such standardized data formatting includes data in matrix form, with samples in rows, data features in columns (or vice versa), and a timestamp assigned to each row. A key computational step for RC+S data is the derivation of the precise time assigned to each row, which we will refer to as DerivedTime. DerivedTime should be in unix time (a standardized time format for describing a point in time; the number of elapsed seconds from 1 January 1970 in UTC, with a method to account for different time zones), to allow for synchronization with external data streams, symptom reports, or tasks. Furthermore, we ideally would like all separate datastreams to be on the same timebase, aligned to common DerivedTime timestamps (such that we can analyze multiple data streams recorded simultaneously—for example correlating time and power domain data with patient movement detected *via* the accelerometer). Below, we describe our implemented approach to navigate the specialized native format of RC+S data to achieve this desired, standardized output format (**Figure 2**).

The result of this approach is to provide a table (combinedDataTable) containing time series data from all data streams with a calculated DerivedTime value for each sample, and tables with relevant metadata and settings which can be applied to select periods of interest in combinedDataTable. DerivedTime is inclusive of the beginning of the earliest starting data stream to the end of the latest finishing data stream, in steps of 1/Fs of the time domain data stream (*Fs* = 250, 500, or 1,000 Hz). CombinedDataTable is filled with data from all datastreams; if there is not a sample for a given time step, the entry is filled with a NaN. Thus, this neuroscience-analysis-ready table can be quite large to store on disk (leading to prohibitively long read/write times for long recordings). Therefore, there are two main functions to execute to achieve the desired final data table: ProcessRCS.m followed by createCombinedTable.m

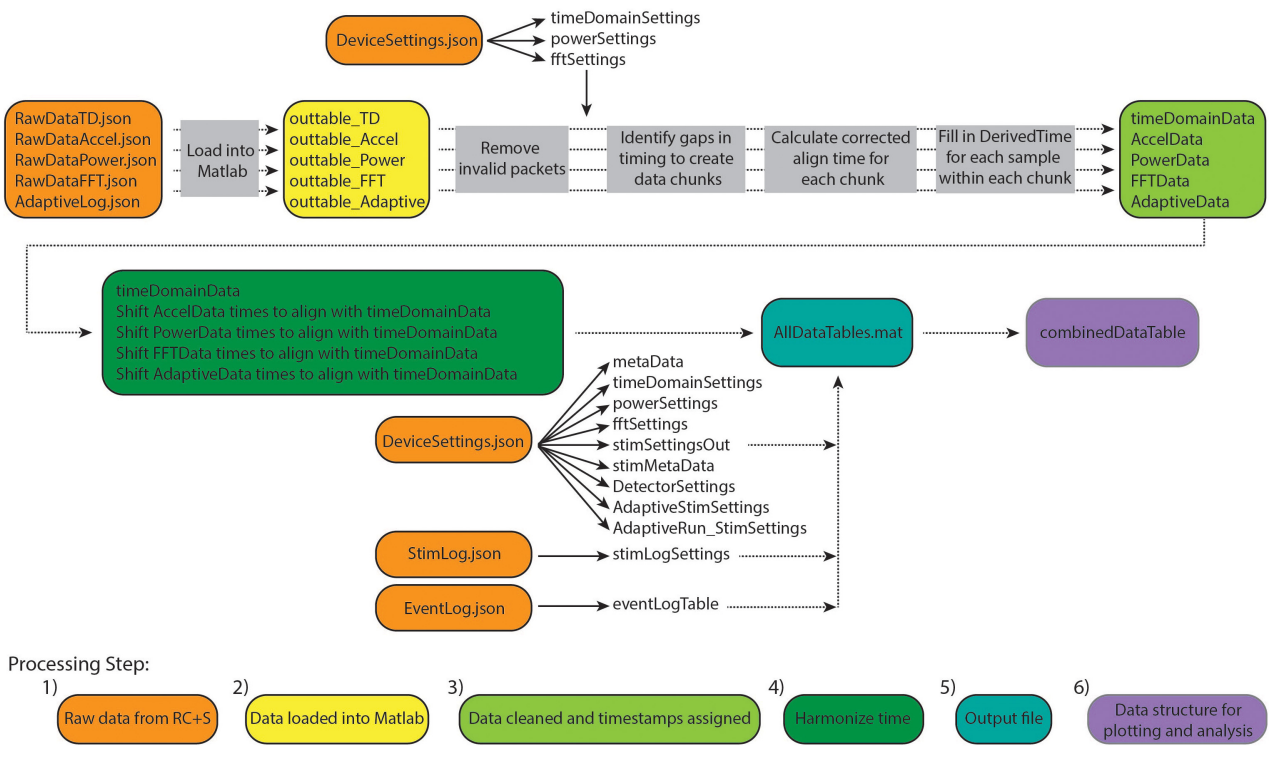

FIGURE 2 | Overview of Summit RC+S data parsing and time alignment. Raw JSON files (orange) are loaded into Matlab (yellow). For each time series data stream, packets with invalid data are removed and timing variables are used to calculate DerivedTime for each sample (light green). Samples in each data stream are aligned to DerivedTime for time domain data, which has the highest sampling rate (dark green). These data tables are saved in a.mat file (using a combination of tables and sparse matrices) along with tables containing settings information and metadata (blue). Finally, combinedDataTable is created which can be used for plotting and user-specific analyses (purple).

(**Table 3**). In the following sections, we describe the rationale behind the implementation of these functions.

Steps 1 and 2: Raw Data From RC+S Loaded Into Matlab

Large raw data are loaded from JSON files into Matlab using the turtle_json toolbox ([2]included in our toolbox repository), which can parse large files rapidly. In cases where JSON files are malformed (typically with closing brackets omitted), fixes are attempted to read these data. Each data stream is read independently, and empty or faulty raw data files will result in continuation of processing omitting that data stream.

Step 3: Data Cleaned and Timestamps Aligned

We continue processing of each data stream independently. There are multiple time and counting related variables present for each packet of data (**Table 4**). We identify and remove packets with meta-data that is faulty or which indicate samples will be hard to place in a continuous stream (e.g., packets with timestamp that is more than 24 h away from median timestamp; packets with negative PacketGenTime; packets where PacketGenTime goes backward in time more than 500 ms; packets where elapsed PacketGenTime disagrees with elapsed timestamp by more than 2 s).

Upon inspection of empirical patient and benchtop (Stanslaski et al., 2012; Powell et al., 2021) data sets, we found that none of the time related variables associated with each packet of data could independently serve as DerivedTime. **Table 4** describes why each variable cannot be used for DerivedTime. In the case of PacketGenTime, the difference between PacketGenTime of adjacent packets, when no packets were dropped, does not equal the expected amount of elapsed time (as calculated using the number of samples in the packet and the sampling rate); the amount of this offset varies between packets. This presents a serious problem—in cases of missing time, we would lose the stereotyped 1/Fs duration between samples, which would introduce artifacts in time-frequency decomposition. In cases of overlap, there is no way to account for having more than one value sampled at the same time.

We next sought to use timestamp and systemTick in concert to create DerivedTime, and then convert to unix time using one value of PacketGenTime. However, we observed from empirical data (both recorded from an implanted patient device and using a benchtop test system) that one unit of timestamp (1 s) did not always equal 10,000 units of systemTick. The consequence of this was offset between systemTick and timestamp that accumulated over the course of a recording (multiple seconds error by the end of a 10-h recording). While using these values may be acceptable for short recordings, we chose to move away from this implementation because one of the strengths of the RC+S system is the ability to stream data for long periods of time. Thus, rather than use any one of these time variables independently, we rely on information provided by all of them to create DerivedTime.

Our implemented solution for creating DerivedTime (**Figure 3**) depends on first identifying continuous "chunks" of data; defined as a continuous series of packets of data sampled without packet loss. Although there is indeterminacy in the timing of individual data packets, the INS device samples continuously at a fixed sampling interval and therefore, within a chunk of concatenated packets, the data sampling is continuous and regular. Our approach aims to align the beginning of continuous chunks of data to unix time and then use the sampling rate to determine the DerivedTime for each individual sample. This process relies on the assumption that only full

[2]https://github.com/JimHokanson/turtle_json

TABLE 3 | Description of functions for creating CombinedDataTable.

Function	Inputs	Outputs
ProcessRCS.m	(1) Path to folder containing raw JSON files (2) (Optional) processFlag to indicate saving/read/overwrite selection (3) (Optional) Alternate method for handling short gaps in data, for advanced users (more information below)	For each data stream: sparse matrix with numerical data, cell array with column labels for sparse matrix, table with non-numerical data; tables with metadata and settings
createCombinedTable.m	All required variables available from AllDataTables.mat or output of ProcessRCS.m (1) Cell array of data streams to be included (2) unifiedDerivedTimes (3) Metadata	combinedDataTable

TABLE 4 | Time and count variables associated with each packet of data from the RC+S system.

Variable	Value meaning	Why insufficient for DerivedTime
timestamp	Elapsed number of seconds since March 1, 2000, in units of seconds. Implemented in INS firmware	Highest resolution is 1 s
systemTick	Running counter, in units of 1e−4 seconds; rolls over every 2^16 values (∼6.5535 s). Implemented in INS hardware	Rolls over every 2^16 values.
PacketGenTime	API estimate of when the packet was created on the INS. Unix time with resolution to millisecond	The difference between adjacent PacketGenTime values does not always equal the expected amount of elapsed time. Aligning by PacketGenTime would result in varying inter-sample intervals
PacketRxUnixTime	Unix time when computer received packet	Highly inaccurate after packet drops
dataTypeSequence	Packet sequence number. Rolls over at 255; does not reset upon start of streaming	Counter, does not provide time

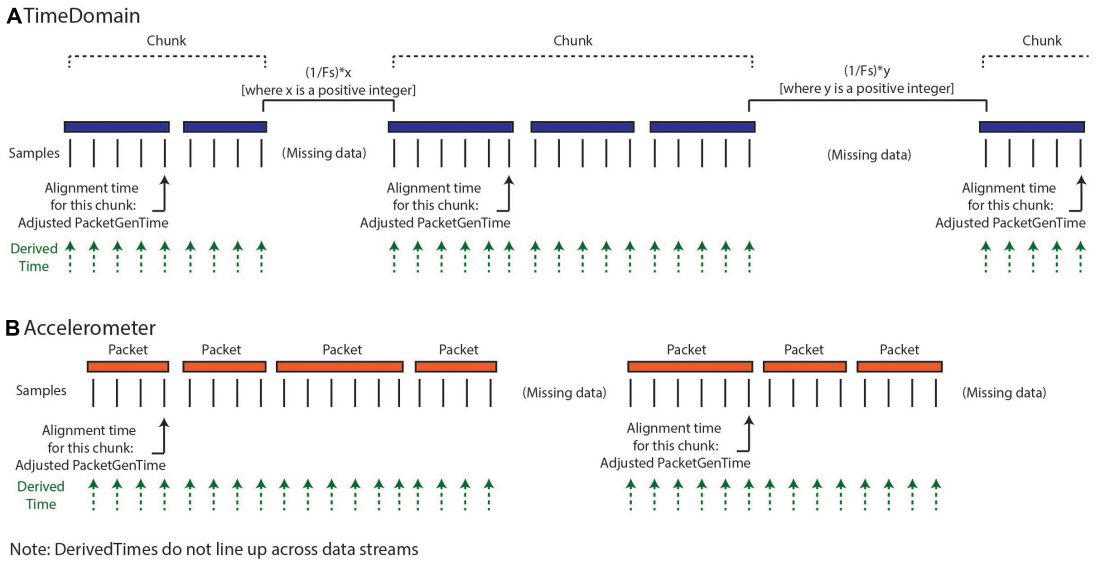

FIGURE 3 | Calculation of DerivedTimes for each data stream. **(A)** The default method for calculating DerivedTimes for short-gap chunks and the only method for long-gap chunks is to align the beginning of continuous chunks of data to Unix time using the adjusted PacketGenTime from the first packet in the chunk, and then using the sampling rate to determine the DerivedTime for each sample. Each DerivedTime is shifted to the nearest multiple of 1/Fs after chunk one in order to preserve consistent intersample spacing. **(B)** DerivedTime is calculated separately for each time series data stream, as each data stream has packets that are sent independently.

packets of data are missing, but there are no individual samples missing between packets. First, we chunk the data—identified by looking at the adjacent values of dataTypeSequence, timestamp, and systemTick as a function of sampling rate and number of samples per packet. Breaks between chunks can occur because packets were removed during data cleaning, because there were dropped packets (never acquired), or because streaming was stopped but the recording was continued. Changes in time domain sampling rate will also result in a new chunk. There are two categories of chunks, short-gap and long-gap. Short-gap chunks follow a gap shorter than 6 s, as determined by timestamp (indicating there was not a full cycle of systemTick); long-gap chunks follow a gap greater than or equal to 6 s (indicating there may have been a full cycle of systemTick). There are two options for how to handle short-gap chunks and only one method for handling long-gap chunks.

For all chunks, we need to align the beginning of the chunk to a Unix time. The first chunk in a recording is aligned using the PacketGenTime of the first packet in the chunk. The default option for handling short-gap chunks is the use of the same approach used for long-gap chunks: we look across all the packets in the chunk and calculate the average offset between each PacketGenTime and the amount of time that is expected to have elapsed (calculated based on sampling rate and number of samples in the packet). We then apply this offset to the PacketGenTime corresponding to the first packet of the chunk, creating the Adjusted PacketGenTime. We can now calculate a time for each sample in the chunk, as a function of the sampling rate. The alternative option for short chunks is to use adjacent values of systemTick to calculate the elapsed time across a gap (systemTick from the last packet of the previous chunk and systemTick of the first packet of the next chunk). This is possible because we have stayed within one full cycle of systemTick values. This approach should only be used when users have verified that their systemTick clock is quite accurate (otherwise error can accumulate over the course of the recording). Whichever process is selected is repeated separately for each chunk.

Lastly, we shift the calculated DerivedTime values slightly for chunks two onward, in order to match the time base of the sampling of the first chunk of data and preserve inter-sample spacing of 1/Fs. Any missing values are filled with NaNs. Again, the above processing is conducted separately for each data stream, as each of these streams have separate systemTick, timestamp, and PacketGenTime values reported per packet. Harmonization of DerivedTime across data streams is conducted later.

Step 4: Harmonize Time

As described above, the optimal format for neuroscience-analysis-ready data is matrix form, with samples in rows, data features in columns, and a timestamp assigned to each row. After creating DerivedTime separately for each time series data stream, we must "harmonize" these times across data streams. By this, we mean samples in each data stream are aligned to the nearest value of DerivedTime from time domain data, which has the highest sampling rate (**Figure 4**). In some cases, data streams may extend before or after time domain data – in these instances, we add values to DerivedTime in steps of 1/Fs (time domain Fs) to accommodate all samples.

Step 5: Output File

If the user selects to save the output of ProcessRCS.m to disk, AllDataTables.mat is created and stored. This file contains a

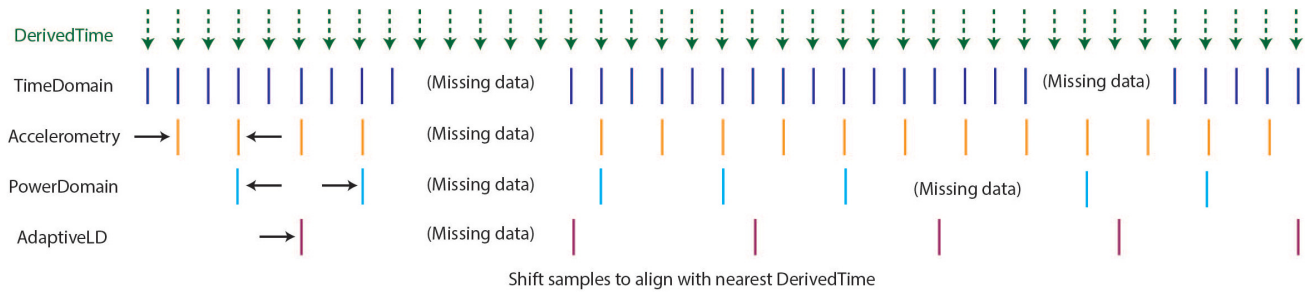

FIGURE 4 | Harmonization of time across data streams to achieve one common DerivedTime timebase. DerivedTime from the time domain is taken as the common time base, as the time domain data have the highest sampling rate. Samples from other data streams are shifted in time slightly to align with the nearest time domain DerivedTime.

number of variables, which separately store data from each datastream and tables with metadata and settings. For each time series, numerical data are stored in a sparse matrix, non-numerical data are stored in a table, and a cell array contains the column headings of the sparse matrix. The purpose of saving these data broken into different tables and matrices is to minimize file size (as the final desired combinedDataTable contains a large number of NaNs and can be quite large).

Step 6: Data Structure for Plotting and Analysis

Outputs from ProcessRCS.m (or variables loaded from AllDataTables.mat) can be used to create combinedDataTable using the script createCombinedTable.m. Whenever a data stream lacks a value for a particular DerivedTime, that entry in the table is filled with a NaN. The table does not contain any columns which are entirely filled with NaNs. The CombinedDataTable variable represents the final data structure for plotting and analysis. All time series data for a given session of RC+S streaming can be contained within this table. The use of Unix time facilitates the synchronization of neural data with external tasks, symptom reports, or across multiple implanted devices. For example, some patients are implanted with two RC+S devices (one in the right hemisphere, one in the left hemisphere) which can be streamed simultaneously. In **Figure 5**, we plot the accelerometry channels from bilateral devices in a single patient after each dataset was independently processed using ProcessRCS.m and combineCombinedTable.m. The movement signals are very closely aligned in time at the beginning and end of an overnight recording, providing an example of validation of the processing algorithm.

Part 2: Data Plotting and Visualization

Analysis of local field potential neural data often consists of several key steps: preprocessing, artifact removal, and spectral analysis. Performing these steps with the Summit RC+S data presents special challenges for a few key reasons: First, small gaps in the data introduce transient artifacts in spectral analysis. Second, RC+S data contains several data streams that are not commonly used in other processing and plotting pipelines (e.g., power time series, adaptive detector). Third, all data streams use different sampling rates. Fourth, data collected at home over hours and days (Gilron et al., 2021) result in multiple recording sessions; some analyses require loading multiple sessions and creating one cohesive structure. Finally, some data streams are usefully plotted together, such as the adaptive detector and associated thresholds.

In order to address these challenges, we have created a Matlab plotting tool to aid in rapidly plotting and analyzing RC+S data directly from the JSON files. Our plotting tool incorporates the functional steps described above to create a cohesive, unified time across RC+S data streams and provides the user the ability to easily plot all data types (**Figure 6A**). Unlike commonly available spectral tools (Fieldtrip, EEGLAB) which assume data are continuous, this tool will perform "gap aware" analysis of the data in the frequency and spectral domain. Data are plotted from multiple data streams with different sampling rates such that alignment is preserved, utilizing the common time base calculated in the first part of the toolbox, described above. Furthermore, we provide an easily executed mechanism to combine and analyze data from multiple sessions (e.g., throughout an entire day of streaming), as well as functions to save and aggregate power spectral density data for downstream analysis (**Figure 6B**). The plotting tools takes advantage of all meta-data parsing and combines this information in the display of plotting results. For example a call to plot a time domain channel will include information of the sense channels and filtering settings (**Figure 6C**, top), and a call to plot current will include information about stimulation channels, stimulation settings, and if changes occurred within the session (**Figure 6C**, second from bottom).

Finally, reporting functions exist to visualize gaps that exist in the data and report event markers (written to the raw JSON file by the API) that the experimenter may have programmed. Typically, these include task timing or patient symptom reports. **Figure 6** provides a schematic of the analyses this tool can perform for data visualization as well as an example call demonstrating the simplicity of use to plot rich data stream visualizations.

Part 3: Power Calculation Analysis Module

The Summit RC+S can be programmed to deliver adaptive stimulation controlled by user-programmed power features and

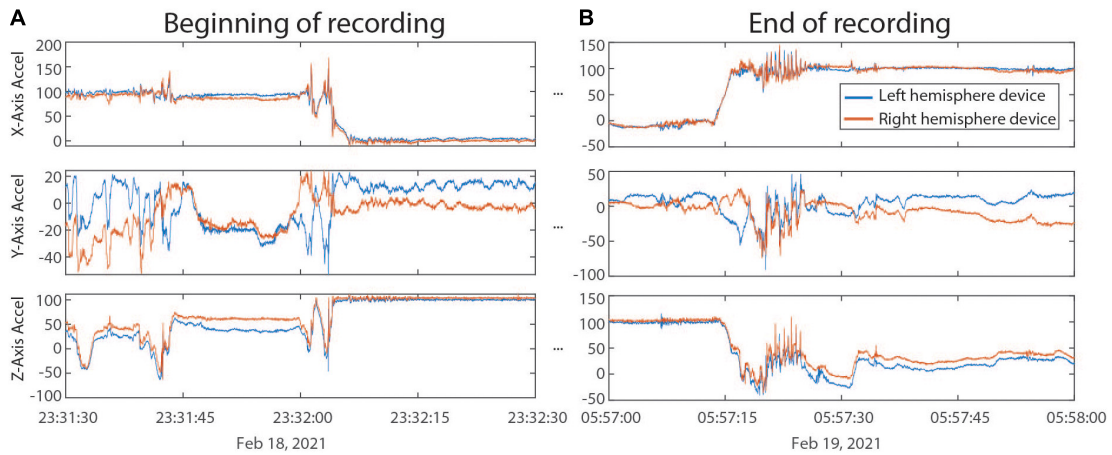

FIGURE 5 | (A) Accelerometry channels from the beginning of an overnight recording from two RC+S devices implanted in the same patient. Detected movement serves as a way of confirming the parsing algorithm, which was applied separately to data from each device, is faithfully recreating time across the recording, without any accumulated offset. **(B)** Accelerometry channels from the end of the same ~6.5 h recording as in panel **(A)**. No accumulated drift is visible between the datastreams across the devices.

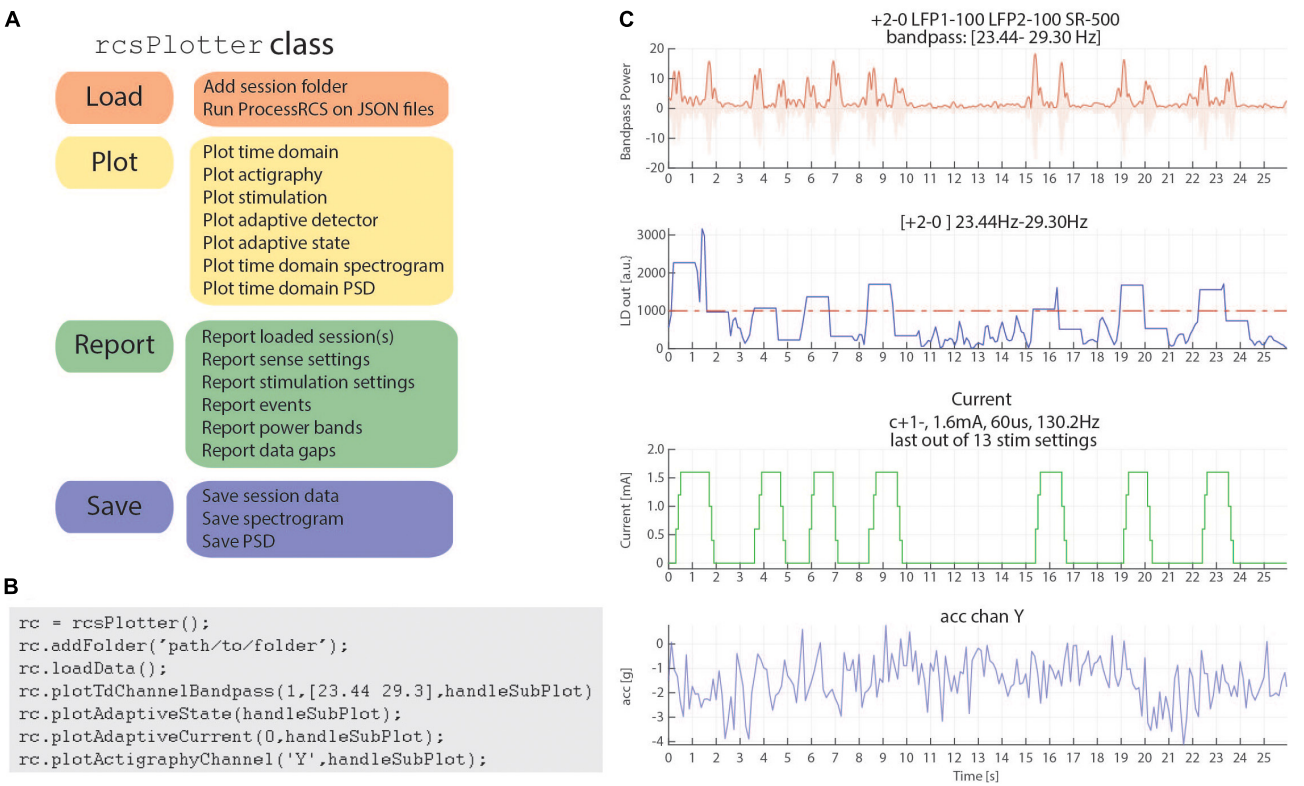

FIGURE 6 | rcsPlotter overview and example. **(A)** Main functions used in the "rcsPlotter" class. These functions are used for loading data which are processed through ProcessRCS.m, plotting all RC+S data streams, reporting values across recordings (such as stim state and event markers), and saving for downstream analyses. **(B)** Example function call for the "rcsPlotter." This shows the simplicity of loading data from an embedded adaptive DBS session and plotting the results. Plots from function call show in panel **(C)**. Each stream has its own dedicated plotting command that will pull in meta data and display it in the subplot title. Adding additional folders (for example, from the same day) only requires one call (and will plot all streams together). There is a "plot" method for each data stream. A list of available methods is available in the function help section. **(C)** This output from the "rcsPlotter" class includes meta-data parameters pulled from multiple JSON files to populate graph titles. Top plot—bandpass time domain data used for embedded detector, sense channels and filter settings indicated. Second from top—output from embedded linear detector output (threshold shown as red dashed line). Third from top—stimulation current and current parameters. Bottom—actigraphy.

detector settings employing LDA. Biomarker discovery and programming of adaptive stimulation are greatly aided by being able to compute inferred embedded power domain outputs from the recorded time domain data off the device. This avoids the need for new data sets to be collected after any changes in device sense settings. Here, we describe an analysis module to calculate off-device power equivalent to the on-device power values using the streamed time domain neural data. This provides an estimate of power that is comparable to the power the device calculates internally and allows the user to calculate different frequency bands and with the option to modify FFT parameters (size, interval, and Hann window %). **Figure 7** provides an overview of the key computation steps in this module.

For the off-device power calculation, time domain signal s(n) is extracted from combinedDataTable, offset voltage is removed, and raw millivolt values are transformed to internal device units using the following equation which accounts for amplifier calibration (Equation 1; **Table 5**):

$$s(n)_{\{rcs\ units\}} = (s(n)_{\{mV\}} - \overline{s(n)_{\{mV\}}}) * \frac{\frac{250 * config\ trimmer\ ch\ gain}{255}}{1000 * 1.2} * fpv_{\{real\ units\}} \quad (1)$$

Then, the overlap of a running Hann window is calculated as a function of sampling rate, FFT interval, and FFT size. The overlap formula is given in Equation 2:

$$\text{Overlap} = 1 - \left(\frac{\text{sampling rate} * fft\ \text{interval}}{fft\ \text{size actual}}\right) \quad (2)$$

For the overlap calculation the device uses an actual number of FFT points of 62, 250, or 1,000 for FFT sizes of 64, 256, or 1,024, respectively. The RC+S offers three Hann windows (window load) settings, 25%, 50%, and 100%. The 100% Hann window is the default Hann window, defined by:

$$\text{Hann window } (n) = 0.5 * \left[1 - cos\left(2\pi \frac{n}{N}\right)\right],\ 0 \leq \text{n} \leq \text{N} \quad (3)$$

with a window length L = N + 1. In the off-device power calculation the user chooses one of the three Hann window settings (**Figure 8**).

In **Figure 9**, the off-device calculation of a benchtop dataset is shown. The time domain raw neural signal s(n) is transformed to the internal on-device units (Equation 1). Then, a window with the size of the FFT is shifted from start to end of the time domain signal using the Hann window (see Equations 2, 3). For each window, the single-sided FFT is calculated, and the biomarker

Requirement: 'AllDataTables.mat' & 'CombinedDataTable' loaded in workspace

```
1) Determine FFT Settings, Frequency Band & Fiel Potential Channel
 newfftSettings.fftConfig.interval = 50 to 10'000 ms
 newfftSettings.fftConfig.size = 64, 256 or 1024
 newfftSettings.fftConfig.windowLoad = '100% Hann', '50% Hann' or '25% Hann'
 freqBand = [f1, f2] (f1 > 0 and f2 < ½ sampling rate)
 lfpCh = 1, 2, 3 or 4

2) Determine FFT Bins
numBins = fftSettings.fftConfig.size/2
binWidth = (fftSettings.TDsampleRate/2)/numBins
lowerBins = (0:numBins-1)*bindWidth
fftBins = lowerBins + bindWidth/2

3) Update Power Settings
powerSettings.fftConfig.interval = newfftSettings.fftConfig.interval
powerSettings.fftConfig.size = newfftSettings.fftConfig.size
powerSettings.powerBands.fftBins = fftBins

4) Determine Actual Frequency Band Bins
 idxBinsA = find(powerSettings.powerBands.fftBins>freqBand(1))
 idxBinsB = find(powerSettings.powerBands.fftBins<freqBand(2))
 powerSettings.powerBands.indices_BandStart_BandStop(1,1) = idxBinsA(1)
 powerSettings.powerBands.indices_BandStart_BandStop(1,2) = idxBinsB(end)

5)  Call Calculate Power Function
[power, newSettings] = calculateNewPower(combinedDataTable, ...
                        newfftSettings, powerSettings, metaData, lfpCh, freqBand)
```

FIGURE 7 | Use of the function calculateNewPower.m to calculate a new power domain time series based on user-defined FFT settings, frequency band, and time domain channel. The steps required before invoking the function include: (1) Define FFT settings, frequency band, and time domain channel. (2) Calculate FFT bins. (3) Define Power Settings using the FFT settings and derived FFT bins. (4) Determine FFT bins within frequency band. (5) Run function calculateNewPower.m passing all required parameters.

TABLE 5 | Variables and constants to transform RC+S signal back to internal on-device units.

$s(n)_{\{rcs\ units\}}$	Raw neural sense channel transformed to the internal RC+S units
$s(n)_{\{mV\}}$	Raw neural sense channel in time domain file (default units = millivolts)
$\frac{250 * config\ trimmer\ ch\ gain}{255}$	Calibrated sense channel amplifier gain (config trimmer ch gain defined in device settings file per sense channel)
$fpv_{\{real\ units\}}$	On-device fixed point value constant to account for real numbers (48,644.8683623726)

power band is computed as the sum of the power of all frequency bins within the defined frequency band multiplied by a gain factor G (see **Figure 9D**). To optimize the match between the off-device and the on-device power series, the FFT gain factor G may be calibrated per dataset (the chosen default value is $G = 2$).

In **Figure 10**, a comparison between the on-device and off-device calculations for a human subject dataset is shown. To assess the difference between the on-device and the off-device calculated power, root mean square error (RMSE), normalized RMSE, and percentage difference for each were evaluated, resulting in 318.03 (RCS units), 0.041 (normalized RMSE), and 1.78% respectively. We normalize using the difference between maximum and minimum for each of the two variables (Power on-device and Power off-device).

DISCUSSION

Deep-brain stimulation is an established or experimental therapy for a number of neurological and psychiatric diseases (Mayberg et al., 2005; Lozano et al., 2008; Mallet et al., 2009; Schlaepfer et al., 2013; Pereira and Aziz, 2014; Fontaine et al., 2015; Moro et al., 2017; Limousin and Foltynie, 2019; Harmsen et al., 2020; Shirvalkar et al., 2020; Krauss et al., 2021). Originally applied in an open-loop paradigm, there has been a surge of interest in delivering closed-loop or adaptive stimulation in response to disease and symptom biomarkers (Neumann et al., 2014; Arlotti et al., 2018; Hoang and Turner, 2019; Provenza et al., 2019). The use of adaptive stimulation may be able to better match the timescale of stimulation therapy adjustments to the timescale of symptom evolution, or may operate on fast time scales to reshape pathological oscillatory bursts (Tinkhauser et al., 2017). The Medtronic Summit RC+S bidirectional device is being tested in a number of clinical trials for therapeutic stimulation to treat a range of diseases (**Table 1**). This device is equipped with advanced sense and stimulation capability, including the ability to record multiple data streams simultaneously (e.g., time domain, accelerometry, power, FFT, adaptive detectors), and to stimulate either in open-loop or adaptive mode. The device is powered *via* a rechargeable battery, thereby allowing patients to stream for long periods without the need for frequent surgeries to replace a primary cell battery. However, fully leveraging these advanced capabilities is limited if researchers and clinicians cannot efficiently access recorded data in a format amenable to conventional analysis to inform device programming. Here, we provide a toolbox which can ingest raw JSON data from the Medtronic Summit RC+S device and provide key outputs and functionality for users. We import raw time series and metadata from all data streams and decode information to human-readable values. Critically, we compute a common time base such that all data streams can be analyzed together with time alignment. While seemingly simple, the technical specifics of how data packets are transmitted from the INS to the external tablet precluded the ability to easily analyze multiple datastreams together with accurate time alignment prior to this implementation. Prior studies relied on averaging time windows for more coarse alignment or looking at datastreams independently. Because our common time base is in Unix time, it further facilitates the synchronization of Summit RC+S data with external sensors and tasks and event-locked epoching. The ability to analyze all acquired datastreams together is fundamental to both our scientific understanding of neural correlates of disease and for

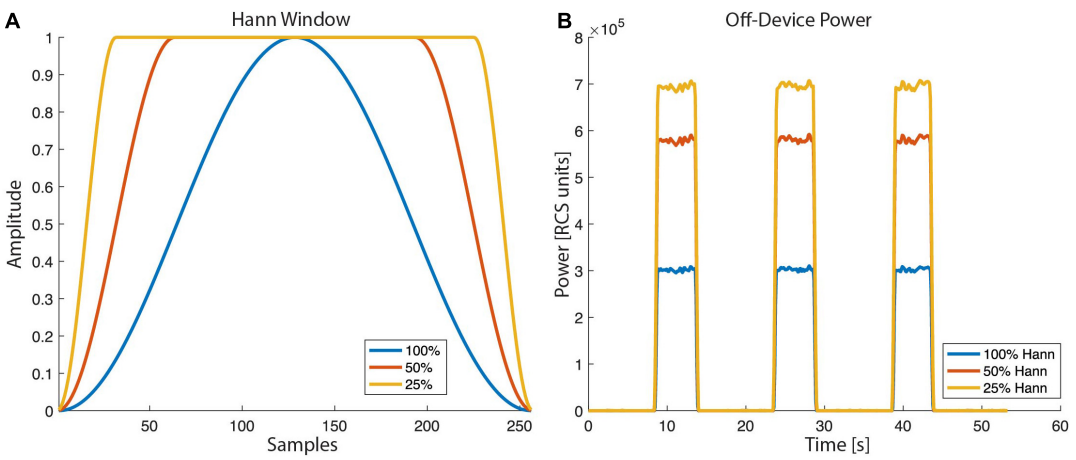

FIGURE 8 | Hann window with "window load" parameter of 25, 50, and 100% as selectable by the RC+S FFT power calculation: **(A)** The shape of the tapper Hann window function. **(B)** Power calculated off-device based on different Hann window load values.

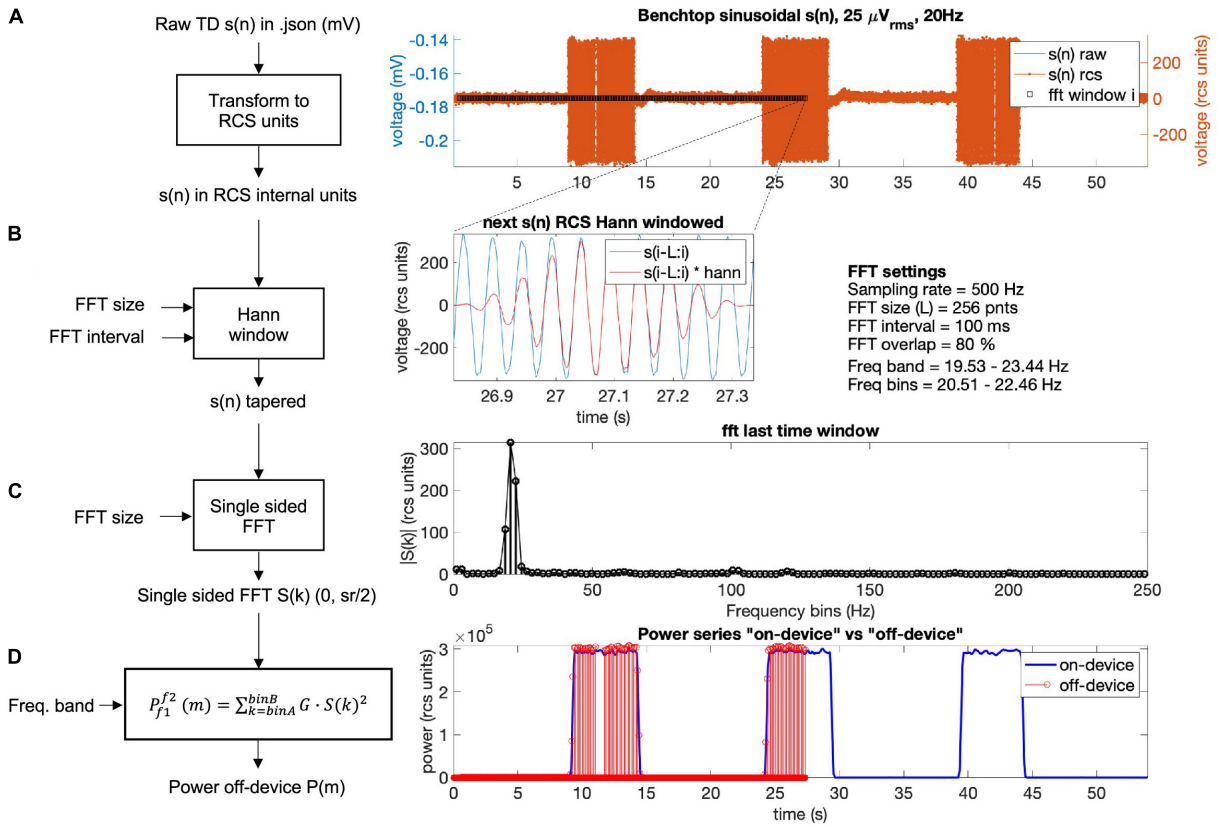

FIGURE 9 | Power calculation off-device replicating the on-device power calculation for a benchtop dataset with three 5 s bursts of a 25 microvolts sine wave at 20 Hz frequency. The calculation is conducted following four steps: **(A)** The raw time domain neural signal *s*(n) (mV) is transformed back to internal device units, RCS units (see Equation 1, **Table 5**). **(B)** To minimize spectral leakage, a Hann window is applied to each new analysis window of the transformed signal *s*(n). The new analysis window (∼26.9–27.3 s) is defined by the size and interval of the FFT (Equations 2, 3). The raw signal within the next time segment is shown in blue and the Hann window tapered signal is in red. **(C)** A single-sided FFT is applied to the Hann tapered signal *s*(n) resulting in an amplitude FFT value per each frequency bin of the complete FFT band (0 to ½ sampling rate). For the exact scaling of the single sided FFT see function "calculateNewPower" (scaling steps 1 and 2) on https://github.com/openmind-consortium/Analysis-rcs-data. **(D)** Power is computed as the sum of squares of each FFT amplitude multiplied by a gain factor G (scaling step 3) for all frequency bins within the frequency band. The on-device power series is shown in blue and the off-device calculated power, up to the last analyzed window in this graph (∼27 s) is depicted in red (using the matlab function stem). The time alignment between the on-device and the off-device signal is accurate as the perfect overlay between sample points at the power signal flanks shows.

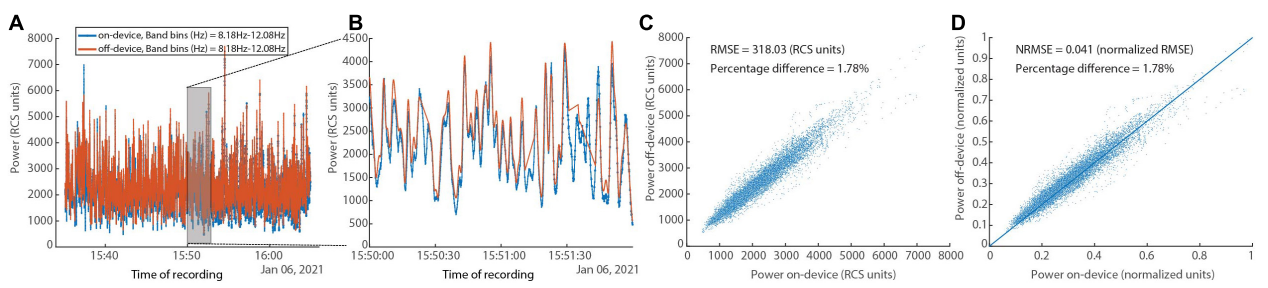

FIGURE 10 | *In vivo* human data set showing on-device and off-device calculated power series for a given frequency band (8.05–12.20 Hz). **(A)** Overlay of power time series for the "on-device" and the "off-device" calculation. **(B)** Zoom into a 2-min segment showing minimal difference between the two power series. **(C)** Scatter plot showing the fit between the "on-device" and "off-device" power values with RMSE of 318.03 (RCS units) and percentage difference of 1.78%. **(D)** Scatter plot showing the fit between the "on-device" and "off-device" power values with normalized RMSE of 0.041 and percentage difference of 1.78%.

accurately understanding how neural activity, stimulation, and symptoms relate for the clinical management of implanted patients. Similarly, viewing these different datastreams together provides a more comprehensive view of the therapy. Our plotting tool allows for easily customized visualization of one or multiple datastreams.

The Summit RC+S system provides technological advances to enable embedded adaptive stimulation. Such therapy has been applied in the treatment of epilepsy (Kremen et al., 2018) and Parkinson's disease (Swann et al., 2018; Gilron et al., 2021). Across indications, the device is programmed to calculate power within predefined frequency bands, and these values are used to determine the current "state," relative to the predefined detector thresholds. The Summit RC+S has two detectors available when operating in embedded adaptive mode, each with a linear discriminant function that allows for up to four input power features. Selecting all the parameters for each computation, detector, and threshold is a challenge in the real-world implementation of this system. Exhaustive testing with patient reports of symptom status (in order to validate performance) is not feasible because of the large parameter space. Therefore, we provide a tool which allows Summit RC+S users to calculate inferred embedded power estimates, off the device, using streamed time domain data. While standard software power calculations can be used to analyze the data for better understanding of neural correlates of symptom status, those computations are less useful in informing programming of the device. Here, we mimic the computation steps performed on the device hardware and firmware in order to obtain values that are comparable to what the device will calculate. The magnitudes of the power values calculated are typically used to set the threshold values in the detector, so it is critical to have off-device computations which do not require a scaling factor or other transform to be comparable to online computations.

Though the Summit RC+S is only accessible *via* an Investigational Device Exemption with no current plans for commercial release, it has a 9-year life span, and is expected to be implanted in over 130 patients across seven indications. Given the research volume planned with these patients (estimated to be over $40 M in NIH funding), a robust toolbox to aid in data analysis and data sharing could prove invaluable for the research groups that will be working on these datasets in the decade(s) to come. Available as a potential alternative, the Neuropace Responsive Neurostimulation (RNS) System is a commercially available device which is capable of sense and stimulation. Specifically designed for epilepsy management, the RNS is a primary cell, cranially-contained device with two 4-contact leads. As the on-board calculation capability of the device is tailored for seizure detection and stimulation is designed to disrupt the progression of seizures, the applicability of this device to other indications is limited. Furthermore, the primary cell battery precludes the ability to stream for long periods of time, which is a key strength of the RC+S. New bidirectional sense and stimulation enabled devices continue to enter the market (e.g., Medtronic Percept). We hope the learnings presented *via* this toolbox can provide guidance to device manufacturers to develop systems which are easily implemented and managed by clinicians and researchers (Borton et al., 2020). Some areas for improvement include: use of only one clock (either on firmware or hardware) for timing related variables; unix-based timing variables or high resolution non-resetting timing variables; transmission protocol which includes packet receipt checking; marking in the raw data when packets are missing; keeping all variables needed for interpreting a given data stream localized to one data file with the same timing variables. While coding of data may be needed to overcome the limited transmission bandwidth available to fully-implanted devices, translation of these codes to human-readable values as early as possible in the user-facing pipeline is desirable. Consistent and streamlined handling of missing data, data streams with different sampling rates, and continuous data with changing parameters are critical for efficient analysis. Thoughtful design at this level will decrease the barrier to entry for new clinicians and researchers, which is common in the medical/academic environment, especially when working with patients who are enrolled in multi-year clinical trials. This is particularly important as more neurological and psychiatric conditions are becoming understood in terms of neurophysiology for both biomarker tracking and adaptive stimulation.

In order to facilitate use and adoption of this toolbox, we provide an extensive README in the shared GitHub repository. We provide example datasets, both patient data (anonymized and shared with informed consent) and benchtop data acquired with known characteristics and input signals, to facilitate user training and to demonstrate features of the toolbox. The repository is actively maintained, with ongoing code review of new features and bug fixes. Some members of the OpenMind Consortium have already incorporated the toolbox into their data handling workflows. The OpenMind Consortium is a group of investigators establishing and sharing best practices for handling and analyzing data from stimulation and recording enabled devices such as the RC+S and Percept.

The presented toolbox includes three key areas of functionality. Future areas for fruitful development are plentiful. The quantity of raw and processed data from patients implanted with Summit RC+S devices is staggering, and efficient databasing is required. This will facilitate both targeted analyses as well as data mining across patients. The toolbox is currently implemented in Matlab, but in the short term a conversion tool can be written to make the data easily accessible by Python. In the long-term, we seek to implement an open-source data standard for Summit RC+S data, Neurodata Without Borders (NWB). The NWB format provides a documented schema on top of the h5 file format and facilitates data readability, sharing, and archiving. Conversion of raw JSON files from the Summit RC+S directly into NWB was not possible because of the unique packet structure and the need to create a shared timebase across all datastreams. With the functionality of the toolbox presented here, we are now able to begin developing conversion modules to create RC+S NWB files. The power computation module we presented serves as a template for future development of analyses—including a similar off-device implementation of the detector engine which utilizes LDA. Such tools can be applied to data collected prior to chronic implant in order to inform personalized targeting (Allawala et al., 2021). Taken together, we hope this toolbox provides infrastructure on which to continue building shared analysis tools for the ongoing development of stimulation therapy using the Medtronic Summit RC+S for the whole neurophysiology community.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data not posted on GitHub will be made available upon reasonable request. Requests to access these datasets should be directed to kristin.sellers@ucsf.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California, San Francisco IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KS, RG, and JA conceived of the presented toolbox. KS, RG, and JA wrote the toolbox code. KS, RG, JA, KL, and PSh tested the code toolbox. KS, RG, and JA wrote the manuscript. PSh, EC, SL, and PSt provided data, funding, and mentorship for the project. All authors contributed to manuscript revision, read, and approved the submitted version.

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CASE REPORT
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Case Report: GPi DBS for Non-parkinsonian Midline Tremor: A Normative Connectomic Comparison to a Failed Thalamic DBS

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Introduction: The clinical efficacy of deep brain stimulation (DBS) for midline tremor has been heterogenous. Here, we present an atypical case with facial and palatal tremor treated with DBS. We aimed to show the difference between the fibers affected by stimulation of the two targets [globus pallidus interna (GPi) and ventral intermediate (Vim) thalamic nucleus] using a normative connectome analysis.

Case Report: A 76-year-old woman with a 4-year history of severe facial and palatal tremor due to craniofacial dystonia. Following a failed bilateral Vim DBS, explantation of preexisting leads and implantation of bilateral GPi leads resulted in the resolution of tremor symptoms following a failed bilateral Vim DBS. We performed a normative connectome analysis using the volume of tissue activated (VTA) as a region of interest. The results revealed that the fiber tracts associated with VTA of GPi DBS had connections with the facial area of the motor cortex while the Vim DBS did not.

Conclusion: This case study suggests the possibility that GPi DBS may be considered for midline tremor, and that the normative connectome analysis may possibly offer clues as to the structures underpinning a positive response. We may refine targets for some of the more difficult to control symptoms such as the midline tremor in this case.

Keywords: tremor, deep brain stimulation, normative connectome, globus pallidus, case report, ventral intermediate nucleus, thalamus

INTRODUCTION

Deep brain stimulation (DBS) is an effective treatment modality for medication refractory tremor disorders. The most common DBS target for tremor has been the ventral intermediate (Vim) thalamic nucleus region. The clinical efficacy for midline tremor however, has had heterogenous outcomes (Moscovich et al., 2013). In this report, we present an atypical case with facial and palatal tremor which was addressed by bilateral globus pallidus interna (GPi) DBS following failure of bilateral Vim DBS. We show the difference between the fibers affected by the two procedures using a normative connectome analysis.

CASE DESCRIPTION

A 76-year-old woman with a 4-year history of severe facial tremor accompanied by minimal tremor in all four extremities. The phenomenology was similar in appearance to jaw tremor in Parkinson's disease (PD) patients, but the dopamine transporter scan (DAT) showed no abnormalities. A laryngoscopic evaluation also revealed a palatal tremor. These tremors were similarly irregular in amplitude and frequency (3–6 Hz), and considered to be a series of symptoms of a movement disorder. She was, therefore, diagnosed with tremor associated with craniofacial dystonia by movement disorders trained specialists. The tremor was refractory to maximally tolerated dosages of anti-parkinsonian medications, a beta blocker, and a benzodiazepine, so a surgical intervention was indicated. Following a multidisciplinary evaluation she underwent DBS surgery.

Bilateral Vim thalamic nuclei were selected for the initial DBS targets to address the midline tremulous movements, and the trajectory was planned to include the medial area of the Vim based on somatotopy (Morishita et al., 2020). A large anterior commissure (AC)-posterior commissure (PC) insertion angle was selected as previously suggested in the literature for this type of case (Moscovich et al., 2013). The patient visited clinic for DBS programing once a month or two, and stimulation intensity was increased to the near threshold level of stimulation-induced side effects. However, DBS therapy was ineffective for more than 2 years although there were no serious adverse events. Since she was suffering from severe social embarrassment due to tremor, she elected to undergo a revision DBS surgery. Based on phenomenology of her dystonic tremor manifesting as similar to PD and in an attempt to address her dystonia, we planned to explant the preexisting Vim DBS leads, and implant new GPi DBS leads bilaterally through the preexisting burr holes. Following DBS surgery, she visited the clinic once a month for DBS programming. The positive clinical effect manifested 2 months after surgery as the facial and palatal tremor nearly resolved. The tremor was hardly recognizable at 1-year follow-up (**Supplementary Video 1**). The DBS electrode position and the programming of the device at last visit following each procedure have been summarized in **Table 1**.

NORMATIVE CONNECTOME ANALYSIS

Based on the clinical outcomes, we hypothesized that there would be a difference in the modulated networks between the Vim and GPi DBS. We, therefore, performed a normalized connectome analysis using the volume of tissue activated (VTA) as a region of interest (Morishita et al., 2021). Considering the limited data volume, the right VTAs were non-linearly mirrored and merged with the left VTAs on an assumption that there is no significant difference in functional localization between the left and right hemispheres. The VTA calculation was performed using Lead-DBS (Horn et al., 2017), and the population-averaged atlas of the macroscale human structural connectome derived from the diffusion-weighted imaging data (Human Connectome Project: https://www.humanconnectome.org/) (Yeh et al., 2018), was used for normative connectome analysis. The results revealed that the fiber tracts associated with VTA of GPi DBS had connections with the facial area of the motor cortex as defined by the A4hf area of the human brainnetome atlas (Fan et al., 2016). While the Vim DBS did not have connections, the tractography associated with the VTA for the GPi DBS may also have connections to the corticobulbar tract (**Figure 1**). We evaluated the number of structural fibers that passed through each brain region defined by Harvard-Oxford cortical/subcortical atlases (Makris et al., 2006) combined with the cerebellum from AAL atlas (Tzourio-Mazoyer et al., 2002). All small parcels of the cerebellum defined in AAL were integrated into one binarized parcel in a similar manner to our previous report (Morishita et al., 2021). The depicted fiber tracts showed that the VTA for GPi DBS had more connective fibers with the precentral gyrus and brain stem than the VTA of Vim DBS. The presented study participant provided informed consent, and this study design was approved by our institutional review board (IRB) (IRB approval number: U21-01-003).

DISCUSSION

This case study suggests the possibility that in some cases GPi DBS may be considered for midline tremor (Patel et al., 2018), and that the normative connectome analysis may possibly offer clues as to the structures underpinning a positive response. This result also suggests that the GPi DBS modulates the corticobulbar tract that connects these regions. To the best of our knowledge, this is the first report showing the differences in the potential mechanisms of action between Vim and GPi DBS in the same tremor patient. We hypothesize that the failure of the first procedure was due to the lead positioning when compared to the overlap of fiber tracts associated with GPi DBS. It is also possible that the DBS electrodes were not positioned in the appropriate area of the Vim nucleus as there have been a variety of thalamic DBS targets inclusive of ventralis oralis and ventralis caudalis nuclei (Morishita et al., 2010).

There have been arguments regarding DBS targets for dystonic tremor including Vim and GPi (Fasano et al., 2014). A recent study reported that Vim DBS may fail to show sustained suppression of dystonic tremor (Cury et al., 2017). Even though GPi DBS outcomes have been also heterogenous (Fasano et al., 2014), GPi DBS may be currently indicated as the first-line DBS target in cases with midline dystonic tremor. It should be also noted that cerebellar DBS might be an option for patients who are refractory to the conventional DBS treatment (Horisawa et al., 2021). Further clinical studies are warranted to identify the most effective target for dystonic tremor.

LIMITATIONS

Even though our case study showed the beneficial effect of GPi DBS underpinned by the normative connectome analysis, there are important limitations. This is a retrospective study using the clinical data, and the stimulation parameters were not optimized based on the simulation by the connectome

TABLE 1 | The electrode position and the stimulation parameters at last follow up.

	Vim DBS*				GPi DBS	
	Left		**Right**		**Left**	**Right**
Lead position (tip of the electrode)						
X	9.8		9.3		19.5	20.9
Y	−3.9		−3.9		2.4	4.8
Z	−0.6		−0.2		−4.4	−5.4
AC-PC angle	69.9		65.5		74.7	78.5
Center-Line angle	32.5		32.0		19.9	14.0
DBS programming	**Program 1**	**Program 2**	**Program 1**	**Program 2**		
Active contacts	0+, 1−	2−, 3+	0+, 1−	2−, 3+	2−, Case+	2−, Case+
Amplitude (V)	2.8	3.1	2.7	3.0	3.8	3.8
PW	180	180	180	180	100	100
Frequency	100	100	100	100	130	130

**Interleaving stimulation settings were applied. AC-PC, Anterior Commissure-Posterior Commissure; DBS, Deep Brain Stimulation; GPi, Globus Pallidus Interna; PW, Pulse Width; Vim, Ventral Intermediate (nucleus of the thalamus).*

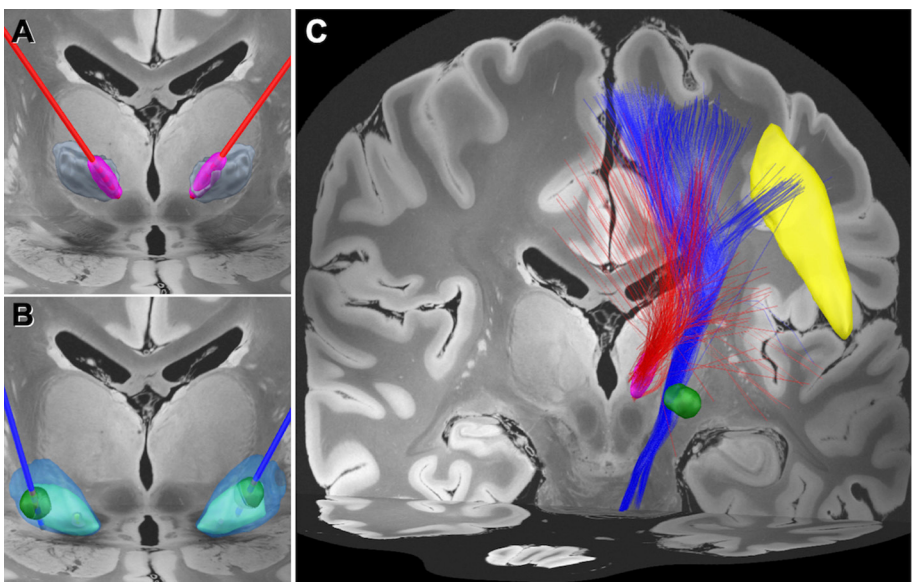

FIGURE 1 | Electrode position and the normative connectome associated with each volume of tissue activated. **(A)** Position of the electrodes (red) and the volume of tissue activated (VTA) (magenta) in the medial area of the ventral intermediate (Vim) nucleus of the thalamus (gray). **(B)** Position of the electrodes (blue) and the VTA (green) in the globus pallidus interna (GPi) (light blue) and externa (GPe) (transparent blue). **(C)** Normative connectome associated with VTA of Vim stimulation (red tractography) and GPi stimulation (blue tractography). The normative connectome associated with GPi stimulation projects to the facial area of the motor cortex (yellow) and the brain stem. The facial area was defined by the A4hf region of the human brainnetome atlas (Fan et al., 2016).

analysis. The recent studies showed that the different functional connectivities are affected between essential tremor and dystonic tremor (Tsuboi et al., 2021), but normative connectome analysis does not take the patient-specific network abnormalities into account. The normative connectome data were also descriptive and not quantified. Therefore, a larger sample size is necessary to confirm our findings with quantitative analysis. The normative connectome analysis, however, provided us with useful information to guide future studies. Though this is a case study, if we continue to use this type of 3-D approach, the hope is that long-term we can refine targets for some of the more difficult to control symptoms such as the midline tremor in this case.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the personal data including the imaging data obtained from the study subjects will not be distributed openly to protect

the patients' privacy. Requests to access the datasets should be directed to https://www.lead-dbs.org/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fukuoka University-Medical Ethics Review Board. 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

TMo and YS designed the study and co-wrote the manuscript. TMo, TMi, and GU collected the clinical data. YS and ST contributed to the image analysis. MO and YT confirmed the diagnosis of the case. TI supervised this study. All authors critically reviewed the manuscript and approved the submitted version.

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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.2021.709552/full#supplementary-material

Supplementary Video 1 | On this clip, pre- and post-operative symptoms are presented on the left and right, respectively. Prior to surgical intervention (2 months prior to surgery), the tremulous movements are recognized in the chin, eyelid, and the palate. All of these symptoms were improved following GPi DBS (1 year following surgery).

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REVIEW
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Implantable Pulse Generators for Deep Brain Stimulation: Challenges, Complications, and Strategies for Practicality and Longevity

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Deep brain stimulation (DBS) represents an important treatment modality for movement disorders and other circuitopathies. Despite their miniaturization and increasing sophistication, DBS systems share a common set of components of which the implantable pulse generator (IPG) is the core power supply and programmable element. Here we provide an overview of key hardware and software specifications of commercially available IPG systems such as rechargeability, MRI compatibility, electrode configuration, pulse delivery, IPG case architecture, and local field potential sensing. We present evidence-based approaches to mitigate hardware complications, of which infection represents the most important factor. Strategies correlating positively with decreased complications include antibiotic impregnation and co-administration and other surgical considerations during IPG implantation such as the use of tack-up sutures and smaller profile devices. Strategies aimed at maximizing battery longevity include patient-related elements such as reliability of IPG recharging or consistency of nightly device shutoff, and device-specific such as parameter delivery, choice of lead configuration, implantation location, and careful selection of electrode materials to minimize impedance mismatch. Finally, experimental DBS systems such as ultrasound, magnetoelectric nanoparticles, and near-infrared that use extracorporeal powered neuromodulation strategies are described as potential future directions for minimally invasive treatment.

Keywords: battery life, neuromodulation, complications, DBS (deep brain stimulation), IPG (implantable pulse generator), longevity, non-invasive, wireless charging

INTRODUCTION

Since its inception, deep brain stimulation (DBS) has revolutionized the management of a broad range of neurological and psychiatric diseases, from movement disorders to epilepsy and obsessive-compulsive disorder. Promising clinical trials have shown preliminary safety and efficacy of DBS as a treatment for disabling symptoms of Alzheimer's disease, depression, and many other conditions (Lozano and Lipsman, 2013; Lozano et al., 2017). The unique ability of electrical modulation of the brain circuits with spatial and temporal accuracy enabled a completely new treatment paradigm complementing pharmacological approaches and lesioning procedures, which lack spatial and temporal control, respectively.

The success of DBS therapy depends not only on patient and target selection but also on the hardware used to generate and deliver the current. The implantable pulse generator (IPG) represents a key part of DBS systems and is the only component that requires programming, recharging, and potential replacement. The goal of the present work is to review the clinical challenges associated with current IPG design, IPG-related complications, and highlight future strategies to improve IPG longevity and practicality. The future potential of extracorporeal powered DBS systems is also briefly explored.

CURRENT IPG DESIGN AND RELATED CLINICAL CHALLENGES

The IPG is the active component of current DBS systems. It contains a battery and a power module, a CPU and program memory, as well as a microprocessor managing all the device's functions, including activation, deactivation, pulsing parameters, internal diagnostics, and communication with external devices. Some IPGs also include recharging capabilities, integrated accelerometers, local field potential (LFP) sensing, onboard signal processing, and analysis capabilities. The technical features of current commercially available IPGs are portrayed in **Figure 1**.

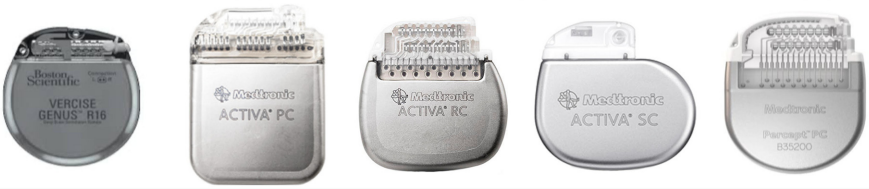
Clinical Challenges With IPGs

Inadequate Longevity and Frequent Replacement Surgeries

Battery longevity describes the period, during which a single IPG will successfully deliver the desired current before surgical replacement. IPG replacement is estimated to account for about 9% of the total cost of DBS therapy in short–term studies but proportionally increases over the lifetime of the patient (Dang et al., 2019). Each IPG replacement surgery is an additional economic, social, and psychological burden for the patient and workload/stress for the clinician. Moreover, subsequent surgeries bring additional complication risks to the patients and their DBS systems (Thrane et al., 2014; Fytagoridis et al., 2016; Frizon et al., 2017; Helmers et al., 2018). Thus, maximizing battery longevity should be a priority in the field.

Battery longevity depends on stimulation parameters, hardware, and patient factors (Bin-Mahfoodh et al., 2003; Fisher et al., 2018; Sette et al., 2019). Patient factors, such as reliability of IPG recharging or consistency of nightly device shutoff, if appropriate and tolerated (e.g., essential tremor, pain), may affect battery longevity. Hardware factors include the battery type (primary cell vs. rechargeable), chemistry and capacity, as well as energy consumption of the idle device. The impedance of the system, which is also a vital factor that affects battery longevity, can be both hardware and tissue-related factor (Butson et al., 2006). Stimulation parameters are the key determinant of the total power, which is strongly correlated with battery life (Fakhar et al., 2013). It is the only battery longevity affecting factor that can be modified by the clinician after DBS implantation. As DBS programming is extensively discussed elsewhere (Ramirez-Zamora et al., 2015; Picillo et al., 2016a,b), we will only briefly mention some of the relatively new, longevity-affecting stimulation techniques that may help to understand the features of IPGs more easily. *Constant-current stimulation (CCS)* is the consistent delivery of electricity to target by compensation for variations in impedance over time. Dynamic voltage changes during CCS have been associated with a greater battery consumption compared to constant-voltage stimulation in the short–term, although this difference disappears over long-term follow-up (Lettieri et al., 2015; Rezaei Haddad et al., 2017). The effect of battery longevity of *Bipolar stimulation*, in which one contact serves as the cathode while another serves as the anode, is disputable. While an earlier study appears to demonstrate an increase in longevity with bipolar stimulation compared to cathodic monopolar stimulation with Medtronic Soletra IPGs (Almeida et al., 2016), we demonstrated a higher battery consumption index with bipolar stimulation with Boston Scientific IPGs in one of our recent studies (Soh et al., 2019). This discrepancy might be due to differences between the devices or battery consumption index calculation methods, as well as the use of different amplitude values for bipolar stimulation between the studies (Soh et al., 2019). *Directional current steering* technologies have a complex impact on battery longevity, which will be discussed in detail in the Future Strategies section (see "Directional DBS" under Future Strategies). *Temporal fractionation* ["interleaving stimulation" as introduced by Medtronic and "Multi-stim Set (MSS)" by St. Jude/Abbott] uses two separate sets of stimulation parameters in an alternating fashion to shape the volume of tissue activation (VTA) delivered through a single DBS electrode. The alternating stimulation programs must share a common frequency but may have different amplitudes, polarities, and pulse widths. It may reduce battery longevity due to the increased pulses required (Ramirez-Zamora et al., 2015). *Vertical current fractionation* involves multiple independent current sources, which apply constant current through each contact of the DBS electrode. Boston Scientific IPGs use *multiple independent current control (MICC)* to control the flow of current through each contact, individually. The safety and efficacy of MICC for STN DBS in PD patients were demonstrated by a double-blind, randomized controlled INTREPID trial (Vitek et al., 2020), however, there are implications for IPG depletion depending on the settings utilized. Abbott IPGs use a less versatile method termed *Coactivation*, which allows for multiple contacts to be stimulated as if they were a single electrode, i.e., no independent control at each contact is possible. There are a limited number of articles

Model	St. Jude (Abbott) Infinity 5	St. Jude (Abbott) Infinity 7	Boston Scientific Vercise PC	Boston Scientific Vercise Gevia	Boston Scientific Vercise Genus P8/P16
No. of channels	2	2	2	2	1/2
Weight (gram)	49	58	55	26	58
Size (mm)	56×50×13	67×50×14	71×50×11	51×46×11	72×50×12
RC	No	No	No	Yes	No
Freq. range (Hz)	2–240	2–240	2–255	2–255	2–255
Pulse width (μs)	20–500	20–500	10–450	20–450	20–450
TF	MSS	MSS	A	A	A
CF	CA	CA	MICC	MICC	MICC
Directional lead	Yes	Yes	Yes	Yes	Yes
MRI safety	C	C	U	C	C
LFP sensing	No	No	No	No	No



Model	Boston Scientific Vercise Genus R16	Medtronic Activa PC	Medtronic Activa RC	Medtronic Activa SC	Medtronic Percept PC
No. of channels	2	2	2	1	2
Weight (gram)	27	67	40	44	61
Size (mm)	52×46×11	65×49×15	54×54×9	55×60×11	68×51×12
RC	Yes	No	Yes	No	No
Freq. range (Hz)	2–255	2–250	2–250	3–250	2–250
Pulse width (μs)	20–450	60–450	60–450	60–450	20–450
TF	A	IL	IL	IL	IL
CF	MICC	No	No	No	No*
Directional lead	Yes	No	No	No	No
MRI safety	C	C	C	C	C
LFP sensing	No	No	No	No	Yes

FIGURE 1 | Features of current commercially available internal pulse generators. Abbreviations: A, areas; C, conditional; CA, coactivation; CF, current fractionation; Freq., frequency; Hz, Hertz; IL, interleaving; LFP, local field potential; MICC, multiple independent current control; MRI, magnetic resonance imaging; MSS, multi-stim set; PC, primary cell; RC, rechargeable cell; SC, single cell; TF, temporal fractionation; U, unsafe. *Percept PC can provide independent current control across 16 electrode contacts, but this function is not yet available on physician's programmer as of March 2021. Not all features or devices are or will be available for a given region and are subject to local regulatory approvals.

that compare the current steering techniques between each other, as well as with conventional monopolar stimulation in regards to energy consumption. A computational modeling study showed that MSS may draw more or less battery current than MICC, while coactivation consistently draws less battery current than both MICC and MSS (Zhang S. et al., 2020). A human study in a Parkinsonian DBS cohort demonstrated that MICC significantly lowered total electrical energy delivered (TEED) compared to monopolar stimulation while similarly improving the functional ambulatory performance (Hui et al., 2020).

Disease-specific longevity is a tremendously important factor that necessitates the discussion with the patients prior to DBS surgery. It is well accepted that IPG longevity varies between conditions due to the variable energy requirements necessary to achieve therapeutic benefit. For example, dystonia and depression often require higher energy settings compared with ET and PD, which depletes the IPG faster (Rawal et al., 2014).

This has considerable implications for the patient as well as the treating physician and patients should be made aware of what this may mean for their treatment in regards to the frequency of battery replacements.

Suboptimal DBS lead placement is another factor that may have an effect on battery longevity. Theoretically, a lead implanted away from the target zone, where stimulation produces above-mean clinical improvement ("hotspot"; Elias et al., 2021) necessitates a larger VTA to engage with the hotspot which in turn results in more energy consumption. This concept must be balanced with the possibility that sub-optimally positioned leads, depending on the vector of deviation from intended and/or the clinical hotspot, may actually limit the maximum voltage/amplitude due to the induction of off-target side-effects. Illustrative of this, Anheim et al. (2008) demonstrated in their prospective study that stimulation-induced adverse effects occur at lower voltage thresholds for the misplaced leads (mean 2.6 V) compared to the optimally placed leads (mean 4.4 V). The lower threshold for adverse effects prevents the use of sufficient energy to achieve an optimum clinical outcome in real-life circumstances, which prolongs battery longevity. Thus, a balance between the energy required for hotspot stimulation and optimal placement of leads with sufficient thresholds for off-target side-effects is of critical importance. Techniques for targeting accuracy using microelectrode recording, impedance monitoring and/or micro/macrostimulation have been long utilized in DBS surgery and were discussed previously in great detail (Hariz, 2002). The insertional effect, which transiently alters parenchymal impedance, may further complicate interpretation of the therapeutic stimulation window intra-operatively but experienced teams can incorporate these data in decision making for final lead placement intra-operatively. Finally, all electrodes should be verified by an imaging modality as an added confirmatory step. In addition to traditional verification techniques utilizing frame-based systems and fluoroscopy, verification of leads can also be achieved with intra-operative CT and/or 3D fluoroscopy. More recently, the use of intraoperative MRI for targeting and electrode guidance has increased in popularity and is routinely used as part of some surgical workflows (Hwang et al., 2021).

Recent battery longevity studies have shown that the newer generation IPGs have decreased battery lifespans compared to their predecessors. For example, the battery lifespan of the Activa PC is 3–4.6 years, compared to the Kinetra, which is 4.3–6.5 years (Fisher et al., 2018; Kiss and Hariz, 2019; Sette et al., 2019; Paff et al., 2020). On the other hand, the lifespan of rechargeable IPGs is estimated to range from 15 (Medtronic) to 25 (Boston Scientific) years, which has yet to be confirmed (Paff et al., 2020). Strategies for deciding between rechargeable and non-rechargeable IPGs have been discussed in detail elsewhere (Okun, 2019; Paff et al., 2020). Another consideration in addition to selecting a rechargeable IPG in patients, who initially were treated with a unilateral system but later needed a contralateral side treatment, is whether conversion to a dual-channel IPG should be considered. The mean longevity of a single channel Activa SC (37 months) is comparable to the longevity of the dual-channel Activa PC (Park et al., 2018). Thus, implanting two Activa SC IPGs may double the number of replacement surgeries required unless the IPGs are depleting simultaneously. At the same time, this must be weighed against the risk of compromising the first implanted unilateral system while tunneling the additional extension wire for the contralateral system. At our center, we often will discuss the pros and cons of both approaches with the patient and defer to patient preference, if there is equipoise between the two strategies.

Bulky Size of the IPGs and Skull Mounting

The size of currently available DBS IPGs necessitates their implantation on the chest wall, as opposed to the skull. The need for tunneling of extension wires to connect the DBS wires in the frontal skull region to the IPG located in the pectoral region requires general anesthesia, increasing the complexity of the second-stage surgery. Additionally, the bulk of the IPG case may cause wound dehiscence, skin erosion, and cosmetic problems, particularly in thin patients. The smaller profile of rechargeable IPGs compared to non-rechargeable IPGs has reduced wound healing and cosmetic problems to some extent (**Figure 1**). Taking into account the thickness of the skull, which is 7–8 mm on average in the frontoparietal region and changes with age (Lillie et al., 2016), the need for even smaller profile IPGs is essential for skull-mounting. The Neuropace responsive neurostimulation (RNS) system (Neuropace, Inc., USA), which includes a skull mounted IPG with maximum dimensions of $60 \times 27.5 \times 7.5$ mm, was approved by FDA in 2013 for epilepsy and has been under use and/or investigation for the treatment of various diseases including epilepsy, Tourette syndrome, binge eating disorder, major depression, posttraumatic stress disorder, and anxiety disorders (Nair et al., 2020; Jarosiewicz and Morrell, 2021). The Neuropace stimulator is placed within a ferrule, which is secured to a full-thickness craniectomy and can be connected to one or two leads (depth or strip), which may be used for stimulating and/or sensing (Jarosiewicz and Morrell, 2021). Neuropace can deliver current-controlled, charge-balanced biphasic pulses with customized stimulation frequency (1–333 Hz), current (0.5–12 mA), pulse width (40–1,000 μs), and stimulation burst duration (10–5,000 ms; Morrell and Halpern, 2016). The most recent, MRI-conditional, RNS-320 has an expected battery life of ∼8.4 years under moderate stimulation settings, in which <5 min of stimulation per day is delivered (Jarosiewicz and Morrell, 2021).

Implantation of IPGs within the skull raises the possibility of new concerns and complications. The spread of infection to the skull, meninges, and brain parenchyma may be of more concern due to their proximity to the brain compared to conventional IPGs. However, a 9-year prospective safety report of RNS systems demonstrated that there were no instances of meningitis or cerebritis among a total of 35 infections over the cumulative 1,895 patient-implantation years, and only one case of osteomyelitis has been reported (Nair et al., 2020; Razavi et al., 2020). Other possible concerns are potential imaging artifacts caused by the device during neuro-imaging and utilization of these systems in younger patients with growing skulls. Additional considerations are increased difficulty of revision surgery due

to bony remodeling and the increased potential for brain lead fracture if there is no strain relief between the IPG and electrodes. In addition to the Neuropace system, another skull-mounted system-Picostim (Bioinduction, Bristol, UK)—is currently under trial (SPARKS trial) for CE approval in Parkinson's disease patients (ClinicalTrials.gov NCT03837314). Developing skull-mounted systems for routine indications for DBS is a priority in the field as it has advantages from both clinical (e.g., surgery can be completed in a single stage without general anesthesia) and patient perspective (e.g., cosmesis). Care will have to be taken in the design and deployment of this approach, especially if rechargeable systems are considered.

Challenges With Recharging of the IPGs

Rechargeable IPGs have successfully enriched the armamentarium of the DBS clinicians with their increased longevity and smaller size. Despite these clear advantages, there are some drawbacks that limit their utilization. While recharging is generally considered easy and convenient, these devices might not be suitable for patients with advanced age and cognitive problems that might prevent them from being able to consistently recharge their devices (Jakobs et al., 2019). Current rechargeable IPGs require a minimal distance between the charging pad and the IPG during the charging session. Some patients find pairing the charging pad and IPG difficult, feel "tethered" during charging, or find it cumbersome to track the charge level of the device (Mitchell et al., 2019). The charge burden is variable among patients and depends on the diagnosis, IPG model, and stimulation parameters. The reported average time of charging is 185.8 (range: 25–830) minutes divided over a mean of 4.5 (range 0.5–14) charging sessions per week, which is perceived as reasonable to most patients (Mitchell et al., 2019). From a surgical point of view, the necessity of superficial IPG implantation (1–1.5 cm beneath the skin surface) may predispose some thin patients to skin erosions.

MRI Compatibility

Around 70% of patients will need an MRI within 10 years of DBS implantation due to comorbidities or device complications (Falowski et al., 2016). MRI-related injuries in the early 2000s in DBS patients led to a considerable number of MRI safety studies being conducted and establishment of MRI guidelines by hardware vendors (Boutet et al., 2020). Fortunately, MRI compatibility of newer devices is improving with almost all currently available IPGs being full-body 1.5 Tesla MRI-conditional (**Figure 1**). Additionally, the new Medtronic IPG, Percept PC, has been tested in 3.0-T MRI environments and found to be MRI-conditional when eligibility criteria are fulfilled. Nevertheless, patients with other IPGs may also be scanned with a 3.0-T MRI, currently off-label but with promising phantom study data which with further characterization from other centers will hopefully enable broadening indications (Boutet et al., 2019). On the other hand, patients implanted with older generation devices may face delays or contraindications to neuroimaging.

Limited Number of Lead Channels

Some clinically complex movement disorder patients may need multitarget DBS and more than two leads concurrently (Parker et al., 2020). While there are spinal cord stimulation IPGs with four channels, commercially available DBS IPGs have a maximum of only two channels, which results in the implantation of at least two IPGs for this rare patient subpopulation.

Local Field Potential (LFP) Sensing Quality

The use of LFP sensing is important in adaptive therapeutic stimulation, as well as in acquiring basic neuroscientific research data by neural recording over time in out-of-clinic environments. In addition to the aforementioned NeuroPace device, Medtronic has released several IPGs with sensing abilities. Initially, as research devices, the first-generation IPG of its kind (Medtronic Activa PC+S) had limitations in signal sensing quality, management of the stimulation and other artifacts, and long–term data recording (Swann et al., 2018a). Even though the second-generation IPG (Medtronic Summit RC+S) provided a substantial improvement over the precedent (Stanslaski et al., 2018), it was not commercialized, whereas Medtronic Percept PC has been commercially available since 2020. The new device can capture LFP signals and allow clinicians to review these signals with respect to custom patient-reported events (i.e., ON or OFF medication state, dyskinesia, tremor, took medication, etc.). The survey mode allows displaying—LFP magnitude (microvolts peak) vs. a frequency band (0–100 Hz)—for all possible contact pairs while the stimulation is off. In a streaming mode, real-time visualization of the stimulation amplitude and the LFP power of a pre-selected frequency band (selected frequency $\pm$2.5 Hz) from a single pre-defined contact pair is possible. While capturing the LFP power in the selected frequency band, the clinician can turn on the stimulation and see the real-time changes in the LFP power while changing the stimulation amplitude. This mode has an online sampling frequency of 2 Hz, but the raw data is sampled at 250 Hz which can be analyzed offline at a later timepoint. There are two low-pass filters at 100 Hz and two high-pass at 1 Hz and, 1 or 10 Hz as defined by the clinician. Some of the limitations of this new IPG are the necessity of two sensing contacts on lead, inability to stimulate on sensing contacts, monopolar/double monopolar stimulation only through contact(s) between sensing contacts, no interleaving, and increased noise with stimulation amplitudes over 5 mA. In addition, the stimulation rates must be at least 10 Hz greater than the selected LFP band of interest (Thenaisie et al., 2021).

In-Person vs. Remote DBS Programming

A secure, web-based, remote, wireless programming system for DBS has been implemented in China since 2014 (Zhang J. et al., 2020). This system is currently available for the IPGs manufactured by PINS Medical Co., Ltd. (Beijing, China) and SceneRay Co., Ltd. (Suzhou, China) and allows clinicians to adjust DBS settings of patients remotely without the necessity of coming to hospital or clinic (Paff et al., 2020). More recently, Abbott announced the launch of its FDA-approved NeuroSphere Virtual Clinic that allows remote programming. Such a feature is paramount with many patients coming from a great distance to specialized centers and in-person programming has been further challenged by the COVID-19 pandemic (Fasano et al., 2020).

TABLE 1 | IPG-related complications and avoidance strategies.

IPG-related complications	Potential avoidance strategies
Infection	Prophylactic perioperative antibiotics Vancomycin powder. Antibiotic envelopes Decreasing the number of replacement surgeries by using long-lasting IPGs (i.e., rechargeable IPGs). Prevention of CSF leak into the pocket.
Subcutaneous seroma/hematoma in the vicinity of the IPG	Avoidance of over-sized IPG pockets Proper hemostasis during surgery. Prevention of CSF leak into the pocket.
Skin erosion	Deeper implantation of the IPG. Proper fixation to decrease motion. Antibiotic envelopes
Wound dehiscence / Exuberant scarring of the wound	Avoidance of small-sized IPG pockets Decrement in the size of IPG.
Uncomfortable feeling around IPG	Subpectoral implantation (Son et al., 2012)
Flipping (Twiddler's syndrome)	Subfascial/submuscular placement of the IPG Two-point anchorage with non-absorbable suture/stitching the pocket to reduce its size Antibiotic envelopes/polyester pouches
Malposition / Migration	Proper fixation Changing to a lower profile IPG Antibiotic envelopes
Malfunction	-
Ineffective recharging / Shielded Battery Syndrome	Implantation of IPG no more than 1.5 cm beneath the skin. Fixation of the adaptor beneath the IPG.

IPG-RELATED COMPLICATIONS AND AVOIDANCE STRATEGIES

IPGs can be associated with a number of complications, which constitute a major priority for the multidisciplinary team to anticipate, prevent, and manage. The main IPG-related complications include infection, flipping, skin erosion, malposition, and malfunction (**Table 1**; Fenoy and Simpson, 2014; Jitkritsadakul et al., 2017). These complications not only cause interruption of therapy but inflict a great economic cost. The cost of a single DBS system removal or revision is approximately US$ 12k, while the average reimplantation cost of a DBS system can reach up to US$ 41k depending on the health system and IPG model used (Chen et al., 2017; Wetzelaer et al., 2018). As the overall cost of health care is rising in many countries, efforts to reduce excess costs related to surgical site infections and other complications are paramount. Herein, we discuss the most common early and delayed IPG-related complications while highlighting strategies for prevention and management.

Early Complications

Theoretically, several different IPG-related complications can be encountered at any time after the implantation but some are more prone to happen earlier in the first 3–6 months, while some more often occur in a delayed fashion. Among the IPG-related early complications, the most serious is an *infection*, which, in severe cases, may necessitate the removal of all DBS hardware (Voges et al., 2006; Fenoy and Simpson, 2014). Other IPG-related early complications include the development of *subcutaneous seromas or hematomas* in the vicinity of the IPG, *skin erosion, wound dehiscence, IPG flipping, ineffective recharging, malposition, uncomfortable feeling around IPG*, and *malfunction* primarily due to faulty production (Voges et al., 2006; Fenoy and Simpson, 2014; Benam et al., 2019).

DBS hardware infection has a reported incidence of up to 15% of cases (Joint et al., 2002; Oh et al., 2002; Voges et al., 2006; Sillay et al., 2008; Fenoy and Simpson, 2014), with most occurring within 6 months of surgery (Sillay et al., 2008; Fenoy and Simpson, 2012; Frizon et al., 2017). The IPG-originated infection rate is reported as 2% after the primary implantation and ranging from 0.7% to 6% for IPG replacement surgeries (Thrane et al., 2014; Fytagoridis et al., 2016; Frizon et al., 2017; Helmers et al., 2018). Most case series suggest the rate of infection is increasing with the number of previous replacement procedures (Thrane et al., 2014; Fytagoridis et al., 2016; Helmers et al., 2018), while Frizon et al. (2017) demonstrated the opposite, with infection rates of 0.4% for the 1st, 1.8% for the 2nd and 0% for the 3rd and subsequent replacement surgeries. IPG infections typically present with erythema, swelling, and purulent discharge from the pulse generator pocket incision. The most commonly identified infectious agents are *S. epidermidis* and *S. aureus*, with the latter being the most difficult to treat without hardware removal (Sillay et al., 2008; Fenoy and Simpson, 2012; Frizon et al., 2017; Helmers et al., 2018). Avoidance of infection must be one of the highest priorities at the time of surgery. Some evidence suggests spreading vancomycin powder throughout the IPG pocket during insertion may reduce infection rates (Rasouli and Kopell, 2016; Abode-Iyamah et al., 2018). Vancomycin powder is inexpensive and widely available. Additionally, the administration of perioperative antibiotics should follow local protocols and typically does not exceed 24 h.

For the past decade, antibiotic envelopes have been implemented for cardiac implantable electronic devices (CIED) to prevent infection. As an example of antibiotic envelopes, the TyRx (Medtronic, Dublin, Ireland), which contains rifampin and minocycline, prevents hardware infections by eluting these antimicrobial agents in the local tissues for more than 7 days following the procedure. Antibiotic envelopes may also prevent IPG migration, erosion, or Twiddler syndrome as a result of its porous mesh structure that triggers dense fibrous connective tissue ingrowth (Osoro et al., 2018). Several reports related to the field of cardiac surgery have demonstrated that antibiotic envelopes are both effective and cost-efficient (Tarakji et al., 2019; Mittal et al., 2020; Pranata et al., 2020). A large, multicenter, randomized trial including 6,983 patients (Tarakji et al., 2019; Mittal et al., 2020) reported a 40% reduction in major CIED infections and a 61% reduction in pocket infections within 12 months of placement. While antibiotic envelopes have yet to be studied for infection

prevention in DBS patients, it seems reasonable to apply these findings to DBS IPG insertion considering the similar size and implant location especially in the case of implanting an IPG in a higher risk patient (e.g., diabetic, immunosuppressed, etc.).

When an IPG infection does occur, antibiotic therapy should be initiated immediately in an attempt to save the DBS system and prevent more rare and severe complications such as cerebritis and brain abscess. Algorithms for managing DBS hardware infections vary among institutions. Depending on the severity of the infection, some centers may initiate a trial of antibiotic therapy while others will promptly remove the IPG and/or other portions of the hardware in addition to treatment with intravenous antibiotics between 4–8 weeks. Once the infection is cleared, IPGs can be safely re-implanted after 2–3 months (Lyons et al., 2004; Temel et al., 2004; Sillay et al., 2008; Boviatsis et al., 2010; Fenoy and Simpson, 2012). If there is a high risk of withdrawal syndrome, IPG and extension cables can be removed and a contralateral side IPG with new extensions can be implanted in the same operative session under appropriate antibiotics (Helmers et al., 2021). For patients with high stimulation settings necessitating frequent battery changes, switching to a long-lasting IPG [i.e., rechargeable Activa RC or Vercise Gevia are estimated to have life-spans of >15 years (Thrane et al., 2014; Fytagoridis et al., 2016; Helmers et al., 2018)] should be considered as a means of reducing the risk of infection from repeated surgical procedures, as well as healthcare costs (Hitti et al., 2018).

Ineffective recharging of rechargeable IPGs may occur when the IPG is implanted too deep beneath the skin and/or at a suboptimal angle to allow effective communication between the IPG and recharging device. Per manufacturer recommendations, rechargeable IPGs should be implanted approximately 1.5 cm beneath the skin. In the case that an adaptor has been used to connect an older generation DBS lead system to a new-generation rechargeable IPG, it is possible for the adaptor and wires to migrate between the IPG and the skin, impeding the recharging process. This situation has been termed "*shielded battery syndrome*." In the case of shielded battery syndrome, relocation of the wires and adaptor is necessary (Chelvarajah et al., 2012).

Delayed Complications

Delayed complications of IPGs arise mostly due to suboptimal fixation or placement and device wear and tear. The incidence of *IPG malfunction* is reported in the literature as 0.1% to 13.8% (Lyons et al., 2004; Doshi, 2011; Umemura et al., 2011; Fenoy and Simpson, 2014). Device malfunction should be suspected when the IPG does not respond during interrogation, or when there is an unexplained decline in clinical benefit. Hardware damage, such as fractured DBS leads and extension wires, should be ruled out with X-ray and impedance testing. If IPG malfunction is suspected and other causes of system malfunction have been excluded, exchange of the IPG is unavoidable (Lyons et al., 2004; Blomstedt and Hariz, 2005).

Infection can also be seen as a late complication. Frizon et al. (2017) demonstrated that 20% of all IPG-originated infections occur after 6 months; however, in their series they could not identify a variable associated with a significant increase in the risk of infection, such as steroids, anticoagulant, and aspirin use; body mass index; hypertension; diabetes mellitus; and coronary artery disease. Although these variables may theoretically increase the infection rates, this has not been borne out in the DBS case series that present long-term complication rates (Baizabal Carvallo et al., 2012; Frizon et al., 2017).

Other late complications of IPGs may arise from *suboptimal positioning*. Over time, poor positioning of the IPG can lead to discomfort and/or poor cosmesis. In their 728-patient DBS cohort, Fenoy and Simpson reported only four patients (0.5%), who required a repositioning surgery due to a flipped, uncomfortable or malpositioned IPG (Fenoy and Simpson, 2014). There are reports suggesting subpectoral IPG implantation over subcutaneous implantation to achieve a more favorable cosmetic outcome, as well as less patient discomfort (Son et al., 2012; White-Dzuro et al., 2017). *Exuberant scarring of the IPG wound* may cause both poor cosmetic results and bowstringing (wire tethering), which is a considerable cause of pain-related discomfort and limitation of neck movements in DBS patients (Miller and Gross, 2009). *Migration of the IPG* can occur, especially with older IPG models. In such cases, revision of the subcutaneous pocket or relocation is warranted (Blomstedt and Hariz, 2005; Messina et al., 2014). Changing to a lower profile rechargeable IPG can help in such situations. *Skin erosion over the IPG* is another challenge, especially if the skin of the patient is very thin, which is a common issue with dystonic and anorexic patients (Frizon et al., 2017).

Another delayed complication involves twisting of the extension wires as the IPG flips over within the subcutaneous pocket. Although different types of flipping syndromes are described in CIED literature, only *Twiddler's syndrome* (IPG rotation around its vertical axis) has been described in DBS patients, which typically presents with DBS system malfunction. Its prevalence was reported as 1.3–1.4% of all DBS implanted patients in two different case series (Burdick et al., 2010; Sobstyl et al., 2017). A plain X-ray will show twisting of the extension wires often accompanied by migration or fracture of the extension wires or leads (Sobstyl et al., 2017). Twiddler's syndrome is mitigated with subfascial/submuscular placement of the IPG with two points of anchorage with non-absorbable suture and stitching the pocket to reduce its size (Sobstyl et al., 2017), as well as antibiotic envelopes or polyester pouches may be useful by increasing fibrous tissue formation that may limit IPG movement (Osoro et al., 2018). Some of these complications are illustrated in the photographic and radiographic form in the review by Morishita et al. (2010).

FUTURE STRATEGIES TO IMPROVE IPG LONGEVITY AND PRACTICALITY

Recent innovations that have the potential to improve IPG longevity and/or practicality include novel stimulation patterns,

material properties of the DBS system, skull-mounted generators, as well as enhanced wireless power transfer techniques.

Improving IPG Longevity by Alternative Stimulating Patterns

Directional DBS

Directional DBS (dDBS) refers to DBS with segmented leads that allow for shaping the electrical field perpendicular to the lead towards a specific brain region. Rebelo et al. (2018) provided some of the first evidence that the dDBS can consume less energy than conventional DBS (cDBS). They reported a 31% reduction in therapeutic current strength (TCS) and an overall 6% decrease in TEED compared to that estimated for all leads programmed as the best omnidirectional alternative. Similarly, in the early results of the Abbott-sponsored PROGRESS trial, dDBS achieved a similar clinical benefit compared to cDBS at a significantly lower (39%) TCS, which may have a considerable effect on energy consumption (Ramirez-Zamora et al., 2020) (www.ClinicalTrials.gov NCT02989610). Programing of directional leads is slightly different from the programming of conventional leads, as the density of charge is higher given the small surface of these segmented leads. The maximally allowed amplitude is 3.4 mA per contact based on the recommended threshold of tissue damage on the charge density of 30 mC/cm^2 (Pollo et al., 2014). Understanding the nuances of dDBS programming is paramount to maximizing the potential energy savings of such systems.

Cycling DBS

ON/OFF cycling is a frequently used parameter, particularly for the anterior nucleus of thalamus stimulation in epilepsy patients (Fisher et al., 2010). It is a potential approach to reduce energy delivery; however, acute stimulation studies showed a decreased treatment effect with cycling DBS compared to conventional DBS in ET (Swan et al., 2016), PD (Montgomery, 2005), and epilepsy (Molnar et al., 2006) patients. To demonstrate the efficacy of cycling DBS in ET patients, a prospective, randomized, double blind clinical trial has been designed and it is currently recruiting patients (www.ClinicalTrials.gov NCT04260971). Utilization of *Theta Burst DBS*, cyclic stimulation for 100 ms followed by a pause of 100 ms (Horn et al., 2020) or 200 ms (Sáenz-Farret et al., 2021) with a pulse width of 60 μs and a frequency of 50 Hz, may be beneficial for refractory axial symptoms of PD patients. Further research including battery consumption is needed in this field.

Ramped-Frequency DBS

Swan et al. (2020) recently evaluated a novel stimulation pattern termed ramped-frequency stimulation (RFS) in ET patients. These RFS patterns consisted of a harmonic progression of 15 instantaneous pulse frequencies that decreased from 130 Hz to 50 Hz, 130 Hz to 60 Hz, or 235 Hz to 90 Hz. These patterns were compared with constant frequency stimulations (CFS) that correspond to the mean pulse rates of the respective RFS patterns. Significant tremor suppression relative to "off" stimulation was shown with three different stimulation parameters: (i) 130 Hz CFS (greatest symptom relief), (ii) 82 Hz CFS, and (iii) 130–60 Hz RFS. There were no significant differences in tremor suppression between any RFS trains and their respective frequency-matched CFS trains. Thus, they suggested that tremor-related thalamic burst activity might result from burst-driver input, rather than from an intrinsic rebound mechanism. RFS may exacerbate thalamic burst firing by introducing consecutive pauses of increasing duration to the stimulation pattern. The balance between the energy conservation by the reduction of the average frequency of stimulation with RFS and the energy expenditure to drive this pattern is not known and warrants further investigation.

Square Biphasic Pulse DBS

The cDBS waveform consists of a rectangular biphasic pulse, with an active, high-amplitude and short-duration phase, followed by a passive, low-amplitude, and charge-balancing phase. Using square biphasic (sqBIP) pulses (with active rather than passive charge-balancing phase) is a novel method and shows similar, or even greater therapeutic benefit over cDBS in the treatment of PD, ET, and dystonia patients (Akbar et al., 2016; Almeida et al., 2017; De Jesus et al., 2019). However, the battery consumption was found significantly higher in sqBIP DBS than cDBS (Akbar et al., 2016), thus the utility of sqDBS with current non-rechargeable IPG configurations may be of limited value.

Replacing High-Frequency Stimulation With Low-Frequency

Low-frequency stimulation (LFS, <100 Hz) in PD has several advantages and drawbacks compared to conventional high-frequency stimulation (HFS, >100 Hz; Di Biase and Fasano, 2016; Su et al., 2018). LFS may be superior to HFS in akinesia, gait, and freezing of gait sub-scores, whereas HFS may induce better responses for tremor. LFS is associated with a decrease in the total electrical energy delivery and may help extend battery longevity. The mechanism of action of LFS may be different from that of HFS (i.e., maximum effectiveness achievement in ventral STN, or its possible effects on PPN activity; Su et al., 2018), which necessitates further evaluation before routine clinical application.

In 2017, Brocker et al. (2017) used a genetic algorithm (GA), which is an optimization technique based on principles from biological evolution, to design an optimized temporal pattern of stimulation. They coupled GA with a model of the basal ganglia in the design of an optimized stimulation pattern. The authors found out that the GA DBS (average frequency of 45 Hz) performance was equivalent to high-frequency (185 Hz) DBS in the bradykinesia-related finger-tapping task. The predicted changes in UPDRS motor sub-scores produced by stimulation with the GA pattern were equivalent to those produced by 185 Hz. However, the suppression of Parkinsonian tremor by GA DBS was somewhat lower than by HFS, which is in line with the abovementioned studies comparing LFS with HFS.

Variable Frequency Stimulation (VFS)

This is a novel DBS paradigm consisting of delivering both HFS and LFS interleaved in varying patterns using the PINS Medical IPGs (Jia et al., 2018). In a four patient pilot study, VFS was found superior to conventional HFS in the treatment of appendicular, as well as axial symptoms and freezing of gait (Jia et al., 2018).

The effect on battery conservation is unknown and yet to be investigated.

Adaptive DBS

Adaptive DBS (aDBS; closed-loop or responsive DBS) is a technique in which the delivery of the stimulation is modulated by the real-time sensing data *via* a feedback mechanism. aDBS can be amplitude-responsive, which refers to using the amplitude of signals to estimate the degree of circuit dysfunction, i.e., level of beta (13–30 Hz) LFP activity in STN (Kühn et al., 2008), or phase (timing) responsive, where pulses of stimulation are timed to a particular phase as in the treatment of tremor (Meidahl et al., 2017). The goal of this type of stimulation is to widen the therapeutic window by optimizing the delivery of the stimulation to correct the degree of circuit dysfunction. Transitioning from continuous stimulation to the responsive stimulation of aDBS is also expected to decrease the amount of energy consumption. Furthermore, several human clinical trials (Little et al., 2013, 2016; Rosa et al., 2017; Swann et al., 2018b; Velisar et al., 2019; Opri et al., 2020; He et al., 2021) have assessed the average energy saving associated with aDBS compared to continuous DBS in a similar time period and showed a range of energy-saving percentage of 38–73%. The characteristics and energy consumption percentages of these trials are given in **Table 2**.

Computational Models and Functional MRI Response Patterns for Optimization of DBS Programming

Apart from stimulation patterns, using a neuroanatomically based computer model for programming in PD patients provides comparable efficacy and less battery consumption over traditional, monopolar review-based programming, which has been demonstrated by the pilot GUIDE trial (Pourfar et al., 2015). A recent advance in the field of DBS programming is utilizing fMRI response patterns and machine learning algorithms to optimize DBS parameters. Our group demonstrated that DBS at optimal settings in PD patients produces a characteristic brain activation pattern on functional MRI with selective recruitment of motor circuits. This pattern can be used to predict optimal stimulation settings for individual patients and early identification of optimal settings may improve IPG longevity (Boutet et al., 2021).

Improving IPG Longevity by Electrode Material Selection

The conventional microelectrodes are comprised of noble metals such as gold (Au), Platinum (Pt), and Iridium (Ir), which are highly corrosion resistant in biofluids, however, their performance is limited by the mechanical mismatch between the electrode and neural tissue, which can lead to scarring, high impedance, and low surface area which restricts their charge injection capacity (CIC) (the maximum deliverable charge per unit area) (Cogan, 2008). Alternative materials have been under investigation for years with the goal of increasing the electrochemical surface area and reducing impedances. A lower impedance is expected to result in lower power usage and longer battery life. Examples of alternative microelectrode materials include ceramics (e.g., titanium nitride and iridium oxide), conducting polymers, nanoporous Pt, Pt grass, carbon nanotube arrays, and laser pyrolyzed graphene (Won et al., 2020). Recently, Wang et al. (2019) demonstrated the performance of microelectrodes made from graphene fibers coated with Pt. These microelectrodes have an unrivaled CIC with the ability to record and detect neural activity with an outstandingly high signal-to-noise ratio (SNR) in an area as small as an individual neuron; thus, making them potentially interesting candidates for use in closed-loop systems.

Improving IPG Practicality by Using Enhanced Wireless Power Transfer Techniques

Current commercially available rechargeable systems use *near-field short-range inductive coupling* wireless technology, which allows for power transfer across an exclusively short distance. The distance between the charging pad and the IPG battery can be increased by different wireless power systems such as: (1) *Magnetic resonant coupling systems* (Shin et al., 2017); which comprise resonant circuits that greatly increases coupling and power transfer between coils; (2) *Far-field RF transmission systems* (Park et al., 2015), which uses high-gain antennas or optical systems that reflect and refract electromagnetic radiation into beams and focus them on the receiver; and (3) *Ultrasonically powered* (Hinchet et al., 2019) *or Solar-powered* (Tokuda et al., 2018) *Wireless Battery Systems*. All the above-mentioned technologies may enable area wireless power coverage in the future. Patients can hang a transmitter coil in the walls of their living rooms that will wirelessly power and recharge their batteries while they are freely moving in the house. A commercially available prototype-Freedom-8A Wireless Spinal Cord Stimulator System (Stimwave, Pompano Beach, FL, USA)—is composed of a surgically implanted stimulator lead and a receiver that receives energy from a wearable transmitter and a battery. The transmitter and battery couple, which is called "Wearable Antenna Assembly", is worn above the skin, couples the RF energy on the receiver located under the skin, and can be recharged externally (Bolash et al., 2019). A similar system is available with a baseball cap implanted transmitter for peripheral nerve stimulation (StimRelieve LLC, Miami Beach, FL, USA; Weiner et al., 2017).

TECHNOLOGICAL ADVANCES TOWARDS EXTRACORPOREAL POWERED NON- TO MINIMAL-INVASIVE DBS SYSTEMS

With the unprecedented advancement in technology over the past few years, several approaches have been taken to activate neurons non- to minimal-invasively without requiring an internal power source. Some examples of such advances include ultrasonically powered systems, magnetically activated nanoparticles, temporally interfering electric fields, and near-infrared stimulation (**Figure 2**).

Ultrasonically Powered Systems

Wireless, leadless, battery-free, and small (1.7 mm^3 in volume), StimDust is a recently developed neural stimulator that is powered ultrasonically by a hand-held external transceiver.

TABLE 2 | Clinical trials of adaptive DBS with stated energy consumption.

Author, Journal, Year	Disease, Patient #, Target	Biomarker	Study protocol	Clinical effect	Mean Total Electrical Energy Delivered (TEED) during stimulation period	Average energy saving**
Little et al. (2013)	PD (8 patients), unilateral STN	LFP beta activity (if exceeds threshold, voltage increases)	DBS OFF, aDBS, cDBS and random DBS comparison *via* externalized extensions up to 7 days after lead implantation	Motor scores during aDBS improved better than cDBS by 29% (unblinded) and 27% (blinded)	aDBS (132 +/− 21 uW) cDBS*(270 +/− 37 uW) *$p < 0.0001$	51%
Little et al. (2016)	PD (4 patients), bilateral STN	LFP beta activity (if exceeds threshold, voltage increases)	DBS OFF and aDBS comparison *via* externalized extensions 2–6 days after lead implantation, L-dopa ON/OFF.	Motor scores are 43% better with aDBS than DBS OFF.	aDBS (223 + /− 31 uW) cDBS (estimated)(491 +/− 44 uW)	55%
Rosa et al. (2017)	PD (10 patients), unilateral STN	LFP beta activity (if exceeds threshold, voltage increases)	aDBS and cDBS comparison *via* externalized extensions 5 and 6 days after lead implantation, L-dopa ON/OFF	The clinical scores were not significantly different between aDBS and cDBS. aDBS was more effective on dyskinesias.	aDBS (44.6 + /− 47.9 uW) cDBS*(158.7 + /− 69.7 uW) *$p < 0.0005$	73%
Swann et al. (2018b)	PD (2 patients), unilateral STN	Cortical gamma band activity (if exceeds threshold, voltage decreases)	aDBS and cDBS comparison. aDBS delivered by Activa PC+S *via* Nexus D3 (patient tethered) and E interfaces (patient free).	Similar bradykinesia and dyskinesia scores for cDBS, Nexus D3 and E (Pt 1). N/A for Pt 2.	N/A	38% (Nexus D3) 39–45% (Nexus E)
Velisar et al. (2019)	PD (13 patients), 20 STN leads	LFP beta activity (dual threshold)	DBS OFF, aDBS and cDBS comparison. aDBS delivered by Activa PC+S *via* Nexus D3 interface.	aDBS significantly improved bradykinesia and tremor over DBS OFF.	N/A	44%
Opri et al., 2020	ET (3 patients), unilateral M1 subdural leads—VIM DBS lead	Movement onset by LFP of M1 and VIM (15/25 Hz) (EMG and inertial sensors used only for tremor evaluation, not as inputs)	DBS OFF, aDBS and cDBS comparison. aDBS delivered by Activa PC+S *via* Nexus D/E interface. Longitudinal follow-up for 6 months.	aDBS and cDBS improved the contralateral tremor scores by 47% and 52% compared with DBS OFF, respectively	N/A	57% (in clinic) 50% (at home)
He et al. (2021)	ET (6 bilateral, 2 unilateral patients), VIM-ZI	VIM LFP while the patient performed tremor provoking movements (Trained models)	DBS OFF, aDBS and cDBS comparison *via* externalized extensions 4 or 5 days after lead implantation.	aDBS and cDBS suppressed the tremor by 52% and 53% compared with DBS OFF, respectively.	N/A	61%

*DBS, Deep Brain Stimulation (aDBS: adaptive, cDBS: continuous); EEG, Electroencephalography; EMG, Electromyography; ET, Essential Tremor; FoG: Freezing of Gait; GPi, Globus pallidus internus; M1, primary motor cortex; LFP, Local Field Potential; N/A, Not-applicable; PD, Parkinson's Disease; PPN, Pedunculopontine nucleus; Pt, Patient; STN, Subthalamic Nucleus; VIM, Ventral intermediate; ZI, Zona incerta. *Statistical significance presents. **Calculated by formula (TEED-cDBS − TEED-aDBS)/TEED-cDBS.*

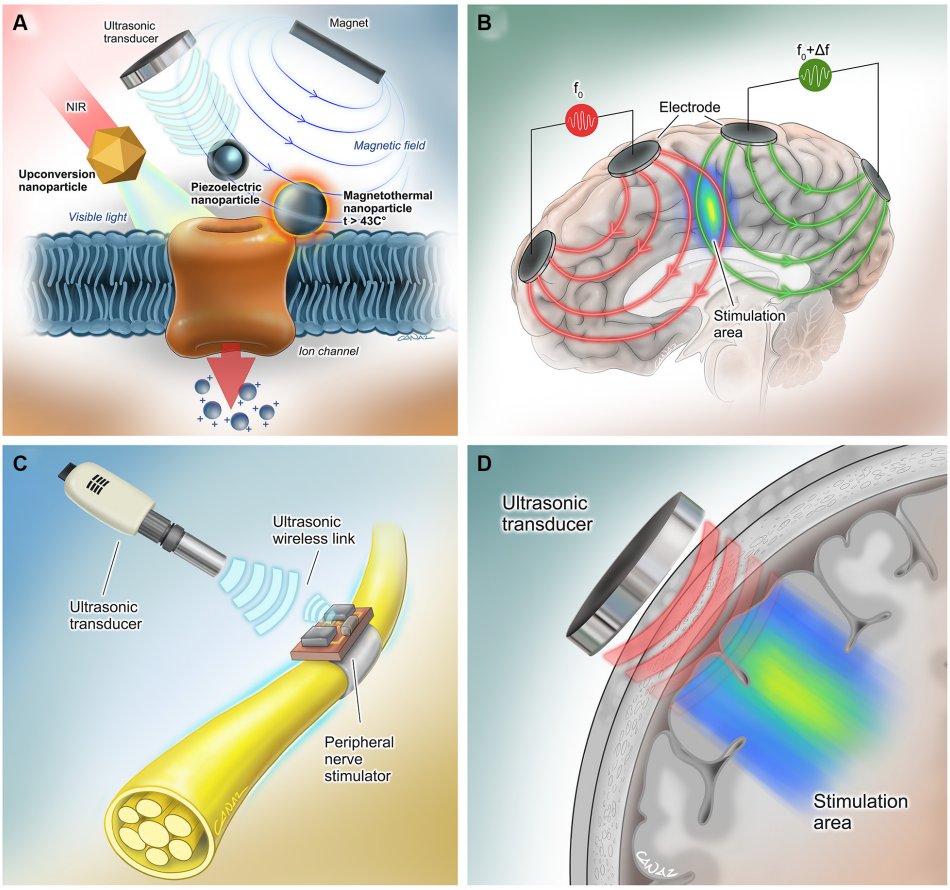


FIGURE 2 | Extracorporeal powered non- to minimal-invasive DBS systems. **(A)** (Left) Transcranial near-infrared light can be converted to visible light by molecularly tailored upconversion nanoparticles for stimulation of genetically modified channelrhodopsin-expressing neurons (Chen et al., 2018). (Middle) Piezoelectric nanoparticles can activate neurons when they are powered using an external magnetic field (Kozielski et al., 2021) or ultrasound (Marino et al., 2015). No genetic modification is needed for this method. (Right) Another method involves activation of genetically modified heat-sensitive capsaicin receptors on neurons by heat-generating magnetic nanoparticles (Chen et al., 2015). **(B)** In the method by Grossman et al., multiple electric fields at frequencies too high to recruit neural firing, but which differ in frequency within the dynamic range of neural firing were delivered. The interference between the two applied fields served to cancel out the high-frequency activity but allowed the emergence of an oscillation corresponding to the difference in the two frequencies that allows electrical stimulation of the neurons in the interference region (Grossman et al., 2017). **(C)** Neurons can be activated by wireless, leadless, battery-free, and small (1.7 mm^3 in volume) neural stimulators that are powered ultrasonically by hand-held external transceivers (Piech et al., 2020). **(D)** Transcranial ultrasound has the potential to be used as a neuromodulation tool even in the absence of a neurostimulator device (Fomenko et al., 2020). Reproduced with the permission of Dr. Gokhan Canaz (Cura Canaz Medical Arts).

The system includes a piezoceramic transducer that acts as the antenna of the system, an energy-storage capacitor, and an integrated circuit, which can efficiently harvest ultrasonic power, decode downlink data for the stimulation parameters and generate current controlled stimulation pulses, even when embedded in porcine tissue at a depth of more than 5 cm. Safety monitoring and alignment are provided through an ultrasonic backscatter. *In vivo* efficiency was demonstrated by stimulating the sciatic nerve of rats, which resulted in neuronal activation (Piech et al., 2020). Ultrasound can also be exploited in combination with piezoelectric materials, such as barium titanate nanoparticles (BTNP), in order to generate direct-current output, induce Ca^{2+}/Na^{+} influx, and elicit neural stimulation (Marino et al., 2015). In the future, a wearable ultrasound transceiver as a baseball cap may be utilized for neural stimulation in humans *via* this method, following minimally invasive implantation of such stimulator devices. Of note, ultrasound has the potential to be used as a neuromodulation tool, even in the absence of these millimeter-thick neurostimulator devices (Fomenko et al., 2020).

Magnetoelectric and Magnetothermal Stimulation by Injectable Nanoparticles

This approach involves the use of magnetoelectric nanoparticles (MENPs) produced from magnetostrictive $CoFe_2O_4$ nanoparticles coated with piezoelectric $BaTiO_3$ (Kozielski et al., 2021). *In vivo* studies have demonstrated that MENPs injected cells can be activated under remote non-resonant frequency magnetic stimulation, which is sufficient to cause neural activation to change animal behavior.

In another similar neural excitation technique, injected magnetic nanoparticles exploited thermal energy rather than generating electrical fields to activate genetically introduced heat-sensitive capsaicin receptor TRPV1 on neural cell membranes and elicit depolarization (Chen et al., 2015).

Near-Infrared Stimulation *via* Upconversion Nanoparticles

The application of optogenetic methods in humans may be a revolutionary modality for neurostimulation. The first human optogenetic clinical trial has been ongoing for the treatment of retinitis pigmentosa patients (ClinicalTrials.gov NCT02556736). A demonstration of safety and feasibility in such a study may open the door for human research for deep brain stimulation *via* optogenetics. A promising study by Chen et al. demonstrated a novel DBS modality, in which extracranially applied tissue-penetrating near-infrared (NIR) light replaces the visible light source leads in conventional optogenetics. Molecularly tailored upconversion nanoparticles (UCNPs) were injected into deep brain tissues to convert transcranial NIR irradiation to visible light for activation of channelrhodopsin-expressing neurons (Chen et al., 2018). In the future, DBS may be performed using stereotactically injected viral vectors with UCNPs and wearable NIR light sources. However, this approach may be more difficult to deploy compared to the aforementioned alternatives, as it will require an exogenous expression of channelrhodopsins that, although feasible in preclinical models, still have significant hurdles to overcome for translation into human patients.

Temporally Interfering Electric Fields

In 2017, Grossman et al. (2017) presented a method that enables noninvasive stimulation of deep brain structures by delivering multiple electric fields at frequencies too high to recruit neural firing, but which differ in frequency within the dynamic range of neural firing. The interference between the two applied fields served to cancel out the high-frequency activity but allowed the emergence of an oscillation corresponding to the difference in the two frequencies that allows electrical stimulation of the neurons in the interference region. The feasibility of this technique has been demonstrated in mice, whereas chronic application in human brains requires further investigation. However, this method has the potential to change conventional DBS methods and allow the externalization of power sources.

CONCLUSION

At present, DBS IPGs are associated with numerous clinical challenges and are prone to various complications. Advances in DBS IPG engineering constitute one of the most promising areas of growth in the field of functional neurosurgery. With the development of further insights into effective programming, together with novel hardware materials, IPG longevity may be extended. This may in turn result in reduced costs and complications associated with DBS therapy. In addition, the utilization of enhanced wireless recharging techniques may increase the practicality of the current devices. Novel external neuromodulation strategies may allow IPGs to become extracorporeal in the future.

AUTHOR CONTRIBUTIONS

Concept and design: CS, CI-M, MP, and SK. Supervision: SK. Literature search: CS, CI-M, and DA-P, AN. Writing manuscript: CS, CI-M, DA-P, AN, AF, and AZ. Figure and table design: CS, KY, and AZ. Critical review: NL, GI, CH, MH, AL, RM, AF, and SK. All authors contributed to the article and approved the submitted version.

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The Role of Large-Scale Data Infrastructure in Developing Next-Generation Deep Brain Stimulation Therapies

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Advances in neuromodulation technologies hold the promise of treating a patient's unique brain network pathology using personalized stimulation patterns. In service of these goals, neuromodulation clinical trials using sensing-enabled devices are routinely generating large multi-modal datasets. However, with the expansion of data acquisition also comes an increasing difficulty to store, manage, and analyze the associated datasets, which integrate complex neural and wearable time-series data with dynamic assessments of patients' symptomatic state. Here, we discuss a scalable cloud-based data platform that enables ingestion, aggregation, storage, query, and analysis of multi-modal neurotechnology datasets. This large-scale data infrastructure will accelerate translational neuromodulation research and enable the development and delivery of next-generation deep brain stimulation therapies.

Keywords: big data, precision medicine, data infrastructure, neuromodulation, deep brain stimulation

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INTRODUCTION

Precision medicine has changed the face of modern healthcare. Historically, treatments have been developed assuming a one-size-fits-all approach. Now, thanks to advances in multi-modal data collection and analysis, we understand that many diseases are heterogeneous and require personalized treatment strategies. Precision oncology has been at the forefront of this revolution. High-throughput technologies generating large, multi-omics datasets have spurred data-driven approaches to inform risk prediction, disease detection, diagnosis, phenotyping, and identification of new therapeutic targets. Data aggregation platforms emerged as critical tools for structuring and sharing these complex data, driving data utility for both the researchers and clinicians who are developing next-generation, precision therapies (de Anda-Jáuregui and Hernández-Lemus, 2020).

In neurological and psychiatric disorders such as Parkinson's disease (PD), epilepsy, major depressive disorder, and obsessive compulsive disorder, data-driven approaches for disease classification and treatment have yet to gain widespread integration into clinical decision making. Each diagnosis remains a heterogeneous mixture of phenotypes, with limited options for

personalized therapies. However, several studies have demonstrated the value of characterizing patient-specific disease pathophysiology. For example, studies utilizing neuroimaging and neurophysiology have identified putative subgroups of depression, which may be valuable in predicting responsiveness to therapy (Riva-Posse et al., 2014; Drysdale et al., 2017; Williams, 2017; Wu et al., 2020). These initial studies illustrated the utility of a single cross-sectional snapshot of neural circuitry, but acute assessments fail to capture the full complexity of these time-varying disorders.

Transitioning research outside of the acute clinical setting and into longitudinal real-world environments requires tools that can track both neural activity and patient clinical state over the span of years. Implantable neural devices have enabled chronic field potential recordings in brain circuits, with the potential to continuously stream data over the lifetime of the device (Stanslaski et al., 2018; Gilron et al., 2021; Goyal et al., 2021). However, data labeling and contextualization are important for maximizing the utility of these electrophysiological recordings. Thus, simultaneous monitoring of patient state is critical. Digital technologies such as wearable sensors, as well as clinician assessments and patient self-report, provide both objective and subjective measures of patient state (Bot et al., 2016; Pathak et al., 2021; Powers et al., 2021).

The resulting large-size, multi-modal datasets require significant data infrastructure that supports scalable data ingestion, time-syncing, storage, query, and analysis. These systems are complex from a technical, reliability, and compliance standpoint and are beyond the capacity of most individual research groups. Rune Labs has developed a data platform that is uniquely tailored to the needs of the neuromodulation community. We present this as an example of the type of infrastructure that can be used to develop and deliver data-intensive neuromodulation therapies. We discuss advantages of using a common infrastructure, which include ease of data sharing and replication of results, both within and across teams.

UNMET NEEDS IN PRECISION NEUROMODULATION

Longitudinal neural physiology combined with objective monitoring of clinical state is particularly important for disorders that are time-varying. For example, in PD, patients fluctuate between periods of adequate and inadequate symptom control, as dopaminergic medications wear in-and-out (Kalia and Lang, 2015). Conventional deep brain stimulation (DBS) delivers continuous stimulation to the basal ganglia nuclei, regardless of a patient's clinical state. This can lead to both under-stimulation, resulting in inadequately controlled symptoms, or over-stimulation, resulting in unwanted side effects such as dyskinesia (Beudel and Brown, 2016). Adaptive DBS (aDBS) aims to address these shortcomings by using biomarkers to track disease fluctuations and update therapy delivery in real-time. Acute tests of aDBS have demonstrated the feasibility of incorporating a feedback signal into stimulation titration, and studies have matched the clinical efficacy of continuous DBS (Little and Brown, 2020). However, these studies have been limited to short clinical visits, and prolonged tests of aDBS have not yet been shown to be more efficacious than standard DBS (Gilron et al., 2021).

Formulating aDBS paradigms that translate outside of the clinic is first dependent on identifying biomarkers that track clinical state. In PD, several biomarker candidates have emerged that track the hypo- and hyperkinetic states, though they have yet to be validated in chronic settings (Little and Brown, 2020). Similarly in depression, candidate neurophysiological biomarkers have been identified solely in acute settings (Kirkby et al., 2018; Sani et al., 2018; de Aguiar Neto and Rosa, 2019). Accordingly, researchers are adapting their data collection and analysis protocols for longitudinal, at-home recording. These recordings capture the full spectrum of clinical variability and naturalistic human behaviors that cannot be assessed in clinic. Importantly, generating insights from these rich neural time series requires precise integration with other at-home monitoring data, including wearable sensor time series and single time-point reports of patient state. Thus, drawing the links between patient state and neural physiology is dependent on being able to access precisely synchronized data from several data streams.

Furthermore, testing aDBS over long time courses in patients' homes requires efficient data transfer and availability. Both researchers and clinicians need easy access to recorded data such that they can assess algorithm performance and iterate on tests. This involves transferring data from the patient's implanted device to external computers and/or cloud based storage without requiring frequent clinic visits. This transfer must be both efficient and secure. Data from raw device files must then be parsed and represented in an accessible manner to both researchers and clinicians, and these analysis pipelines must be integrated into their normal workflows.

Finally, optimizing aDBS can benefit from data-driven approaches to streamline the programming process. aDBS optimization is currently constrained by a large parameter search space, in part due to increasingly sophisticated electrode designs and stimulating device capabilities. Furthermore, individual variability in electrode locations and neuroanatomy is not taken into account. Data-driven modeling frameworks can be explored to narrow aDBS tuning parameters and guide clinical programming. These modeling approaches are contingent on the ability to query and aggregate large datasets and conduct computationally intensive analyses.

Thus far, lags in technological development have delayed large-scale testing of aDBS in chronic settings. Capabilities of earlier generation implantable neural devices initially limited the ability to do biomarker discovery. As new devices pushed brain sensing into patients' homes, there became an additional need for tools that chronically evaluate patient state. Developing patient- and researcher-facing applications, in addition to data infrastructure that integrates these large data sets, requires software engineering resources and time. Thus unlocking the full utility of these rich datasets requires a scalable and efficient data platform.

A DATA INFRASTRUCTURE SOLUTION

Rune Labs has developed a scalable, HIPAA-compliant, cloud-based data platform designed for (1) time-synchronization and aggregation of multi-modal datasets (2) real-time data access, and (3) data analysis at the scale of multiple terabytes, directly in the cloud. The platform is optimized for datasets generated in neuromodulation research, such as longitudinal time series data from a variety of devices, including but not limited to neural implants, wearable sensors, and patient-facing phone-based applications.

System Architecture

The technology's architecture is organized as a multi-step pipeline (**Figure 1A**). First, patient data are uploaded—either in batches or in real time—from all devices such as neural implants, wearable monitors, and mobile applications. Data from internet-connected devices such as wearable and mobile devices are uploaded automatically. Data from neural implants can be directly uploaded via HTTPS, or automatically synchronized via third party cloud storage platforms, such as Box, reducing the need for manual file transfer. With each upload, a permanent copy of the original data is securely stored and versioned, and a data catalog is updated to mark its location, ownership, and details. New data are immediately processed upon arrival with a high-availability upload application programming interface (API) that maintains at least 99.9% service uptime. This is achieved with (1) containerized deployment, whereby daily code updates are rolled out with only 10% of containers taken offline at a time, so that the cluster as a whole remains responsive, and (2) service level agreements with Amazon Web Services that guarantees service uptime (AWS Service Level Agreements, 2021).

Then, data pass through an ingestion layer, which parses proprietary or open source data formats and outputs time series signals together with device-related meta data, such as recording configurations (electrode pairs, sampling rate, etc.) and stimulation settings (frequency, amplitude, ramp rates, etc.) (Sellers et al., 2021). Importantly, full integration into both patient and researcher workflows ensures that users need not be involved in the engineering processes that handles data transfer, upload, and parsing (**Figure 1B**). Patients are primarily tasked with managing devices that collect data, and researchers have access to the resulting time-synchronized datasets, while remaining removed from the engineering details in **Figure 1A**.

Ingested data are stored in a structured time series database. A distributed Write-Ahead Log (WAL) is used to scale data-write horizontally across compute clusters, acting as a surge-protector so that the system is resilient to spikes of new incoming patient data. The WAL data are dispatched into an indexed time-series data store that aligns the multi-modal streams in the time domain. This layer services real-time random access to any segment of the data, across one or many patients and devices. The same WAL data are concurrently double-dispatched to a replicated data lake, where much larger cross-patient query and analysis can be performed at petabyte scale.

Finally, all data are available through a Python-based API and software development kit (SDK). Because complete datasets are parsed for both time series and meta data components, data are easily queried and accessed for either cloud or local compute (**Figure 1C**). This reduces the need for research groups to manually inventory and curate data, using variable organization schemes that may hinder reproducibility across teams.

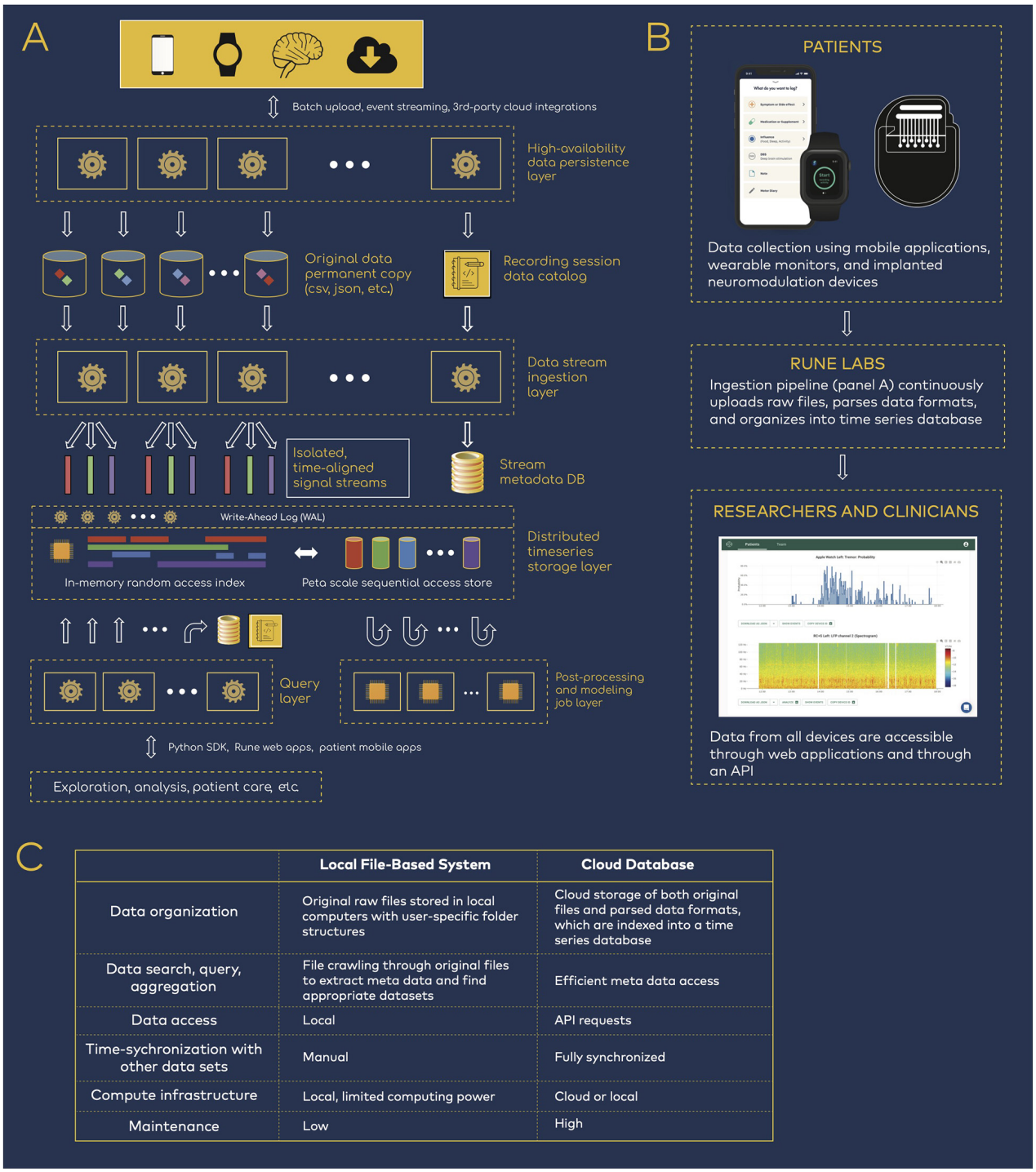
Figure 2A shows an illustrative example of a raw data file from the Medtronic Summit RC + S system and its parsed, human readable format. Given the size and scale of the multimodal continuous time series collected in neuromodulation research, data ingestion represents a large computational effort (**Figure 2B**). Industry-scale databases offer an efficient, safe, and standardized approach to handling these large datasets. Analysis-ready data are accessible reliably through an API (**Figure 2C**). To test API performance, we accessed data using 1,800 randomized API requests with a 100% success rate. The mean data request size was 290.3 $\pm$ 56.0 MB, with an execution time of 7.3 $\pm$ 1.2 s. Combined across all queries, a total of 522.6 GB of data were downloaded in 3.6 h. These performance tests capture a baseline level representative of the platform at its current state. As the platform is updated over time to leverage new designs and tools, performance is expected to continually improve.

The entire system architecture—from ingestion to data access through the API—facilitates data sharing and analysis reproducibility within and between research teams. First, all datasets are treated immutably and versioned, from the raw file through parsing, pre-processing, and post-processing steps. The origin of each initial and intermediate dataset is recorded, including the algorithmic code applied between each input/output layer. This ensures that all versions of accessed data can be traced. Second, data access through an API enables scientific collaborators to share analysis code that is not dependent on local machine file/directory configurations or individual data parsing algorithms.

Development Process

The Rune Labs platform is developed using industry-level data pipeline tools with leading standards for code documentation, maintenance, and security audits, including secure handling of sensitive patient health information. Amazon Web Services' set of HIPAA-eligible services guarantee both reliability and compliance. Data at rest are encrypted universally, and all connections inside and out of the network perimeter are secured by Transport Layer Security. All personally identifiable information is isolated to a single part of the platform topology and secured, allowing the vast majority of the internal services to act entirely on de-identified data.

All development is structured through a process of collaborative design, architectural review, automatically enforced code test coverage and quality standards, and explicit security and risk assessment checkpoints. The Standard Development Lifecycle is designed around the FDA-mandated format of validation and verification. Risk matrices are created for all new features, outlining possible failure modes and security attacks, mapped to the corresponding standard FDA severity and probability indices, implemented mitigations, and finally



	Local File-Based System	Cloud Database
Data organization	Original raw files stored in local computers with user-specific folder structures	Cloud storage of both original files and parsed data formats, which are indexed into a time series database
Data search, query, aggregation	File crawling through original files to extract meta data and find appropriate datasets	Efficient meta data access
Data access	Local	API requests
Time-sychronization with other data sets	Manual	Fully synchronized
Compute infrastructure	Local, limited computing power	Cloud or local
Maintenance	Low	High

FIGURE 1 | Data infrastructure for neuromodulation research. **(A)** Rune system architecture. Patient data spanning neural physiology, wearable physiology, and mobile applications step through several processing layers that parse, synchronize, and store the multi-modal data streams. **(B)** Data flow from patients to researchers and clinicians. The data infrastructure pipeline is integrated into research workflows, such that researchers have easy access to patient data but are removed from the process of managing the data transition and ingestion. **(C)** Comparison of local versus cloud-based data management.

the respective validation and verification over those mitigations. In order to maintain stability as the platform continuously evolves to follow the research community, new functionality is wrapped in conditional execution containers so it can be vetted thoroughly against subsets of patient data before being enabled universally. This latter pattern enables safe and rapid integration

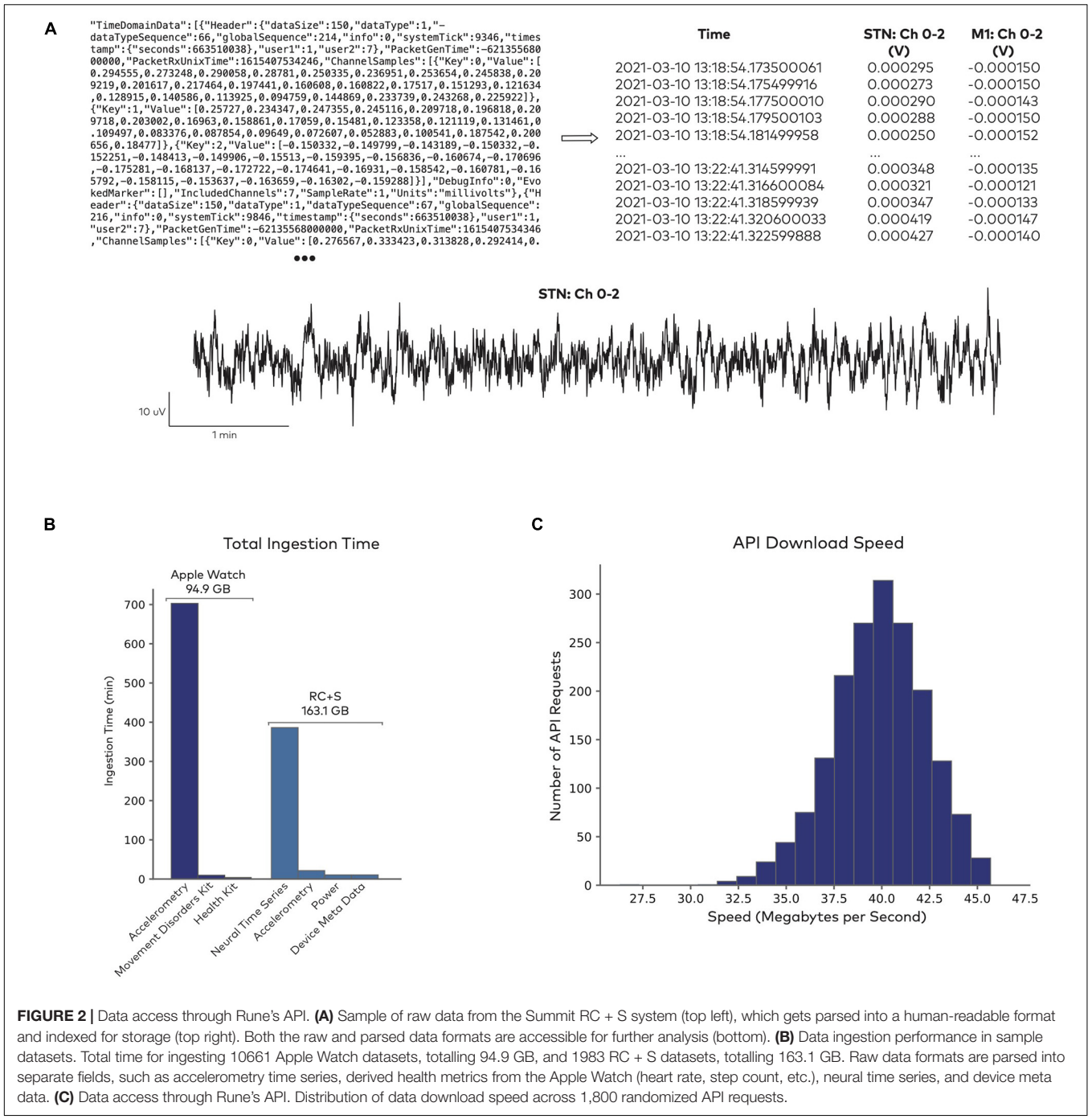


FIGURE 2 | Data access through Rune's API. **(A)** Sample of raw data from the Summit RC + S system (top left), which gets parsed into a human-readable format and indexed for storage (top right). Both the raw and parsed data formats are accessible for further analysis (bottom). **(B)** Data ingestion performance in sample datasets. Total time for ingesting 10661 Apple Watch datasets, totalling 94.9 GB, and 1983 RC + S datasets, totalling 163.1 GB. Raw data formats are parsed into separate fields, such as accelerometry time series, derived health metrics from the Apple Watch (heart rate, step count, etc.), neural time series, and device meta data. **(C)** Data access through Rune's API. Distribution of data download speed across 1,800 randomized API requests.

of new devices and data types. It therefore ensures a safe, scalable, and efficient solution for data access, aggregation, and sharing.

SHARED DATA PLATFORMS AND NEUROMODULATION THERAPY DEVELOPMENT

Traditionally, neuromodulation researchers have created in-house systems, applications, libraries, and toolkits to manage data generated during clinical trials. However, effectively managing the increasingly large and complex datasets requires a significant investment in software engineering. Furthermore, individual research laboratories may not be equipped for maintenance, compliance, and lifecycle management of data software that has been custom-developed for single trials or projects. Thus the end of a project—or even the departure of a key researcher—can pose a major hurdle for long-term utilization of valuable datasets.

An alternative is for researchers to leverage data platforms that are shared in common with other research groups and clinical

teams. These "out-of-the-box" systems have the advantage of long-term stability, compliance, and scalability for patients, clinicians, and researchers. Embracing collaborative data platform ecosystems can save time and eliminate redundancy, accelerating the translation of technologies from laboratory to clinic (Borton et al., 2020). The use of common data platforms may also facilitate open-sourcing de-identified datasets, enabling researchers to combine data from different patients, projects, and research centers.

Existing data sharing options, including both data archives and databases, are not currently optimized for chronic neuromodulation datasets. Data archives serve as a repository for sharing data files, which can include both variable data formats (DABI, 2021) or common data structures (Dandi Archive, 2021). However, unlike databases, archives do not enable efficient data query for the large-scale data that are produced with chronic recordings. Similarly, existing databases in the neurology space were developed to support data in acute or cross-sectional study designs, and they primarily service different data modalities, such as neuroimaging (D'Haese et al., 2015). Chronic multi-modal time series data are not optimally served by existing data archive and database options, though a specific data solution is necessary for managing these growing datasets.

When deciding whether to use a shared data platform to support a project or clinical trial, researchers will have to weigh several factors. Custom, internally developed software may be suitable for small feasibility studies. However, a common data platform offers several advantages. First, a data platform utilizes validated data pipelines for the neuromodulation device, wearable device, or other data source. Multi-modal data sources can be difficult to synchronize and ingest, and validated data pipelines can reduce errors. Second, a common data platform enables the synthesis of datasets across trials, centers, or patient cohorts. Finally, a common data platform facilitates collaborative analysis. Accessing data from the cloud with a documented API/SDK facilitates easy code sharing and ensures that all collaborators are working from the same datasets.

CONCLUSION

The future of DBS therapies is shifting toward personalizable, precision medicine. Researchers and clinicians are generating growing datasets that are increasingly difficult to manage and analyze. Here, we described an example of a data infrastructure platform that unblocks access and utilization of complex, multi-modal datasets for researchers and clinicians to develop next-generation neuromodulation therapies. As neuromodulation researchers adopt these types of data platforms for supporting development of new therapies, we can expect larger trials across multiple centers, more reproducibility of key analytical results and programming strategies, and faster discovery of new biomarkers and therapeutic targets.

AUTHOR CONTRIBUTIONS

WC wrote the manuscript with support from LK, MK, and BP. RG edited the manuscript. MK designed the data platform. PS assisted with analysis. BP conceived the original idea. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: WC, LK, MK, PS, and BP were employed by Rune Labs. RG was a consultant for Rune Labs.

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BRIEF RESEARCH REPORT
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Suppression and Rebound of Pallidal Beta Power: Observation Using a Chronic Sensing DBS Device

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Pallidal deep brain stimulation (DBS) is an increasingly used therapy for Parkinson's disease (PD). Here, we study the effect of DBS on pallidal oscillatory activity as well as on symptom severity in an individual with PD implanted with a new pulse generator (Medtronic Percept system) which facilitates chronic recording of local field potentials (LFP) through implanted DBS lead. Pallidal LFPs were recorded while delivering stimulation in a monopolar configuration using stepwise increments (0.5 mA, every 20 s). At each stimulation amplitude, the power spectral density (PSD) was computed, and beta power (13–30 Hz) was calculated and correlated with the degree of bradykinesia. Pallidal beta power was reduced when therapeutic stimulation was delivered. Beta power correlated to the severity of bradykinesia. Worsening of parkinsonism when excessive stimulation was applied was associated with a rebound in the beta band power. These preliminary results suggest that pallidal beta power might be used as an objective marker of the disease state in PD. The use of brain sensing from implanted neural interfaces may in the future facilitate clinical programming. Detection of rebound could help to optimize benefits and minimize worsening from overstimulation.

Keywords: deep brain stimulation, Parkinson's disease, local field potential, electrophysiology, beta power oscillations

INTRODUCTION

Deep brain stimulation (DBS) is an invasive neurosurgical therapy which can be applied for select movement and neuropsychiatric disorders. The classical procedure consists of implanting electrodes in the brain and delivering continuously electrical stimulation through an implanted battery source referred to as an impulse generator. Although the subthalamic nucleus (STN) has been the most common brain region targeted, the globus pallidus internus (GPi) has been increasingly used especially in cases with dyskinesia, cognitive issues and a need for long-term medication adjustment flexibility (Okun et al., 2009; Follett et al., 2010).

One challenge in DBS treatment has been the complexity of choosing the optimal therapeutic settings. DBS therapy can be adjusted by changing the stimulation frequency, pulse width, and amplitude which is deleivered via a standard square wave pulse. There are thousands

of possible DBS programming combinations making algorithms important to drive practical delivery of care in the outpatient setting (Kuncel and Grill, 2004; Anderson et al., 2018). The complex therapeutic options can lead to laborious programming sessions aimed at identification of the optimal stimulation settings. Several algorithms have been developed in effort to improve the therapeutic setting selection including techniques which employ a volume of tissue activation analysis (Frankemolle et al., 2010; Krack et al., 2019) along with local field potentials (LFP) (Hoang et al., 2017).

A number of studies have shown that STN beta power (13 – 30 Hz) is correlated with Parkinson's disease (PD) symptom severity, particularly rigidity and bradykinesia (Weinberger et al., 2006; Ray et al., 2008), and that the pathological beta signal will be attenuated by effective therapeutic STN stimulation (Bronte-Stewart et al., 2009). Recent advancements in the DBS technology have provided broader access to neural activity near the electrode and access during actual stimulation (Goyal et al., 2021). This advance has the potential to facilitate translation of existing research findings into the clinical environment and to enable the development of more objective approaches for DBS programming. Using a chronic sensing-enabled neurostimulator recently approved for commercial use (Medtronic Percept), Feldmann and colleagues observed robust changes in the STN beta power during stepwise monopolar stimulation could be used as a method to select optimal therapeutic settings (Feldmann et al., 2021). Although GPi DBS is increasingly used for the treatment of PD, with a number of intraoperative pallidal physiology studies (Silberstein et al., 2003; Eisinger et al., 2020) and chronic recordings (Lu et al., 2020; Neumann et al., 2020) shown potential correlates of symptoms, chronic sensing GPi physiology remains largely unknown and its potential to assist in determining optimal therapeutic programming settings remains to be demonstrated.

We report a single PD participant receiving unilateral GPi DBS treatment implanted with a novel sensing-enabled neurostimulator. We recorded the neural signals in the GPi region during DBS treatment and we analyzed the relationship between the changes in neural signals and symptom improvement. We hypothesized that pallidal stimulation would reduce the beta power and correlate with symptom improvement and that this technique might be useful as an objective measure to guide future DBS programming.

METHODS

Study Participant

This study was approved by the Institutional Review Board (IRB) of the University of Florida (IRB#202002433). A 57-year-old male with a 10 years history of PD was recruited and consented according to the Declaration of Helsinki. The written consent form was approved by the local ethical committee. The participant was diagnosed as the akinetic and rigid subtype of PD with minimal tremor symptoms. He was on 1100mg L-Dopa equivalent daily dose of PD medication prior to receiving his DBS therapy. The Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score at baseline was 34 OFF medication and 21 ON medication. He was implanted with unilateral GPi DBS of left hemisphere.

Surgical Procedure and Electrode Localization

A DBS electrode (Medtronic Model 3387) was implanted in the GPi, as previously described (Foote and Okun, 2005). The surgical planning was performed using a modified digital Schaltenbrand-Bailey deformable atlas overlay over an MRI FGATIR sequence for targeting (Sudhyadhom et al., 2009), and microelectrode recording was performed along the planned trajectory to verify the presence of GPi neurons along the trajectory (Mann et al., 2009). A month following the DBS electrode implantation, the impulse generator (Medtronic Percept), a chronic sensing-enabled neurostimulator, was implanted into the right subclavicular region. This DBS device is a commercially available non-rechargeable neurostimulator delivering constant current and was enabled for LFPs sensing.

The final position of the DBS electrode was verified using post-operative non-contrast CT head imaging which was fused with the pre-operative MRI FGATIR using a 3D affine transformation. The same modified digital Schaltenbrand-Bailey atlas used for DBS implantation surgery was used to verify the electrode position relative to the target region.

Study Protocol

Electrophysiological recordings were collected during the initial monopolar review visit 1 week following neurostimulator implantation. The electrophysiological recordings were collected with a sampling rate of 250 Hz as limited by the neurostimulator. The participant arrived in the visit in OFF medication state (at least 12 h after the last medication intake). First, a 2-min baseline LFP recording off stimulation was performed to determine the baseline characteristics of the three non-adjacent bipolar recording contact pairs (0–2, 1–3, and 0–3). Second, the clinical programmer examined the effect of stimulation delivered at each contact sequentially from the most ventral to the most dorsal contact by slowly increasing the stimulation amplitude while pulse width and frequency were kept constant at 90 μS and 130 Hz until the participant reported persistent stimulation induced side effects. During stimulation testing using contact 1 and 2, the LFPs were recorded continuously from contact 0–2 and 1–3, respectively. The stimulation amplitude was increased by 0.5 mA increments starting at 0 mA up to the side effects threshold, with a minimum of a 20 s waiting period between each amplitude change. In addition to the LFP, spectral power at the pre-defined frequency was simultaneously recorded, with a 1.26 ms sensing blanking and was averaged over 3000 ms. The power band was defined as the maximum beta peak at rest (17.57 ± 2 Hz for contact 0–2 and 23.44 ± 2 Hz for contact 1–3) by visual inspection on the Medtronic programming tablet. The defined spectral band power was collected by Percept PC at a rate of 2 Hz (500 ms per data point) with 3000 ms averaging window. After the waiting period, the clinician performed an assessment of contralateral upper limb rigidity and bradykinesia using the

UPDRS item 22 and 23, respectively, to evaluate the therapeutic benefit of each stimulation amplitude.

Data Analysis

The LFPs collected were exported to a standard JSON format file that was parsed and imported to Python 3. The raw time-domain LFP recordings were filtered between 1 and 100 Hz to remove drift and stimulation artifacts, then transformed to time-frequency plot using standard spectrogram with 1-s Hamming window and 0.5-s overlap. To quantify the stimulation-induced power changes, 15 s of data free of artifact, excluding 2 s of data immediately before and after stimulation changes were used to avoid stimulation transition artifacts; these were selected at each stimulation amplitude and the power spectral density was computed using Welch's periodogram method with 1-s hamming window and 0.5-s overlap. The beta power which was simultaneously streamed was also averaged at each stimulation amplitude and was correlated with the symptom severity score from UPDRS motor assessment by applying a Spearman's correlation.

RESULTS

Baseline Characteristics and Electrode Localization

Figure 1A shows the power spectral density computed from the three sensing-enabled stimulation contact pairs (0–2, 1–3, and 0–3). A large peak in the beta band (13 – 30 Hz) was observed in bipolar sensing contact pairs 1–3, with the maximum power occurring at 23.44 Hz. Contact pairs 0–2 and 0–3 had minimal activity in the beta band and were instead characterized by stronger low frequency oscillations (1 – 10 Hz). These results suggested that contact 1 was likely localized closer to the beta source. **Figure 1B** shows the final electrode positions relative to the GPi. The most ventral contact (contact 0) was inferior to the GPi border, contacts 1 and 2 were within the GPi, and the most dorsal contact (contact 3) was located on the border of GPi and GPe.

Beta Power Reduction With Pallidal Stimulation

Figure 2A shows the time-frequency plots of LFPs recorded from contact pair 1–3 while delivering stimulation from contact 2. The stimulation was slowly increased by a 0.5 mA increment from 0 mA to 5 mA, and hand tingling and mouth pulling was induced by the procedure at higher thresholds. The incremental stimulation amplitude is shown on the lower panel. Note that the stimulation changes were associated with transient artifacts. To quantify the effect of stimulation, the PSDs were computed at each stimulation amplitude, excluding a 2 s period at the stimulation transitions, and this is shown on **Figure 2B**. A reduction in beta and low gamma power with increased GPi stimulation was observed and we show this in both figures. Interestingly, a slight rebound in beta power was observed when stimulation amplitude was closer to the side-effect threshold.

Figure 2C shows the time-frequency plots of LFPs recorded from contact pair 0–2 while delivering stimulation from contact 1. Similar stepwise increment was performed at contact 1 and the stimulation PSDs were shown in **Figure 2D**. A narrow beta peak was observed at 17 Hz, but this peak was not correlated with symptom improvement. A reduction in broader high beta power was also found when stimulating from contact 1 and recording LFPs from contact 0–2 (**Figure 2D**) but not as significant as contact 2.

Relationship of Beta Power and Symptom Severity

Of the two primary symptom measurements, only bradykinesia shows improvement with stimulation while rigidity remain at a score of 1 throughout the full therapy range; therefore, rigidity was not reported in the correlation analysis. **Figures 3A,C** shows both the distribution and the median of the average beta power (17.57 $\pm$ 2 Hz for contact 0–2 and 23.44 $\pm$ 2 Hz for contact 1–3) at each stimulation amplitude and this is displayed as a box-violin plot for LFP recorded from contacts 0–2 while stimulating on contact 1 and contacts 1–3 while stimulating on contact 2. Contact 2 best controlled the participant's symptoms. Increased stimulation amplitude resulted in a reduction in beta power, with a considerable change at 1 mA at contact 2. Interestingly, the participant experienced a worsening of bradykinesia with a stimulation amplitude above 4.0 mA and the worsening was associated with increased beta power. The bradykinesia scores across stimulation amplitudes (**Figure 3A**) were significantly correlated with the average beta power values (**Figure 3B**) and analysis with a Spearman's correlation coefficient revealed 0.84 (p = 0.0013). Contact 1 LFP does not show correlation with symptom improvement (**Figure 3D**, p = 0.28) and contact 1 therapy has a narrower therapeutic window than contact 2 (**Figure 3C**).

DISCUSSION

In this study, a novel sensing-enabled DBS device was applied to an individual with PD implanted with GPi DBS. LFPs were recorded while delivering stimulation, at contact 1 and 2 sequentially, and by slowly increasing stimulation amplitude until side effects were encountered. The bradykinesia severity and rigidity were recorded at each stimulation amplitude and was correlated with the LFP feature.

Real-time neuronal recordings during threshold testing revealed a beta desynchronization when electrical stimulation was delivered to the target region. The beta desynchronization was stronger for the sensing contact pair 1–3 than for contact pair 0–2. This matched the baseline characteristics which also revealed a stronger beta peak when sensing at contact pair 1–3. This result matched with the imaging which revealed that the electrode contacts were located within the GPi. The beta power was strongly correlated with bradykinesia improvement when we measured in the acute clinic setting. The improvement was consistent with previous intraoperative (Wang et al., 2018; Piña-Fuentes et al., 2019;

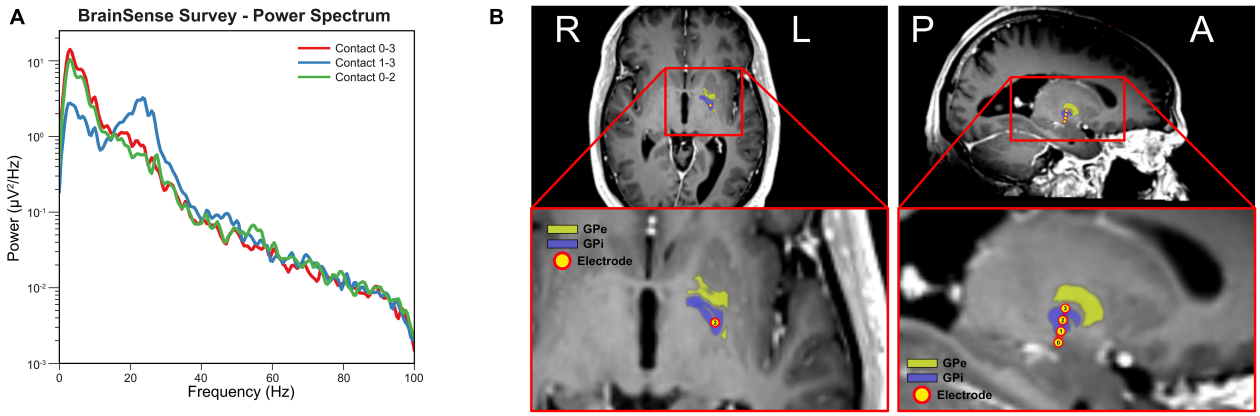

FIGURE 1 | Electrode localization and baseline electrophysiology. **(A)** Power spectral density for each sensing-enabled contact pair showing a beta peak at 23.44 Hz for sensing contact pair 1–3 (data recorded during off stimulation). **(B)** Electrode contacts were identified in the fused post-operative CT image and pre-operative T1 MRI image. Electrode trajectory was close to a vertical trajectory (AC-PC angle 74-degree and central line angle 5-degree). Electrode contact 0 was outside of the GPi border while contact 1 to 3 were inside of GPi border. (Yellow atlas: GPe; Blue atlas: GPi; and Yellow dots: electrode contacts).

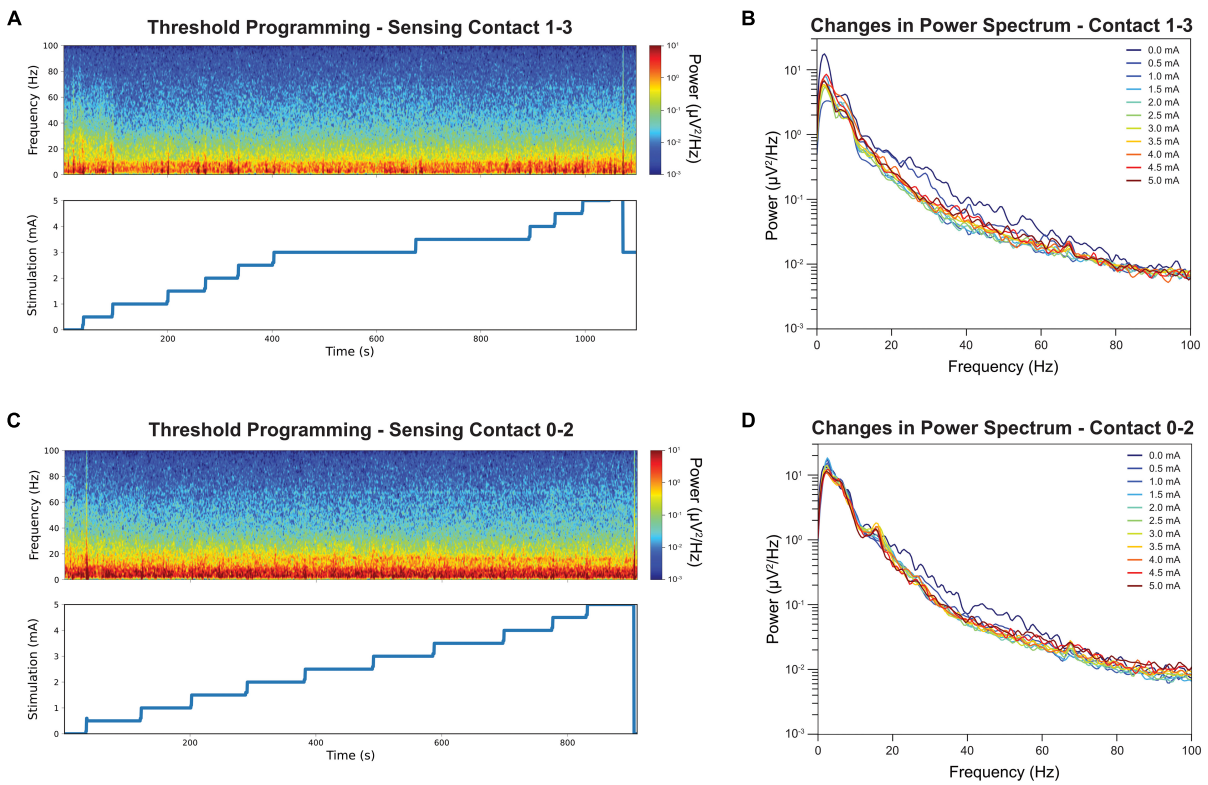

FIGURE 2 | Time-frequency analysis during stimulation threshold testing and their corresponding stimulation amplitude is displayed. Note the stimulation amplitudes are up to but not exceedings the side-effect threshold for stimulation contact 2 **(A)**. The color denotes the absolute power at each time point, with the red indicating strongest power and the blue lowest. Sensing contact 1–3 revealed a reduction of power in the beta band in spectrogram when the stimulation amplitude was increased. The average power spectrum at each stimulation amplitude for stimulation contact 2 **(B)**. Increased stimulation amplitude was associated with a decrease in beta band power. The same time-frequency analysis was repeated for contact 1 as comparison **(C)**. Increased stimulation amplitude was associate with a smaller decrease in beta band power **(D)**.

Eisinger et al., 2020) and externalized lead studies (Burgess et al., 2010). However, rigidity score was not changed by the stimulation in either therapy contact pairs. Our results suggest that GPi beta power correlates with bradykinesia severity and might be used as an objective marker for selecting the optimal stimulation amplitude for treatment of bradykinesia.

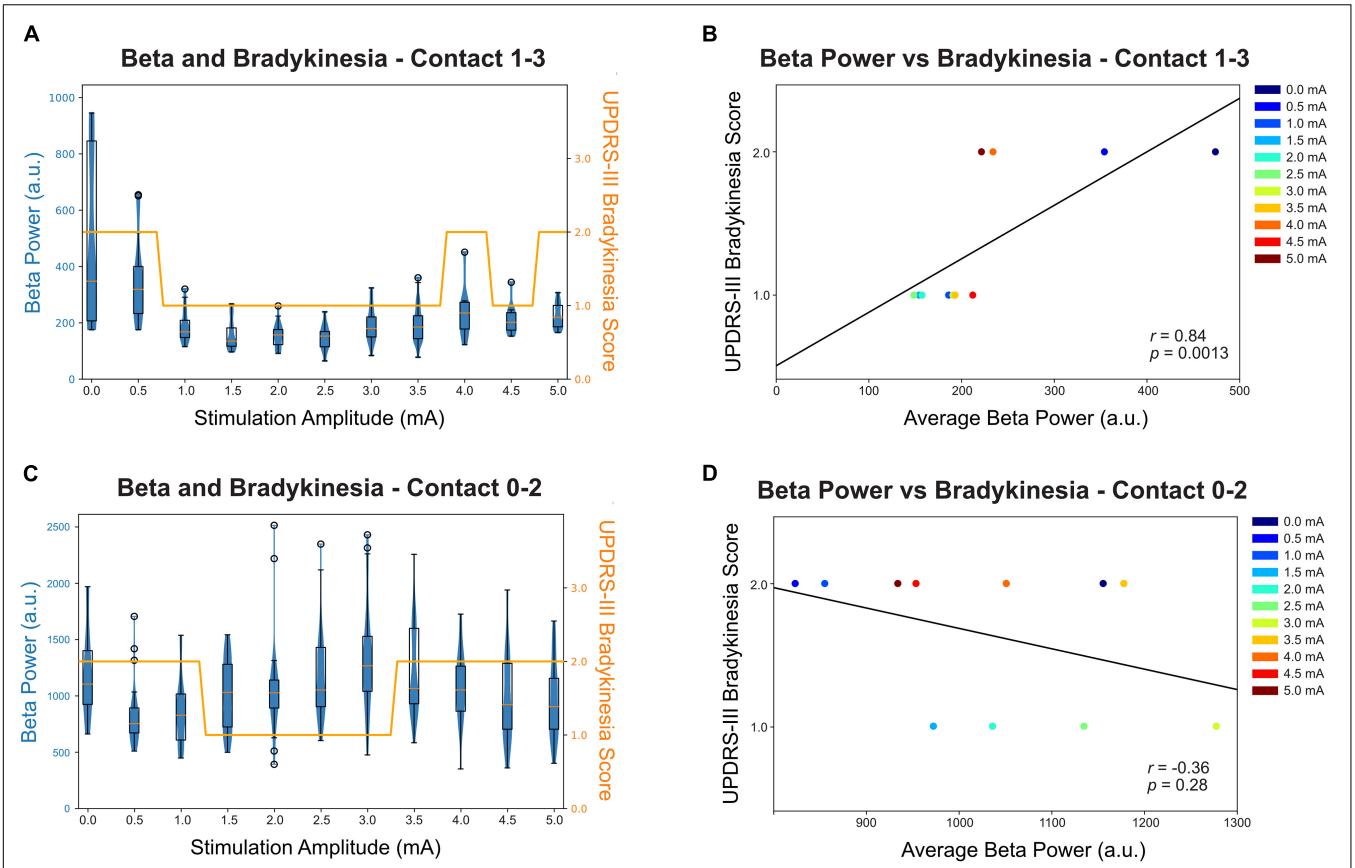

FIGURE 3 | Relationship between beta power (recorded from contact 1–3 when stimulating at contact 2) and bradykinesia score (UPDRS Part 3 subitem 23). **(A)** The beta peak power (23.44 Hz) for contact 1–3 was averaged over each stimulation amplitude and shown in a box-violin plot with whisker at 150% of the interquartile distance and outliers were marked as circles. Each datapoint indicates a 500 ms power value collected by Medtronic Percept neurostimulator at the specified frequency band. The bradykinesia scores were plotted in the same scale for comparison. **(B)** The correlation between average beta power and bradykinesia score at each stimulation amplitude for contact 1–3. The beta power was statistically significantly correlated with bradykinesia scores, with increased beta power correlated with worse bradykinesia ($p = 0.0013$). **(C)** The beta peak power (17.57 Hz) for contact 0–2 was averaged over each stimulation amplitude and shown in a box-violin plot with whisker at 150% of the interquartile distance and outliers were marked as circle. **(D)** The correlation between average beta power and bradykinesia score at each stimulation amplitude for contact 0–2.

This procedure could be practical and useful for clinic-based settings.

Interestingly, the beta power rebounded when the stimulation amplitude was increased above 3 mA, and this rebound was associated with an increase in bradykinesia severity. Worsening of motor symptoms at higher stimulation amplitudes has been observed in previous clinical but not physiological studies (Baizabal-Carvallo and Jankovic, 2016; Hu et al., 2018), but the nature of these phenomena has remained unknown. The causal relationship as to whether the worsening of symptoms with overstimulation was induced by the beta increase or alternatively by induced side effects cannot be determined from our small dataset. However, the rebound of the beta power can provide useful information regarding the therapeutic window for DBS programming in addition to finding to therapy level that provide maximum benefits.

A limitation with the current protocol is the selection of peak beta frequency for tracking. In our study, contact pair 0–2 has a peak frequency at 17.57 Hz at baseline but this frequency is in fact uncorrelated to symptom improvement (**Figure 3D**). Although post-processing shows slight reduction of broader high beta power (**Figure 2D**), none of the frequency band were statistically correlating with symptom improvement nor capturing the rebound effect. Another limitation is the sequence of stimulation stepwise increment used in the protocol. The suppression and rebound of beta might be an effect of cumulative stimulation and using a protocol that randomize therapy amplitude during recording can account for the sequential relationship and reflect the true physiological behavioral of excessive stimulation. Thirdly, the clinician-rated bradykinesia scores and rigidity scores may not fully capture the minor changes in symptom severity. In the current study, rigidity severity has not changed with any level of stimulations while the bradykinesia severity only altered by one point. Objective measures such as sensor-based measurement may be able to capture the miniature changes and offer better correlation with neural signals.

This study provides preliminary evidence for the feasibility of using real-time neuronal recordings to choose optimal DBS

programming settings. Future studies focusing on more long-term evaluation of biomarkers across a larger sample size will likely guide which individuals with PD GPi DBS may benefit from this technique and possibly which may possibly benefit from closed-loop stimulation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Florida Institutional Review Boards. 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

JC: data collection, data analysis, and drafting of article. JW: data collection and reviewing of article. KJ and MO: reviewing of article. KF: surgery and reviewing of article. CH: reviewing of article and concept development. All authors contributed to the article and approved the submitted version.

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"Nothing to Lose, Absolutely Everything to Gain": Patient and Caregiver Expectations and Subjective Outcomes of Deep Brain Stimulation for Treatment-Resistant Depression

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Background: How "success" is defined in clinical trials of deep brain stimulation (DBS) for refractory psychiatric conditions has come into question. Standard quantitative psychopathology measures are unable to capture all changes experienced by patients and may not reflect subjective beliefs about the benefit derived. The decision to undergo DBS for treatment-resistant depression (TRD) is often made in the context of high desperation and hopelessness that can challenge the informed consent process. Partners and family can observe important changes in DBS patients and play a key role in the recovery process. Their perspectives, however, have not been investigated in research to-date. The aim of this study was to qualitatively examine patient and caregivers' understanding of DBS for TRD, their expectations of life with DBS, and how these compare with actual experiences and outcomes.

Methods: A prospective qualitative design was adopted. Semi-structured interviews were conducted with participants (six patients, five caregivers) before DBS-implantation and 9-months after stimulation initiation. All patients were enrolled in a clinical trial of DBS of the bed nucleus of the stria terminalis. Interviews were thematically analyzed with data saturation achieved at both timepoints.

Results: Two primary themes identified were: (1) *anticipated vs. actual outcomes*, and (2) *trial decision-making and knowledge*. The decision to undergo DBS was driven by the intolerability of life with severe depression coupled with the exhaustion of all available treatment options. Participants had greater awareness of surgical risks compared with stimulation-related risks. With DBS, patients described cognitive, emotional, behavioral and physical experiences associated with the stimulation, some of

which were unexpected. Participants felt life with DBS was like "a roller coaster ride"—with positive, yet unsustained, mood states experienced. Many were surprised by the lengthy process of establishing optimum stimulation settings and felt the intervention was still a "work in progress."

Conclusion: These findings support existing recommendations for iterative informed consent procedures in clinical trials involving long-term implantation of neurotechnology. These rich and descriptive findings hold value for researchers, clinicians, and individuals and families considering DBS. Narrative accounts capture patient and family needs and should routinely be collected to guide patient-centered approaches to DBS interventions.

Keywords: deep brain stimulation (DBS), neuromodulation, depression, informed consent, expectations, subjective outcomes, ethics, neurotechnology

INTRODUCTION

There is a pressing need for novel and effective treatments for people living with treatment-resistant depression (TRD). Approximately one-fifth of all people who experience depression will not respond to existing evidence-based therapies (Fava, 2003). Deep brain stimulation (DBS) is a potential treatment for depression currently being investigated. Primary outcome measures used in clinical trials of DBS for depression include the Hamilton Rating Scale for Depression (Hamilton, 1960) and Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979). While valuable for assessing subjective changes in depression symptoms as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), these measures do not provide a comprehensive picture of the intervention's overall impact and often do not fully capture participants' beliefs about the benefit they have gained (de Haan et al., 2015; Mayberg, 2018). What "well" looks like and what is considered a "success" is also highly specific to each individual (Fins et al., 2017).

Qualitative investigations with those who undergo DBS is one method for gaining a more holistic and comprehensive understanding of intervention outcomes. Despite the growing recognition and need for patient-centered care and the elevation of patient voices within medical research and clinical practice (Greenhalgh et al., 2016; Sidhu et al., 2017; Braun and Clarke, 2019), few qualitative studies with this population have been conducted. Acquiring qualitative data from health care recipients and lived experience experts (e.g., patients, caregivers) is vital for improving the translation of clinical research outcomes into standard practice and health care (Institute of Medicine, 2001). In addition to highlighting an intervention's successes and failures, qualitative data can reveal the meaning and significance of changes experienced by patients, for both themselves and those closest to them.

Patient expectations about the likely benefit of undergoing DBS can affect clinical outcomes (Okun and Foote, 2004; Maier et al., 2013), as well as raise challenging ethical questions when trialing DBS for mental illnesses, such as TRD (Bell and Racine, 2013). A handful of qualitative studies have explored the relevance of questions including whether individuals with severe and refractory depression have the capacity to consent to an experimental procedure and whether their decision to participate is motivated by unrealistic expectations of personal benefit (Christopher et al., 2012; Fisher et al., 2012). Fisher and colleagues interviewed 31 people enrolled in two DBS for depression trials and assessed their decision-making and capacity to consent using semi-structured interviews. All participants demonstrated intact capacity to consent; however, therapeutic misconception was present amongst some (i.e., participants viewed the study's purpose as specifically helping their mental health rather than producing generalizable knowledge and underrated risks and overrated likelihood of personal benefit). The authors note that similar degrees of therapeutic misconception are represented in other clinical and non-clinical populations; therefore, they concluded that people with TRD do not appear uniquely susceptible to therapeutic misconception. Based on these results, informed consent processes for the two DBS trials were considered by the authors as sufficiently robust (Christopher et al., 2012).

Post-DBS qualitative data provides some different perspectives on these ethical issues. Klein et al. (2016) conducted focus groups and interviews with 15 recipients of DBS for either TRD and obsessive-compulsive disorder (OCD), exploring their attitudes toward emerging closed-loop DBS systems. In doing so, participants reflected on their own experiences of enrolling in an experimental DBS trial. Some perceived that depression-related cognitive and emotional vulnerabilities impacted their comprehension of information and how they evaluated the associated risks ("I could have cared less about the risks" p. 145). Some recalled a sense of desperation to rid themselves of depression with which high hopes and unrealistic expectations emerged. These findings suggest that nuanced consideration is needed when it comes to the process of conducting robust informed consent with this population.

The current study extends upon the existing research by exploring how these important pre-intervention ethical issues (e.g., decision-making capacity, awareness of risks/benefits, and expectations) are related to participants' post-intervention outcomes and experiences. Caregivers (spouses, family members) were also included in the study. Caregivers have remained absent

within psychiatric DBS research despite the fact they often play a significant role during all stages of clinical trial participation (e.g., decision-making, attending medical and research-related appointments, observing changes in the participant after DBS) (Klein et al., 2016; Thomson et al., 2019a). The purpose of the current study was to gain in-depth knowledge and insight into the experience of preparing for, and living with, DBS for TRD. To achieve this, semi-structured interviews were conducted with key stakeholders (e.g., patients and caregivers) before and after DBS. More specifically, the study aimed to examine: (1) factors influencing the decision to pursue DBS; (2) participants' knowledge and understanding of DBS for TRD, including potential risks and benefits; (3) expectations held by patients and caregivers prior to DBS; (4) the subjective outcomes of the intervention; and (5) how outcomes compare with original expectations.

MATERIALS AND METHODS

This exploratory study employed a prospective qualitative design and iterative thematic analysis approach. This article reports on the experiences of a subset of participants enrolled in a clinical trial of DBS for TRD (Australian New Zealand Clinical Trials Registry: ACTRN12613000412730)[1]. Separate and non-overlapping findings from the current sample examining personal and relational changes following DBS are reported elsewhere (Thomson et al., unpublished).

Participants

A consecutive sampling approach was used to recruit participants actively enrolled in the clinical trial who were awaiting surgery. These participants met Stage V criteria for TRD according to the Thase and Rush (1995) classification. This is the most severe classification with individuals failing to respond to adequate courses of all evidence-based therapies, including pharmacotherapy (all antidepressant classes and combination/augmentation strategies), psychotherapy (including but not limited to cognitive behavioral therapy) and non-invasive brain stimulation [electroconvulsive therapy (ECT), transcranial magnetic stimulation]. All participants had presented to the Victorian Mental Health Tribunal and received approval to undergo DBS for depression. The first-author (CT) recruited DBS candidates and their respective caregivers to the current study, providing them with verbal and written study information. All who were approached, agreed to participate in the study. The sample consisted of six DBS candidates and five caregivers (see **Table 1**). One candidate did not have a caregiver and participated independently.

Procedure

Semi-structured interviews were conducted either face-to-face (at participants' home, research center) or via telephone/video-conference (for participants living interstate). Patients and caregivers were interviewed separately to allow for open discussion. Interviews were conducted by the first-author (CT), a female psychologist with training in qualitative methods and experience interviewing DBS patients, caregivers and clinicians (Thomson et al., 2019b, 2020). Pre-surgery interviews (n = 11, M = 46 min, range = 34–58) occurred 3–15-weeks prior to surgery. These interviews explored participants' decision-making process, awareness and understanding of associated risks and benefits, and expectations and beliefs about potential outcomes (see **Supplementary Material** for interview schedules). Further probing questions were asked to elicit greater depth of information and responses were reflected back to participants to ensure interviewer understanding. Participants then underwent DBS surgery, with electrodes implanted in the bed nucleus of the stria terminalis. Surgery and recovery from surgery was medically uncomplicated for all participants. After a recovery period, participants commenced a randomized schedule of active and sham (control condition) stimulation settings, to which they were blinded. Over 5 months, five stimulation settings were trialed: one inactive, two low level (2 volts), and two moderate level (4 volts). Following this, stimulation continued in an open-label manner, with settings optimized according to each individual. Post-surgery interviews (n = 10, M = 55 min, range = 36–86) occurred 9–11-months after surgery and approximately 3-months into the optimization phase. These interviews explored participants'

[1]Inclusion/exclusion criteria, extensive demographic data, surgical information (including lead placement), and full psychometric outcomes from the clinical trial will be reported in a subsequent publication (in preparation). Any correspondence regarding this efficacy study should be directed to paul.fitzgerald@monash.edu

TABLE 1 | Participant demographic information.

Variable	Patients (n = 6)		Caregivers (n = 5)	
Gender	Women = 5	Men = 1	Women = 2	Men = 3
Relationship type			Spouse = 4	Parent = 1
Work status	Unemployed = 5	Volunteer = 1	Employed = 4	Retired = 1
	Mean (*SD*)	**Range**	**Mean (*SD*)**	**Range**
Age (years)	52.3 (16.9)	26–73	59.6 (11.7)	45–75
Education (years)	14.3 (2.1)	12–17	14.4 (1.3)	12–15
Time since diagnosis (years)	18.3 (12.3)	8–42		
Relationship length (years)			37 (12.3)	24–50

experiences living with DBS, their subjectively perceived outcomes, and reflections on their pre-surgery beliefs and expectations. One candidate did not complete a postoperative interview as it was deemed too burdensome. Field notes were maintained and regular debriefing occurred between co-authors (CT, AC, RS). All interviews were digitally recorded and transcribed verbatim by a professional transcription service. Transcriptions were reviewed for accuracy and de-identified (by CT).

Qualitative Analysis

An iterative thematic analysis approach was chosen as it is suitable for exploring a single phenomenon (e.g., undergoing DBS) from different perspectives and can be used to highlight similarities, differences and inconsistencies in perspectives across time (Braun and Clarke, 2006). The analysis was conducted within a realist paradigm, which assumes a direct relationship between language and meaning or experiences. Therefore, participants' language was assumed to represent the reality of their lives and reflect the meaning they assign to their experiences. The analysis and interpretation were conducted with a psychological lens, although the process of peer debriefing allowed input from different perspectives and disciplines (neuroethics, social science, neuropsychology) (Yilmaz, 2013).

Transcript data was imported into and organized using NVivo 12 software (QSR International Pty Ltd., Doncaster, Australia). Thematic analysis was conducted according to the six-step process outlined by Braun and Clarke (2006). This involved: familiarization through repeating listening and reading of interviews, initial generation of codes, searching for themes, reviewing and refining themes, defining and naming themes, and reporting using representative quotes with pseudonyms to protect confidentiality. The analysis process was iterative and inductive (data-driven), aligning with the "codebook" approach to thematic analysis (Braun and Clarke, 2020). Cross-coding was conducted on a subset (6) of interviews (by CT, AC, RS), with discussions held amongst the coding team to develop and refine a coding structure. All interviews were subsequently coded by the first-author and interviewer (CT). Data saturation, the point at which no novel themes were identified in analysis, was reached at interview 9 of the pre-DBS interviews (total of 11) and 9 of the post-DBS interviews (total of 10). The "Consolidated Criteria for Reporting Qualitative Research" (COREQ) was used to support transparent and comprehensive methodological reporting (Tong et al., 2007).

RESULTS

The thematic analysis revealed two primary themes that are presented within the current article (**Table 2**). Primary themes developed longitudinally with secondary themes reflecting specific timepoints (pre-/post-DBS). Patient and caregiver perspectives are represented across all themes, with example quotes presented in **Tables 3**, **4**.

Anticipated vs. Actual Outcomes

In anticipation of DBS, participants shared beliefs about potential responses to stimulation. Most recognized that responses could vary considerably person-to-person and rather than being a one-off procedure, much testing and talking was needed to optimize settings. Some patients felt they would perceive no difference in stimulation settings unless one was exerting a beneficial effect. Others flagged potential "strange problems" e.g., hypomania, impatience or becoming "too over-reactive." The prospect of the inactive (control) setting was particularly worrying for some, but was understood as a research requirement. The anticipated time it would take for patients to detect a beneficial setting varied from fairly immediate (as heard in "miracle" stories) (Racine et al., 2007), to a couple of weeks or months. One patient felt confident they would know if the treatment was working, having experienced distinct, albeit brief, periods of wellness in response to other treatments. In contrast, one caregiver was concerned their loved-one may not recognize improvements they were experiencing, as had occurred with another experimental treatment.

Participants distinguished between what they were expecting from the procedure and what they hoped the outcome would be. As an experimental trial, some held no expectations at all or considered their probability of remission in light of outcomes from other trials. With extensive histories of non-response to standard depression treatments, some were inclined to consider "no benefit" the most likely outcome and entertained few hopes to avoid later disappointment. In contrast, one patient described their expectations in positive, absolute terms ("I expect to recover"), explaining optimism was necessary to give them determination to proceed. This affirming mindset appeared balanced by a realistic understanding of the trial's experimental nature. One patient and caregiver had held initially high expectations after seeing a positive case study in the media; however, these were tempered after discussions with the clinical trial team and receiving further information. Many emphasized how

TABLE 2 | Thematic analysis matrix.

	Anticipated vs. actual outcomes	Trial decision-making and knowledge
Pre-DBS	• Anticipated responses to stimulation • Balancing hopes and expectations • Approaches to aid recovery	• Process of decision-making • Awareness and weighing of risks • Knowledge and preparedness
Post-DBS	• "A roller coaster ride" • Responses to stimulation adjustment • Reflections on expectations: "work in progress"	• Reflections on preparedness • Knowledge transfer • No regrets

TABLE 3a | Anticipated vs. actual outcomes—pre-DBS.

Anticipated responses to stimulation
Patient 1: *My understanding is that most people can't actually differentiate between when the stimulation is on or off to start with and you would therefore not be likely to differentiate between one set of stimulation parameters and another except in the case that a particular set of stimulation parameters did in fact provide a benefit.*
Patient 4: *I've read of patients where they've basically had it switched on and it's worked straightaway and they've felt better straightaway. . .I'm probably being unrealistic but I would expect to know within a day or two if it was going to be the right frequency for me.*
Caregiver 3: For me, a number of weeks probably would be quickly [for a response]. . .I'm not expecting instant results but I'm not sure if it's going to be weeks or months before we get to that stage.
Balancing hopes and expectations
Patient 3: *An expectation and a hope are very different things, in my mind. I don't expect anything, because when you've been in my position for as long as I have, you can't expect anything. They tell you to expect to get better with every new medication they put you on, when they augment your medication, when they try a new therapy. You learn not to expect anything, because you just become disappointed and end up plunging further in. Whereas if you don't ever hope, you don't get knocked down, essentially. There's a chance, but it's a very detached kind of feeling. It's very clinical. . .there's a chance and I'll take that chance.*
Patient 4: *I expect to get better. I expect to recover. . .I expect to go back to work. I expect to go back to my social life. I expect to be able to travel. . .I expect to be happy and I expect not to wake up every day and wish I was dead. . .I expect to not wake up and start crying and say god help me through another day. . .Yeah but maybe I'm being a bit overoptimistic about the whole procedure but I just need to think of it in very, very positive terms because it's such a big thing to go through. . .I can't not do that because I'll just give up. I just couldn't go through with it if I didn't think it was going to be very beneficial.*
Patient 6: *I'm not expecting—nobody's telling me I'm going to get a total recovery. But 50 per cent of where I used to feel, 20 years ago. More energy. More interest. More just more, more, more of what's surrounding me. More of the family. That would do me.*
Caregiver 6: *We've been there and we've hoped so many times, had it dashed that many times, I don't know if. . .I've got it in me to hope for a cure anymore. It's an awful thing to say, isn't it?. . . Well, you work up and you get knocked out again. So, much better to be delightfully surprised than to be up there and come crashing down again. . .Anything has to be an improvement. I'd accept crumbs, but a big slice of the cake would be better [laughs]. I'll take anything.*
Approaches to aid recovery
Patient 3: *I'm under no illusion that I probably will be on medication for the rest of my life. . .I never found talking based therapies of any use, so I wouldn't actively pursue that. . .[I'm] wanting to hopefully have a bit more of a social network. . .Hopefully being able to join a sport. . .one, to make friends, but two, the physical activity does help with stress reduction as well as depression. . .That would be lifestyle things. But as far as having counselling, no.*
Patient 5: *[Continuing] probably what I'm doing now, I think. I have, as I say the psychiatrist and she's very supportive too, but then the psychologist, she'll work on different things I'm going through at the time. . .Yeah, unless there's some magic, and it's really good, well I would be continuing them.*
Caregiver 5: *We realise that she's still going to have like five months of trialling the different modes. . .She needs to keep on seeing a psychiatrist and counsellor. . .and we know that the medication is going to keep on going for some time until we find out what the results are going to be. So, we realise there's still going to be a lot of support and a lot of time and effort put into it.*

TABLE 3b | Anticipated vs. actual outcomes—post-DBS.

"A roller coaster ride"
Patient 4: *It's like you're on a roller coaster, and you think you're better and you get so happy because you think you're better and then you crash again. . .That's extraordinarily disappointing. . .It's very subtle, and I really expected it would be boom, boom, boom and you're better, I didn't think it was going to take this long. They probably don't need to tell you that in the beginning, do they?*
Patient 5: *[It's been] very changeable. . .It's really constantly changing. . .It depended on the adjustment. . .Initially I'd get very hot. . .one time I got very anxious. . .[Or] I might have an initial time where—a bit more energy and probably a little bit more interest in things but it wouldn't last.*
Caregiver 2: *I think that the differences are quite pronounced. It's worked and it's definitely transforming, and it's going to take some time for her to work through it. . .We're getting there, but it doesn't come without its own set of drama.*
Responses to stimulation adjustment
Patient 1: *I would say with the last setting. . .there's perhaps some improvement in my sleep. I guess some small and very fleeting kind of perception of improvement in mood generally and that kind of pervasive pessimism. It's kind of small and very fleeting.*
Patient 6: *That [adjustment] was really, really, really dramatic. It really was. I couldn't stop talking. I was talking to every man and his dog. I was wired. It was very frightening. . .No, this was all way over the top.*
Caregiver 4: *[Patient name] had a very bad experience during the trial period where she reacted badly. . .as in setting that didn't suit. Generally, when there is an adjustment, there will be a little bit of time where she—I don't know how to really describe it, but anyway it upsets her system somehow, her body, her mind.*
Reflections on expectations: "work in progress"
Patient 2: *I can see it getting to the top. It's taken a little bit of time to get used to being happy and all the emotions that go with that. . .I was right down at the bottom and now I'm getting closer to the top—and liking it.*
Caregiver 3: *I think it's still a work in progress, yeah. The fact that I've said that there have been times where she has been motivated and what have you. . .I do think that we can see that the stimulator is having an effect. Sometimes the effect may be a little bit over the top [laughs] but yeah, I'm still hopeful that we will get a result.*
Caregiver 5: *[I'm] still hopeful. . .because it seems to be. . .a number of options. . .Four by eight vaults by four by eight vaults, well it's a lot of options. . .I'm probably an optimist and hopefully there's something there that means it's going to help. How long do you keep on doing it for, I don't know?*

meaningful even a small or partial improvement would be for their quality of life.

In addition to DBS, participants were aware that engaging in additional therapies and practices would likely be required to aid recovery. Continuation of current approaches e.g., medication, psychotherapy, routine exercise etc. was still considered necessary to maximize rehabilitation and recovery. Some felt they would need to re-focus on lifestyle factors, including sleep hygiene, diet, exercise, and social connection. New input from counseling or social work services was recognized by participants for supporting psychosocial rehabilitation, e.g., regaining life-skills, re-establishing spousal relationships.

At the follow-up interview, majority of participants indicated their life after DBS had felt like "a roller-coaster ride." This was regardless of their subjectively perceived outcome; meaningful improvement ($n = 2$), little (transient/subtle) to no benefit ($n = 3$),

TABLE 4a | Trial decision-making and knowledge—Pre-DBS.

Process of decision-making
Patient 1: *Initially, I spent a lot of time reading about it to try to understand the rationale behind it. . .the model of depression which underlies this as a treatment because it's quite a different model from most biochemically focused models. I spent some time reading the peer review literature reporting on various types of clinical trials elsewhere. Simultaneously with that, I had had many discussions with my own psychiatrist about what other options there might be in a context where you've tried lots and lots and lots of treatments with no real benefit. I did spend quite some time weighing up the costs and benefits. . .both in the sense of risk but also. . .the effort required to engage with this.*
Patient 4: *I really don't like the idea of your brain being operated on but if you've decided this is what you need to do—and I would sum it up in one sentence. I would do this in a heartbeat rather than live with the agony of depression for the rest of my life. And you can quote that one. It's a good quote. . .I really don't have any other options left. I've searched the whole world for something and there is none. There's always an answer to a problem but I looked pretty hard and I think that this is probably my best solution now.*
Patient 5: *Over all the time there's been two people that said to me 'give it a go,' other than that people have been non-committal, which I can understand. It's a huge thing to do, and it's a huge commitment and everything. Yes, so it is my decision but it's a very lonely place at times when you're just on your own wondering what you should do.*
Caregiver 2: *We're both aware it's very much a research project. She's actually said on a couple of occasions she wants to help that cause. Not only does she want herself to get better but she wants to further that science so other people can benefit from it. So, she's more than willing to go through that.*
Awareness and weighing of risks
Patient 1: *I'm conscious that there are some risks associated with the surgery, that are potentially catastrophic but with a very low probability. . .There are risks associated with anaesthetic in general, there's a risk of stroke, there's a risk of. . .a small bleed in the brain. It would not be defined as a stroke but might nonetheless cause some impairment. So, it might be transitory or permanent. There's a risk of infection of the wound, there's a risk of infection, less commonly, of the brain itself. A stroke itself could have a whole range of effects in terms of paralysis and language function.*
Patient 2: *The process of having the ECTs and general anaesthetics and that. . .it's sort of made the process [of DBS] less scary because I've gone through all of that and having the ECT and all the risks of that was probably the same as having the DBS. The only thing is, if the DBS works then I don't have to have any more of the ECTs.*
Interviewer: *What about after surgery, when you've got the stimulation running, do you know about some of the side effects associated with the stimulation?*
Patient 3: *Not really. I imagine, short of recovery, once it's in and it's settled that you wouldn't really be aware that it was there at all.*
Knowledge and preparedness
Patient 4: *Yeah, they've given me huge amounts of information. I've been very well informed. Over-informed to the point where you're just like I don't want to know about it, just do it.*
Caregiver 2: *We've had a couple of different information packs sent to us from the team. . .We've had probably I'd say at least 40 discussions about it with various people on the team. . .Yeah, we've had plenty of information on it. . .We can't say we weren't forewarned!*
Caregiver 3: *I'm probably not at all informed as to what happens after the surgery. . .I know she's going to have to go back a few times to. . .change the settings and that kind of stuff but I haven't been given any information on what to expect really, after the surgery. I think [patient] has been given that info but I haven't really been given too much on that side of things. . .No doubt I will get more information on it as we go down the track but yeah, I. . .don't know exactly what to expect, going forward.*

or increased depression (n = 1). Participants described a variety of responses they thought were due to stimulation settings. Positive changes included: a lift in mood (subtle to substantial), expressions of joy (tears/laughter), improved sleep, increased energy, more interest in people and surroundings, more talkative and engaged, and increased motivation to do things (shopping, create things, see people). In two cases, positive stimulation effects were sustained, while others only experienced transient benefits (2–3 days). Undesirable responses that participants attributed to stimulation settings were: increased irritability, anxiety, urges to self-harm, cognitive effects (confusion, poor memory and problem-solving), manic episodes, disturbed sleep, acne, and further decreases in mood, energy, motivation, and confidence. A general sense of unease ("off kilter," "really crook") was also common. These experiences were mostly transient and remitted with stimulation parameter adjustments. Turning the device on and off (in order to conduct medical procedures or patient self-experimentation with the device) was associated with: panic attacks, dissociative experiences, sensations of a childhood memory, and manic episodes. Other experiences, some related and others unrelated to DBS, also contributed to the roller-coaster experience, including surgery-related anxiety and trauma, adjusting to new emotions (joy, anger, pride), suicide attempts (n = 2), managing social reintegration, relationship difficulties (with caregiver and non-caregivers), medical issues, and family bereavement.

When reflecting how outcomes compared with initial expectations, most felt their situation was still a "work in progress." Some who had only experienced glimpses of a positive effect remained hopeful that effective device settings could be identified. However, the question of how long to persist was raised. One patient who had no existing expectations was "neither disappointed nor surprised" with their apparent lack of benefit. Those who had experienced benefit were in the infant stages of wellness, navigating various new experiences. In one case psychological support was important for guiding the patient's adjustment. Some participants offered percentage indicators of recovery (varying from 40 to 70% improvement). While these exceeded prior comments that "any improvement" would do, a desire for more to be gained post-trial was present. One patient who became interested in DBS after viewing a positive media story expressed disappointment that they had not experienced such an immediate or dramatic effect.

Trial Decision-Making and Knowledge

In anticipation of surgery, candidates discussed their decision to pursue DBS. Most were introduced to DBS by their treating psychiatrist, where it was raised as an experimental

TABLE 4b | Trial decision-making and knowledge—post-DBS.

Reflections on preparedness
Interviewer: *Do you think that looking back that you felt fully informed of all the potential risks and side effects associated with DBS?*
Patient 4: *I actually don't remember. I don't remember, because when you're depressed your memory was rubbish. You're not interested. . .and they're telling you, you could die, and you go actually I don't care, I want to die anyway, so what difference does it make? No, I mean they probably did inform me, I'm sure legally they had to, but I wasn't listening.*
Interviewer: *[. . .] Has there been anything that's come as a surprise through this process? Anything that you perhaps didn't expect coming in to it?*
Patient 4: *Absolutely, I didn't realise it was going to be such a tough journey finding frequencies and such a long journey, and such a rollercoaster. . .thinking "I'm on it, I'm getting better, this is great," and then two days later you go bang and you're back to where you are. . .[I] didn't know it was going to be so hard, that was a big surprise, and I didn't need to know it beforehand. Because I couldn't have coped. What you don't know can't hurt you sometimes.*
Interviewer: *Yeah, so do you think if you'd been told that prior, that it could be very variable fluctuations, a very long process, that that might have turned you off?*
Patient 4: *I would have still gone ahead with it, but I would have been extremely upset about it and it would not have helped me at all. In fact, I don't think you should tell people. It may not be as hard for everybody else anyway.*
Knowledge transfer
Patient 1: *It is an onerous thing to pursue, it really is. You really would not want to be doing it lightly and you would not want to be doing it if you had other kind of reasonable alternatives. But that said, 15 years of depression is pretty jolly onerous too. It's a little bit difficult to disentangle.*
Patient 5: *[You probably need to know] that it is a long process. You probably don't realise probably just how long—but to be well informed. I think to be well informed, which if you're going through the DBS program and you go to that panel, they question you a lot so you have to be informed. . .I think if people are like me, I find it hard retaining things and that sort of thing but I really had to work at being informed and to understand everything.*
Patient 6: *I think if I had to impart one piece of knowledge or advice to somebody starting off contemplating DBS, is to be prepared for a long, drawn-out process. It's just not going to happen overnight, and these things take on a character all of its own. There's nothing you can do as an individual to hasten the process. You've got to wait. . .everybody's working very, very hard to get you there, but it just doesn't happen overnight.*
Caregiver 6: *If they were in the situation as me, I'd say actually, go for it. . .I've got no regrets, and we'd exhausted everything we could think of. . .I mean, I think it's something you've got to think about seriously, and ask all the questions, and there's plenty of opportunity to do that. Don't expect electric light overnight. . .it's not just like changing a course of something for something else. It is—you could almost say a lifestyle change, because. . .once it's there, it's there, to the best of my knowledge. . .It's going to be part of you, and you've got to live with it, and you've got to live with that recharging. . .But do sit down and talk about it and think it through. Because it's not like putting on a new pair of shoes, you are having brain surgery.*
No regrets
Interviewer: *Knowing what you know now and what your outcomes have been, would you undergo the DBS surgery again if you had decision to make again?*
Patient 1: *Yes, I think I would. I suppose precisely because when there are no other alternatives the only thing you can do is roll the dice.*
Patient 2: *I was sort of hoping that it's going to fix it straight away, and then when it didn't. . .it was like, 'oh maybe I shouldn't have done it', because it was quite stressing, as it all got toward it. . .to go through all that—the torture of the surgery—but then as it improved, I'm sort of thinking, I'd recommend it. . .Even though stressful in the process and very long. . .Yeah. I mean, it was all worth it.*
Patient 5: *Would I do it [again]? I think that's a hard question to answer because it's still in the process. I might say to you today I don't know that I would but then things might change in a month or two months or three months. I said I wouldn't have the surgery again, but if there was the possibility of something I probably would.*

approach being trialed for treatment-resistant individuals. Others encountered it while researching alternative treatments online. All had treating clinicians willing to support their application into the clinical trial. All patients had conducted some personal research into DBS, including reviewing the peer-reviewed literature (those with higher education, academic experience) to searching Google and YouTube (case studies, footage of surgery). This research was mostly driven by patients themselves, but occasionally by caregivers with patients then viewing their findings. Some caregivers conducted limited research, as they trusted the patient's judgment and the experts supporting them. While independent research and discussions with medical professionals were influential, the lack of treatment alternatives was the driving force behind most patients' decision. All felt confident they had exhausted all alternative treatment options and while DBS was considered "pretty hard core," as the only option left, patients were willing to pursue something "extreme." Being approved for DBS provided hope some caregivers felt was keeping their loved one from suicide.

Participants recalled many surgical risks associated with DBS (e.g., stroke, brain bleed, infection, seizure, general anesthetic complications, death). While concerning, most were comforted knowing it was a routine surgery for movements disorders (i.e., Parkinson's disease, essential tremor) with low chance of adverse events, and had trust in the surgeon's skill. The surgical risks were often compared with those associated with undergoing ECT, with hope DBS would reduce future need for ECT. Awareness of stimulation-related adverse events appeared less well known, although mania/hypomania, sleep disturbances, and adverse mood effects (anxiety, agitation) were raised by some. One caregiver considered these a part of the research process for finding the best settings, while another expressed concern their loved one would not report adverse effects and attempt to endure them.

Participants generally felt well-informed of the risks and benefits, having held multiple discussions with the clinical trial team, the surgical team, and their treating clinician over many months and years. One patient noted they "had to be" well-informed in preparation to sit before the Victorian Mental Health Tribunal. Some patients felt having an opportunity to talk to others with a DBS implant (not necessarily for depression), would be beneficial to understand more about the physical aspect of having the device.

After DBS, participants reflected on how informed and prepared they had been prior to surgery. Some patients were surprised by the physical discomfort resulting from the implanted device e.g., tenderness behind ear where wire runs, pain in chest where implantable pulse generator (IPG) rests when sleeping on side and while driving due to seatbelt rubbing against IPG. While acknowledging the difficulty in pre-empting such outcomes, one patient felt they would have preferred the IPG on the opposite side had they been given a choice. And while prepared for surgery from a procedural perspective, one patient felt unprepared for how personally confronting the experience was, and highlighted the importance of comfort and reassurance from medical staff during the procedure. Participants generally felt well-informed regarding risks and procedures, but were surprised by how long the whole process was (e.g., getting Tribunal approval, scheduling surgery, conducting clinical trial tests, and regularly adjusting parameters). The number of research center visits required had also been a surprise to some, with both caregivers and patients acknowledging they may have not fully absorbed this information prior.

Participants were asked what advice they would give others considering DBS for depression based on their experience. The most common perspective was that it must be a last resort and all less invasive options need to be tried first. Being well-informed and prepared was considered essential, while remembering it is a research trial and a positive outcome, like you might read or hear about, is unlikely. Being prepared for a "long, drawn-out process" was also emphasized. Many felt that if someone (patient or caregiver) were "in the same boat" as they had been and were considering DBS, they would recommend it, even if their outcome had not been overly positive.

Participants were also asked to consider if they had their time again, would they still decide to undergo DBS (or support their loved-one to)? Most participants felt they would, regardless of their experience and present outcome. The lack of alternatives was again sighted as a worthy reason to attempt it, and those who had experienced no benefit felt their situation could change, so it was yet to be determined whether it was worthwhile.

DISCUSSION

Through prospective semi-structured interviews with key stakeholders, this study sought to gain in-depth knowledge and insight into the lived experience of DBS for TRD. Through this process, key ethical issues were explored including: informed consent, decision-making capacity, intervention expectations, and subjective outcomes. The relevant findings and implications of each are discussed below.

Informed Consent and Decision-Making Capacity

In most instances, participants demonstrated reasonable knowledge and understanding of DBS for TRD, including awareness of potential risks and benefits. Patients reported feeling both well-informed and prepared, having participated in extensive consenting discussions. All had been evaluated by the Victorian Mental Health Tribunal in order to receive permission to undergo DBS. This process involves a hearing held between three tribunal members, the DBS candidate, a support person (if needed), and the clinical/research team. The panel assesses the candidate's suitability for the procedure and capacity to consent to it. The majority of the candidates indicated that they found this experience anxiety-provoking and onerous. It could be argued that this requirement stigmatizes those with mental illness compared with other neurological indications for DBS where neurocognitive impairment is common (i.e., Parkinson's disease) (Thomson et al., 2019a). While the efficacy of DBS for depression remains under investigation, however, this safeguarding procedure should ensure that only people with acceptable levels of understanding and preparedness who are well supported by an appropriately knowledgeable and experienced clinical team proceed to surgery.

Despite demonstrating comprehension and retention of information required to make an informed decision, some post-DBS comments indicated that this had little bearing on the candidates' decision and acknowledged the impact depression had on their engagement with this information (e.g., impaired memory, concentration difficulties, challenges making independent decisions, hopelessness/nihilism). Hopelessness, suicidal ideation and reduced concern for preservation of ones' life ("I want to die anyway" Patient 4) affected appraisals of surgical risks and desperation to be relieved from persistent depression in the absence of alternatives meant participants were willing to take a chance. Others have noted the difficulties involved in establishing meaningful informed consent for DBS in the midst of extreme hopelessness, desperation, and a lack of alternatives (Bell et al., 2010; Klein et al., 2016). Given the severity of mental illness, poor quality of life, lack of treatment prospects, and risk of dying by suicide possessed by people with TRD, it is reasonable and expected that their appraisals of risk and decision-making will be influenced by hopelessness and nihilism. These inherent features of TRD should be recognized, acknowledged and balanced alongside persistent efforts to conduct thorough and comprehensive consent. Further patient-led research is needed to understand how best to provide information about DBS and maximize participant comprehension and appreciation, particularly of long-term risks and outcomes.

Participants were aware of the short-term risks (i.e., risks posed by undergoing surgery). DBS surgical risks are well-documented, and given their life-threatening potential, it is unsurprising that these were in the forefront of participants' minds during pre-DBS interviews. Less certainty was expressed regarding stimulation and device-related risks. This aligns with findings in Parkinson's disease, where patient and caregiver awareness of surgical risks was superior to stimulation-related risks such as transient personality and behavioral changes (Thomson et al., 2020). Patients in the current study experienced various stimulation-related effects that remitted following adjustment (e.g., anxiety, irritability, disturbed sleep, mania, self-harm urges). While transient, some of these were unsettling and distressing for participants, contributing to their "rollercoaster" experience. Uncharacteristic and problematic stimulation-dependent behaviors (e.g., impulsive and reckless

decision-making while manic) also have the potential to impact the individual and their relationships in the long-term (Agid et al., 2006; Mosley et al., 2019; Thomson et al., 2019b).

Participants demonstrated some awareness, but ultimately an underappreciation of, long-term risks and consequences of DBS. Such consequences included the time-burden associated with regularly recharging the DBS device (discussed at length in Thomson et al., unpublished) and the travel/time-burden associated with frequent visits to the research center (to complete clinical tests, stimulator adjustments and monitor effects). This was particularly the case for those living interstate and caregivers with work commitments. Full pre-surgical appreciation of these long-term implications appeared inhibited by the urgency to pursue a novel treatment. When people express their situation "can't get any worse" or they "have nothing to lose" (Caregiver 6), emphasizing how participation in a clinical trial and receiving DBS could alter and complicate daily life is particularly important (de Haan et al., 2015; Thomson and Carter, 2020). As one caregiver described it—DBS is "a lifestyle change." While patient and caregiver journeys with DBS were rarely straightforward, all indicated they would make the same decision if they had their time again. For the reasons that: (1) they had derived some benefit from DBS, (2) they felt hopeful they may yet still, or (3) in order to have the question "will it work?" answered.

Intervention Expectations

High expectations have been highlighted as another aspect of informed consent that require careful management given the potential for disappointment and negative postoperative outcomes (Bell et al., 2009, 2010). In other populations (Parkinson's disease, epilepsy), unrealistic expectations have been associated with poorer psychosocial adjustment and subjective, psychometric and functional outcomes (Wilson et al., 2001; Haahr et al., 2010; Maier et al., 2013; Hasegawa et al., 2014; Baertschi et al., 2019). Media stories are often implicated in the development of unrealistic expectations. Media portrayals of DBS are overwhelmingly positive, depicting best-case scenarios with limited reporting of associated risks (Racine et al., 2007; Gilbert and Ovadia, 2011). Media coverage of DBS for depression generally presents the "miracle cure" narrative (Dobbs, 2006; Talan, 2008; CNN, 2014; PBS, 2016). The other extreme, the "horror story," is depicted to a lesser extent (Egan, 2015). Such coverage can result in blind optimism or unfounded fears of DBS, both of which have the potential to damage the scientific development of the emerging intervention (Johansson et al., 2011). In one couple's case, their decision to pursue DBS had been influenced by a positive media story. Despite having gone through a comprehensive consent process about the procedure's experimental nature, they still experienced disappointment with an inadequate outcome. This demonstrates the potency of hope elicited by such narratives, and reflects what Baertschi et al. (2019) refer to as the *emotional* facet of expectations.

Some participants expressed strong hopes for DBS that were held in balance with knowledge and understanding of the intervention's experimental nature and uncertain outcome. Based on interviews conducted with a sample of DBS recipients with Parkinson's disease, Baertschi et al. (2019) identified participant expectations consisting of two distinct components. Some patients could intellectually acknowledge the science and research-based information reinforced by medical professionals (*cognitive* facet), while still holding hopes the treatment would lead to something extraordinarily positive (*emotional* facet). The authors report that these "secret hopes" were not revealed to medical staff pre-operatively. In the current study, hope appeared to be a powerful motivator to proceed with the experimental procedure and intensive clinical trial, regardless of how small or unspoken it was. The degree of hope present in participants' pre-DBS mindsets varied and appeared to serve a protective function. Some participants maintained an optimistic and hopeful mindset in order to have the courage and motivation to follow through with the intervention. While others maintained a rational mindset with minimal acknowledgment of their hopes, for fear of later disappointment (as had been experienced numerous times before). A hopeful mindset is not necessarily problematic (Sotsky et al., 2006), unless of course it reflects a fundamental misunderstanding of the research purpose or prospect of benefit (Horng and Grady, 2003). Indeed, hopelessness (a common symptom of depression itself), has the potential to obscure perceptions of benefit and intervention outcomes (Brent et al., 1998).

Subjective Outcomes

Participants reflected extensively on their experience of living with DBS, including the perceived benefits of the procedure (or lack thereof). The significance of small changes was evident. For example, a patient was relieved to spend minutes rather than hours crying upon waking each morning, and a caregiver was thankful to be able to engage in small conversations with their partner rather than sitting in silence. Such changes were considered meaningful and while many pre-DBS comments suggested that *any* improvement would do, a desire to gain more from DBS was common. In other DBS samples (movement and psychiatric disorders), there is evidence that patients and caregivers shift their expectations for DBS based on their postoperative experiences. This includes patients wanting to achieve goals that were not discussed preoperatively or that medical professionals indicated were unattainable [e.g., "(The patients) shift the goalposts a little" DBS Nurse] (Thomson, 2020). Patients' desired level of control over their DBS stimulator can also alter as they adjust to living with the device (Merner et al., 2021). Families can also develop an increased expectation that adjustment of the DBS settings will resolve any issue they observe in the patient (Klein et al., 2016), a perception that can be frustrating and invalidating for the patient themselves.

Another common reflection from participants was the length and uncertainty of the process of establishing whether DBS had "worked." DBS for any treatment indication requires extensive testing and trialing of stimulation parameters, a process that can expose patients and families to a variety of desirable and undesirable changes. This "rollercoaster" experience of encouraging and disappointing responses was a surprise to most participants, as was the length of the optimization process. In comparison with movement disorders, the process of optimizing settings in depression is complicated

by the lack of consistent acute behavioral and clinical effects (Ramasubbu et al., 2013), with a lag of 2 weeks between adjustment and detectable effects common (Holtzheimer et al., 2012). Regardless of clinical trial protocols, optimization is a complex, time-consuming, and at times imprecise process that can take 12-months or more to complete (Dougherty et al., 2015; Bergfeld et al., 2016; Ramasubbu et al., 2018; van Westen et al., 2021b). While participants were prepared for this, the reality of the process was challenging. Adjusting to the observed changes is rarely straightforward either. In OCD, DBS patients often take time to recognize changes, before gradually making sense of them and integrating them successfully into their lives (de Haan et al., 2015; van Westen et al., 2021a). As one patient with OCD remarked: "DBS is no ON/OFF switch" (p. 12) (van Westen et al., 2021b). It is therefore unsurprising that at 9-months post-DBS many of the current sample considered DBS "still a work in progress" (Caregiver 3).

Implications and Recommendations

The current findings hold a number of implications for informing and consenting participants to clinical DBS research. There have been calls from both neuroethics and scientific communities for the long-term risks and consequences of participation in psychiatric DBS trials to be robustly outlined for potential participants (Hendriks et al., 2019; Goering et al., 2021; Vedam-Mai et al., 2021). This would include thoroughly addressing the burden associated with participation (regular travel to research center, clinical tests), information on the day-to-day impact of DBS (e.g., recharging, stimulation side-effects, psychosocial adjustment), and providing clear guidance on post-trial continuity of care (given DBS can be a life-long intervention that is dependent on specialist care and requires maintenance) (Thomson and Carter, 2020). There are limitations to contractual "disclose and sign" informed consent processes, notably that information presented preoperatively is later forgotten or goes unappreciated. There have been recommendations for more experiential and interactive forms of informed consent in DBS (Bell et al., 2010; Liddle et al., 2019), that draw upon the knowledge of lived experience experts. Such a process could involve corrective feedback and use of narrative accounts from DBS recipients and their families (e.g., videos, written accounts). Those with lived experience can answer questions and provide perspectives that clinical research teams cannot. Information delivered in narrative form is also often well-retained (Mazor et al., 2007; Thomson et al., 2020). Further research is required to establish what forms of narrative evidence are most effective; however, a range of different outcomes and experiences must be represented to ensure personal stories do not set an expectation for a single, best-case scenario (as occurs with media stories). The current findings also demonstrate that participants' desires and expectations for DBS adjust based on their personal experience with the device. As such, informed consent for this long-term and adaptable neurotechnology requires an iterative and ongoing process. This recommendation has previously been made for DBS in Parkinson's disease (Kubu et al., 2018; Liddle et al., 2019; Mosley et al., 2019), and is potentially more relevant in clinical trials of DBS for psychiatric conditions where the risks and benefits are less established.

A further recommendation is for an expansion of DBS clinical trial protocols to include more in-depth, qualitative studies of this kind. Data collected in clinical trials provides important indicators of intervention efficacy and safety; whereas qualitative data provides insight into the experiential effects of DBS and can elucidate unexpected or paradoxical outcomes (e.g., difficulties with psychosocial adjustment). Thus, adopting both approaches will give the most complete picture of the impacts of DBS. The variety of experiential information derived from qualitative studies can be used to better inform prospective patients and caregivers on what to expect. Qualitative research strives for transferability rather than generalizability, and an overview of patient experiences can assist in preparing patients and families for DBS.

A final recommendation is for increased inclusion of caregivers in the research process. This includes informed consent procedures in order for caregivers to have a full understanding of what their loved one is agreeing to and what impact it is likely to have on both of their lives. Research teams often seek informal feedback from caregivers about what they are observing in the patient, whether it be subtle improvements (e.g., increase in energy, activity) or excessive adverse effects (e.g., mania). There is, however, much potential in examining how caregivers themselves are affected by their loved one's participation in a DBS clinical trial (e.g., quality of life, mood and anxiety).

Limitations

The patient sample was small (n = 6) and reflects the small numbers undergoing the procedure for depression in Australia. This sample represents the entirety of those who have received DBS for TRD in Australia since December 2016. For the purpose of deriving in-depth, qualitative information, samples of this size can be sufficient (Crouch and McKenzie, 2006; Guest et al., 2006) and data saturation (commonly used to determine adequate sample size) was reached. This rich and in-depth data has high transferability; however, the specific context in which this data was derived should be held in mind (e.g., target lead location, patient characteristics, geographical location, clinical trial protocol, available psychosocial supports etc.) given the potential for such factors to influence experiences and outcomes.

CONCLUSION

This is the first prospective qualitative study to be conducted with individuals undergoing DBS for TRD, with the added perspective of caregivers. The prospective design ensured participants' knowledge, expectations and beliefs accurately reflected their pre-DBS circumstances and allowed for contrast with actual outcomes and experiences. Caregivers played an important role throughout the DBS process and were impacted by their

loved one's participation in various ways. The progress and development of psychiatric DBS clinical research depends on knowledge acquired through both large-scale, robust clinical trials as well as small, in-depth qualitative studies such as this one.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of the personal nature of the information included within the interview transcripts and in order to maintain participant confidentiality. All relevant data are presented within the manuscript. Requests to access the datasets should be directed to corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Monash University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CT, RS, ER, and AC designed the study and research protocol. CT recruited study participants, collected the interview data, and analyzed the interview data. AC and RS assisted with data analysis interpretation. CT wrote the manuscript. All authors provided critical feedback and contributed to the article and approved the submitted version.

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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.2021.755276/full#supplementary-material

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Distributed Subnetworks of Depression Defined by Direct Intracranial Neurophysiology

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Major depressive disorder is a common and disabling disorder with high rates of treatment resistance. Evidence suggests it is characterized by distributed network dysfunction that may be variable across patients, challenging the identification of quantitative biological substrates. We carried out this study to determine whether application of a novel computational approach to a large sample of high spatiotemporal resolution direct neural recordings in humans could unlock the functional organization and coordinated activity patterns of depression networks. This group level analysis of depression networks from heterogenous intracranial recordings was possible due to application of a correlational model-based method for inferring whole-brain neural activity. We then applied a network framework to discover brain dynamics across this model that could classify depression. We found a highly distributed pattern of neural activity and connectivity across cortical and subcortical structures that was present in the majority of depressed subjects. Furthermore, we found that this depression signature consisted of two subnetworks across individuals. The first was characterized by left temporal lobe hypoconnectivity and pathological beta activity. The second was characterized by a hypoactive, but hyperconnected left frontal cortex. These findings have applications toward personalization of therapy.

Keywords: biomarkers, biotypes, depression, ECoG, EEG

INTRODUCTION

Major depressive disorder (MDD) is a common, highly disabling and potentially deadly disorder that affects more than 264 million individuals worldwide (G. B. D. Disease Injury Incidence Prevalence Collaborators, 2018). Despite significant neuroscientific advances, the biological substrate of depression remains poorly understood and new approaches that facilitate our understanding are critical. The majority of early studies seeking to characterize depression pathophysiology examined specific brain regions [ex. subgenual anterior cingulate cortex (Kennedy et al., 2001; Botteron et al., 2002; Yoshimura et al., 2010)], cognitive networks [ex. default mode

network (Greicius et al., 2007; Bluhm et al., 2009; Grimm et al., 2009; Sheline et al., 2010; Zhu et al., 2012)], or univariate electrophysiological markers [ex. alpha asymmetry (Henriques and Davidson, 1991; Gotlib et al., 1998; Kentgen et al., 2000; Diego et al., 2001; Kemp et al., 2010; Jaworska et al., 2012)]. Yet, there is increasing evidence that depression is characterized by distributed network dysfunction beyond a single brain region or network (Veer et al., 2010; Zeng et al., 2012; Liu et al., 2013).

Recent computational advancements within a network neuroscience framework have enabled researchers to model brain activity with the scope and complexity necessary to understand such distributed processes (Bassett and Sporns, 2017). However, detailed investigations of both the functional organization and coordinated activity patterns of depression networks have been limited by the capabilities of current imaging and electroencephalography (EEG) technologies, both indirect measures of neural activity that require a trade-off between spatial and temporal resolution. Intracranial EEG (iEEG), typically collected in patients with epilepsy for the purpose of seizure localization, has the advantage of high temporal resolution, and provides direct recordings from both cortical and subcortical brain structures. Patients with epilepsy have high rates of co-morbid depression (Hermann et al., 2000; Gilliam et al., 2003; Swinkels et al., 2005; Hermann and Jones, 2006; Fuller-Thomson and Brennenstuhl, 2009; Rai et al., 2012) that shares origin (Schmitz, 2006; Mula and Schmitz, 2009; Vezzani et al., 2011; Gleichgerrcht et al., 2015; Wulsin et al., 2016) and treatment response (Kanner, 2003) characteristics with primary depression. However, owing to heterogenous electrode placement across individuals, previous iEEG studies have been limited to low patient numbers and region-based approaches (Kirkby et al., 2018; Sani et al., 2018; Scangos et al., 2019a).

We hypothesized that we could apply a novel computational approach to a large unique dataset of multi-region, multi-day iEEG recordings in 54 participants to uncover distributed cortico-subcortical networks in depression. To tackle inconsistent network sampling across individuals, we utilized a method called SuperEEG (Owen et al., 2020) that uses the correlational structure of brain activity across the population to create a model of multiregional iEEG activity for each individual despite heterogeneous electrode placement. This model provided a highly detailed representation of brain activity across space and time and allowed us to chart out the inherent organization of the brain into functional networks. Once a generalized map of functional brain network organization was established, we quantified the multi-dimensional nature of corresponding brain dynamics to discover how rhythmic activity riding atop these functional networks differed in depressed and non-depressed individuals (Gu et al., 2018). Because depression has a variable presentation, we further examined how depression-associated circuitry varied across individuals in the depressed group.

We found that depression circuitry was highly distributed across cortical and subcortical structures with global dysfunction in both connectivity and spectral activity. Two unique depression subnetworks present in 89% of depressed subjects were identified. One pattern was marked by decreased connectivity across the occipitotemporal region and dominant beta band activity. The second was characterized by excessive frontal cortical connectivity with decreased activity in the alpha spectral frequency band.

MATERIALS AND METHODS

Patient Characterization

Participants included 54 adults (27 female) aged 20–67 who had medication-refractory epilepsy and were undergoing intracranial mapping with multi-channel iEEG for seizure localization as part of their standard medical care (**Supplementary Table 1**). Neural data from these participants comprised our full dataset and was utilized to build the whole-brain iEEG model of LFP time-series. Participants were screened for depression following electrode implantation and concurrent with neural recordings using the Patient Health Questionnaire-9 (PHQ-9), a 9-item self-report instrument validated for depression screening (**Supplementary Figure 1A**; Spitzer et al., 1999, 2000; Kroenke et al., 2001). A score $\geq$ 10 defined the depressed group (moderate depression) and a score $\leq$ 5 defined the non-depressed control group generating a sample of 23 depressed subjects (56%) and 18 controls (44%). A cut-off score of 10 was selected to define the depressed group because it is the standard threshold used for screening in clinical practice, was defined by the scale's developer, and has been used in large-scale validation studies (Kroenke et al., 2001; Arroll et al., 2010; Levis et al., 2019). The remaining 13 patients were used in the first step of the study (*Model building*) but not the second (*Model utilization*). Data comprised a consecutive series of patients recruited from University of California, San Francisco and Kaiser Permanente, Redwood City, California over a 5-year period. This study was approved by the University of California, San Francisco Institutional Review Board with written informed consent provided by all subjects. Patients' antiepileptic medications (AEDs) were withdrawn as part of standard clinical care. However, to control for possible effects of medication on neural activity in the depressed and control groups we examined the number of patients in each group that were on AEDs associated with depression (Nadkarni and Devinsky, 2005) using a chi squared test.

Electrode Implantation and Localization

Subdural grid, strip, and depth electrodes (AdTech, Racine, WI, United States; or Integra, Plainsboro, NJ, United States) were implanted using standard neurosurgical techniques. The number of electrodes per subject ranged from 33 to 201 (mean = 120, SD = 37). Subjects underwent pre-operative 3 Tesla brain magnetic resonance imaging (MRI) and post-operative computed tomography (CT) scan to localize electrodes in patient-centered coordinates using an open source python package for preprocessing imaging data for use in iEEG recordings (Hamilton et al., 2017). The steps included warping brain reconstructions to a common Montreal Neurologic Institute (MNI) template and merging electrode locations across subjects. Surface warpings were then generated by projecting pial surfaces of the subject and template brains into a spherical coordinate space and aligning the surfaces in that space. Depth warping was then performed using a

combination of volumetric and surface warping (Postelnicu et al., 2009). For visualization, pre-operative T1-weighted MRI scans were pre-registered with the post-operative CT using Statistical Parametric Mapping software SPM12 and pial surface 3D reconstructions were generated using FreeSurfer (Fischl, 2012).

Data Acquisition and Pre-processing

Data acquisition of iEEG recordings were acquired using the Natus EEG clinical recording system at a sampling rate of 1–2 kHz. Standard iEEG/ECoG pre-processing techniques were conducted in python including application of a 2–250 Hz bandpass filter, notch filters at line noise frequency and harmonics (60, 120, 180, and 240 Hz), down sampling to 512 Hz, and common average referencing to the mean of all channels. The data were acquired across a range of behaviors while the patient was in the epilepsy monitoring unit.

Overall Approach

Our overall approach consisted of two steps – a model building step where we identified large-scale functional networks across iEEG electrodes, and a model utilization step where we related the architecture and intrinsic neural activity of functional networks to depression status (**Figure 1**).

Construction of Whole-Brain Intracranial EEG Model

For the model building step, we used a functional connectivity imputation technique, called SuperEEG (Owen et al., 2020) to map continuous iEEG recordings from different patients into a common neural space (**Figure 2**). This method provided an important advance over previous iEEG studies (Kirkby et al., 2018; Sani et al., 2018; Scangos et al., 2019a) that were limited to region-based analyses conducted in small samples due to heterogeneous electrode placement. To generate this model, pre-processed iEEG signals were chunked into 60 s non-overlapping blocks and filtered for putative epileptiform activity or artifacts using kurtosis, a measure of infrequent extreme peaked deviations (Akbarian and Erfanian, 2018; Owen et al., 2020). We then randomly sampled the 60 s intervals across daytime hours (8am–10pm) and concatenated them into 2-h blocks, each representative of naturalistic activity. We then constructed subject-level whole-brain correlational models. To do so, interelectrode correlation matrices were constructed from activity where sensors were present and learned radial-basis function weighted averages were used to generate correlational information at locations where sensors were not present. The subject-level models were then averaged to generate a population-level model. We then used Gaussian process regression based on the population-level model and individual time series for each subject to reconstruct whole-brain local field potentials for each subject. Evaluation of the SuperEEG algorithm has been performed previously on two large independent iEEG datasets using leave-one-out cross-validation (Owen et al., 2020). Reconstruction accuracy was measured by calculating the correlation between the true and reconstructed signals for each held-out electrode from the held-out patients. By using only other patients' data to estimate activity for each held-out electrode, volume conductance or other sources of "leakage" were minimized resulting in a conservative estimate of reconstruction accuracy. Using the same approach as Owen et al. (2020), we compared the reconstruction accuracies obtained by the true held-out models (mean $r = 0.38$) to the reconstruction accuracies obtained by shuffled held-out models (mean $r = 0.00$) in which the interelectrode correlations of the SuperEEG model were permuted uniformly to generate activity patterns that would be reconstructed by chance. As we hypothesized, we found that the reconstruction accuracies for the true held-out models were significantly greater than the reconstruction accuracies of the shuffled held-out models ($t = 13.94$, $p = 1.04e^{-25}$), suggesting that the SuperEEG model reconstructs activity patterns significantly better than chance.

The SuperEEG algorithm requires extensive computational resources. Therefore, we sought to utilize the minimum required information to obtain the majority of information and enable computational feasibility. Using the 10 h benchmark as the largest feasible model we could build, we compared 2, 4, 6, and 8 h models to the 10 h model and found that the difference in adding additional time beyond 2 h was marginal and could be computed at a fraction of the computational cost. We therefore utilized the 2 h model for further analysis (**Supplementary Figure 1B**).

Signal Processing

Standard signal processing techniques were applied to the time-series activity across all reconstructed electrodes. This included continuous wavelet transformation using the Morlet transform wavelet method (6-cycles) (Schiff et al., 1994) performed in 30 s intervals to obtain power spectra in 6 frequency bands (delta = 1–4 Hz, theta = 5–8 Hz, alpha = 9–12 Hz, beta = 13–30 Hz, low gamma (gammaL) = 31–70 Hz, high gamma (gammaH) = 71–150 Hz). Relative power was calculated by dividing the power of each frequency band by the total power across the 6 frequency bands for each electrode. Signals were summarized by taking the mean power across time for each spectral band and were z-scored across patients.

Electrode Clustering Into Functional Modules

After construction of the full-brain correlational model, we next utilized principles of graph theory to identify data-driven functional networks (modules) across it. Our rationale was that the model had learned statistically correlated fluctuations between iEEG signals, akin to functional connectivity, and that a network-based approach could enhance discovery of depression circuitry over a univariate, single-region approach. We used a well-validated modularity optimization technique known as multiscale community detection, which groups electrodes into non-overlapping modules by their correlational relationships (Newman, 2006; Blondel et al., 2008) and has been used to reveal system-level disruptions in disease states (Alexander-Bloch et al., 2010; Chen et al., 2011; Yu et al., 2011; Bruno et al., 2012; Cao et al., 2014; Sun et al., 2014; Keown et al., 2017) including MDD (He et al., 2018). We conceptualize a network module as a distinct

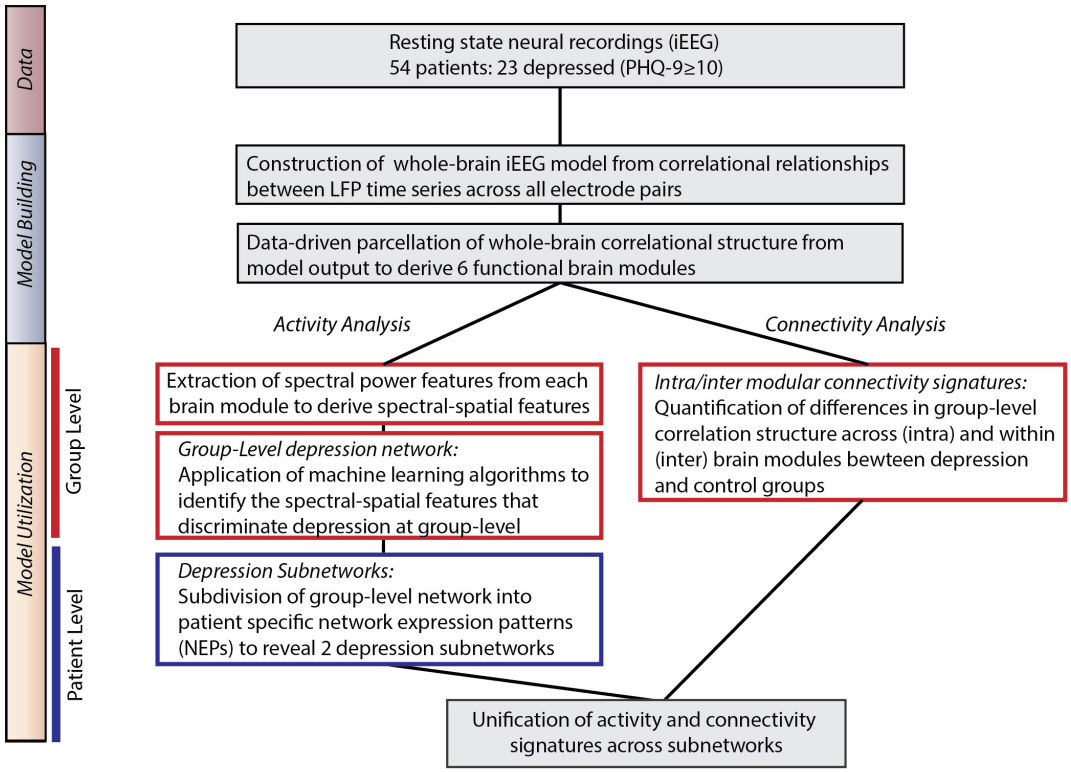

FIGURE 1 | Overall approach. *Model Building:* We utilized direct neural recordings from 54 patients to construct a whole-brain model of iEEG activity based on correlational relationships of neural LFP time series signals across all electrode pairs. We then parcellated this model into functional network modules using graph theory metrics. *Model Utilization:* We used the whole-brain iEEG model to study how brain activity and connectivity measures relate to depression status. We first defined spectral power features across network modules and applied supervised machine learning to identify a group-level network features of depression (*Activity analysis*). In parallel, we identified alterations in functional network connectivity and organization between depressed and control groups (*Connectivity analysis*). Common group-level network features expressed at the individual level were clustered to identify two distinct patterns of altered activity and connectivity.

property of connectivity organization, akin to validated atlas parcellations (Cammoun et al., 2012) but specifically designed for functional rather than structural data. Atlases apply boundaries to brain regions based on structural or functional organization derived from coarse-scale neuroimaging and thus, while they provide a useful validation for our data-driven parcellation scheme, there is no reason to assume their boundaries will perfectly align with neural signals at the millimeter scale of iEEG.

Individual functional connectivity models generated in the whole-brain iEEG reconstruction were used as a starting point in this analysis. Using the Louvain algorithm (Blondel et al., 2008), we identified an optimal parcellation of electrodes into discrete functional modules by maximizing a modularity cost function defined by the following relationships,

$$P = \frac{2}{|K|_F} KJK^T \quad (1)$$

$$Q = \left|(K - \gamma P)^{\circ} G\right|_F \quad (2)$$

where J is a ones matrix, $^{\circ}$ is the Hadamard product and Gi,j is 0 if node pair (i, j) are assigned to different modules and 1 if the pair is assigned to the same module, Q is modularity, K is the connection weights (correlation) between node i and j, P is the Newman-Girvan null model (Newman, 2006) and γ is the weighting of that null model which is tuned to obtain network modules of different sizes. Previous work on module detection (Bassett et al., 2013) demonstrated that tuning this resolution parameter is key to identifying modules at different topological scales of a network. We examined network modularity at values of γ between 0.5 and 2.1. We first assessed the stability of clustering at each value of γ by examining module allegiance (Bassett et al., 2015), calculated by repeating module detection 100 times and evaluating the probability that two electrodes occupied the same module.

Then, in line with previous efforts that have related iEEG network structure to brain parcellations based on anatomy (Betzel et al., 2019), we computed a similarity index (Misic et al., 2016) between the division of electrodes into modules and the division of electrodes into the 234 anatomically distinct brain areas defined by the Lausanne atlas (Cammoun et al., 2012) for the range of resolution parameters (**Supplementary Figure 1C**). Significance was assessed by a permutation test where the null model was generated by randomly assigning electrodes to each module and calculating the confidence interval of the similarity index generated from 1,000 random permutations and tested at

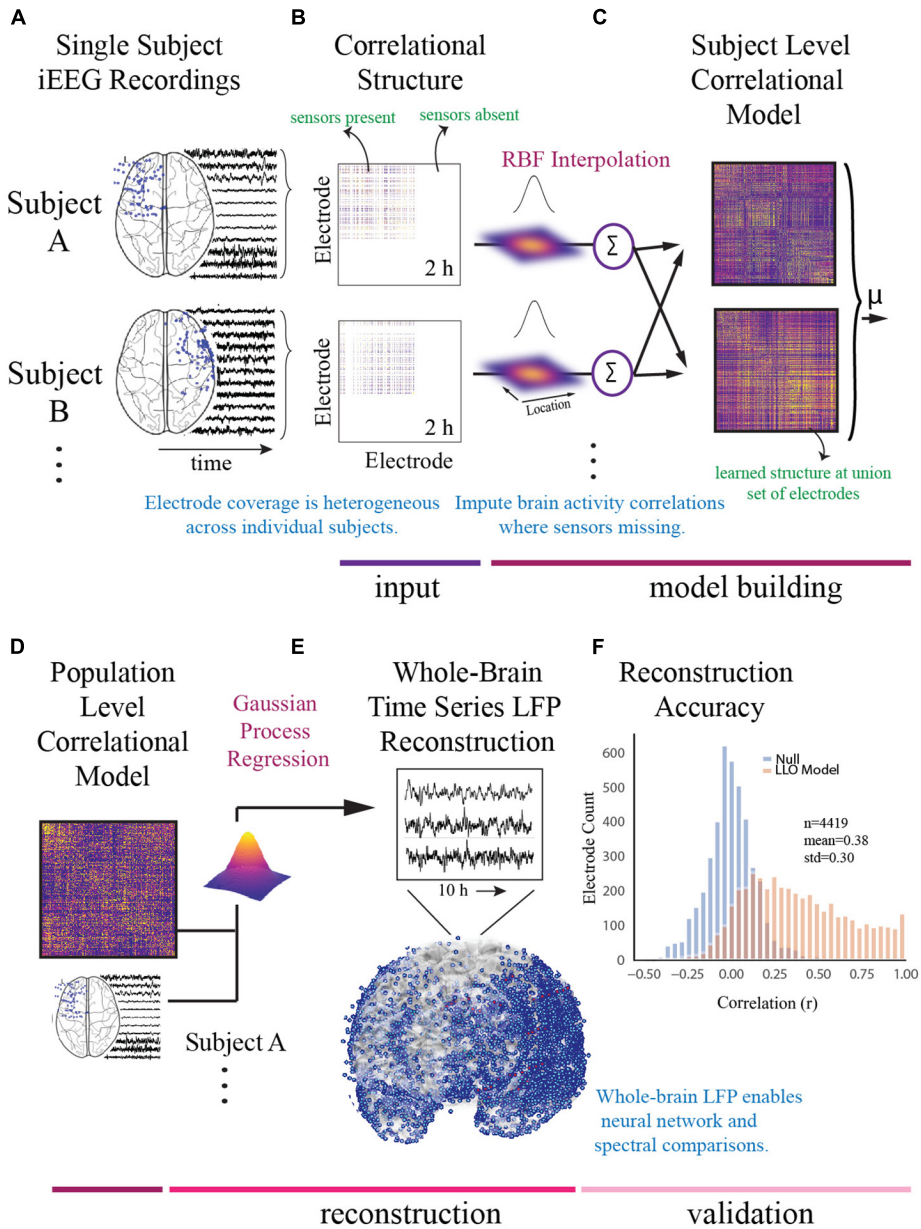

FIGURE 2 | Construction of whole-brain model. **(A)** To generate a multi-subject whole-brain model of iEEG activity, patient's electrode locations across participants were first represented in a common space [Montreal Neurologic Institute (MNI) space]. Electrode locations and sample recordings for a few example patients are shown. Activity was then randomly sampled in 1 min intervals across daytime hours to obtain a stable representation of brain activity across a 2-h period. **(B)** Individual inter-electrode correlation matrices were constructed for each participant at locations where electrodes were present. **(C)** Subject-level full brain correlational models were then predicted using radial basis function (RBF)-weighted averages to estimate brain activity correlations at locations where sensors were not present. **(D)** Subject-level correlational models were then averaged to generate a population level whole-brain correlational model. **(E)** Local field potential activity for each of the 4,244 electrodes was then reconstructed using Gaussian process regression with the population-level model as a prior and activity where electrodes were present as the marginal likelihood. **(F)** The distribution of the electrode signal reconstruction accuracy across true correlational models (orange) compared to reconstruction accuracy obtained from shuffled correlational models. To obtain this distribution we built models with 53/54 patients, and then applied the model to the held-out patient, holding out each patient in turn. Correlation of the true and reconstructed signals were compared for each held-out electrode. Significance was assessed by averaging the patient level Fisher transformed correlation coefficients and comparing the distribution for the true correlational model and the shuffled correlational model using a *t*-test ($t = 13.94$, $p = 1.04e^{-25}$).

significance level 0.05 for a two-tailed test. Two similarity peaks were identified, with values of γ that generated 6 and 1,855 modules, respectively. The peak with the highest modularity (lowest number of clusters) was selected for further analysis due to our goal of examining the brain at a low level of granularity. This selection enabled subsequent classification of activity across

these clusters without overfitting our model. While we report our results based on this most parsimonious match between modules and anatomical structures ($\gamma = 1.19$), we verified that the assignment of electrodes into slightly coarser and slightly finer modules ($1 < \gamma < 2.1$) did not substantially alter our ability to predict subjects with depression (**Supplementary Figure 1C**, red). Finally, we assessed the distribution of electrodes that were assigned to each module across the main anatomical regions defined by Cammoun et al. (2012) (**Supplementary Figure 1D**).

Assigning Names to Modules

We assigned a name to each module by examining the location of each module's most influential electrodes. We utilized the participation coefficient (PaC), which is a degree-based measure of network connectivity that describes a node's functional interaction within and across network modules (Guimera and Amaral, 2005; Rubinov and Sporns, 2010; Bertolero et al., 2015). This metric is typically utilized to identify influential hubs across a large-scale network. We utilized it in our study to identify the location of hubs that were most important for driving connectivity in each module identified through community detection. Groups of electrodes with low PaC values indicate hubs with high intramodular connectivity, also known as provincial hubs (van den Heuvel and Sporns, 2013). Similarly, connector hubs are those with high PaCs and drive intermodular connectivity. The PaC describes the weight of edges from node i to all other nodes in the same module relative to the weight of edges from that node to all nodes in the network according to

$$y_i = 1 - \sum_{c \in C} \left(\frac{k_i(c)}{k_i} \right) \quad (3)$$

where y_i is node i's participation coefficient, C is the set of all modules, $k_i(c)$ is the sum of all correlations between node i and other members of module C and k_i is the sum of all correlations between node i and members of all modules. We calculated the PaC for each electrode across our model, and then selected those with high and low participation values (top/bottom 10%). We then grouped these selected nodes by Lausanne atlas region, eliminating or combining a minority of regions due to having too few electrodes for analysis. We addressed the non-uniform distribution of electrodes across the model by then assigning each Lausanne region a score according to the following hub weight:

$$R_i = \frac{N_i M_j}{T_j} \quad (4)$$

where N_i is the number of selected electrodes (top/bottom 10%) in Lausanne region i, M_j is the number of selected electrodes in Lausanne region i of module j, and T_j is the number of total electrodes across modules in Lausanne region i. Hubs were those Lausanne regions with the highest hub weight. Hub location was identified by averaging the MNI coordinates of electrodes within each hub. The full list of Lausanne regions and hub weights is shown in **Supplementary Figure 2** and **Supplementary Tables 2, 3**. The purpose of the identified hubs in the present report was primarily descriptive and helped relate the computational model to known brain regions and structure; all subsequent analyses utilized the population set of electrodes across the full model.

Model Utilization: Activity Analysis

We next used the whole-brain correlational model to relate the architecture and intrinsic neural activity of functional networks to depression status. We hypothesized that by leveraging the high temporal resolution of iEEG, as well as the direct access to subcortical structures, we could overcome limitations of scalp recordings (Widge et al., 2019). We used a machine learning algorithm validated with leave-one-out cross validation to identify distributed neural circuit features that discriminated depression. We first averaged local field potentials across the electrodes within each module and then decomposed the signals into common spectral bands to identify 36 features (6 frequency bands × 6 modules) where each feature contained information about a spectral power band across one functional module. These features, referred to as spectral-spatial features, served as our starting feature space for entry into our classification pipeline. Transformation with principal component analysis (PCA) (Hotelling, 1933) followed by methods for feature selection and subsequent discrimination have been used on previous iEEG classification problems (Kirkby et al., 2018; Sani et al., 2018). We followed a similar pipeline. PCA enabled us to identify a low-dimensional feature representation of spectrally band-limited neural activity across electrodes that potentially span different modules. It is important to note that while PCA and network module detection reduce the complexity and inherent collinearity in the dataset (Manning et al., 2011, 2012; Kirkby et al., 2018; Sani et al., 2018; Scangos et al., 2019b), they also reflect two non-mutually exclusive properties of brain connectivity (modules) and brain activity (principal components). Specifically, modules demarcate groups of brain regions with correlated *broadband* brain activity, irrespective of the amplitude of the activity, and principal components represent additional state-dependent neural activity that is *band-specific,* such as rhythms and oscillations (Betzel et al., 2019), and may arise from functionally important integrative connections that span between modules (Bertolero et al., 2015; Betzel et al., 2018). This line of thinking closely resembles previously reported accounts of neural co-activation dynamics (akin to principal components) spanning multiple cognitive networks (akin to network modules) that explain inter-individual differences in task performance and cognitive traits. After identifying a principal component representation of cross-module spectral-spatial network features, we utilized logistic regression (with L1 regularization) to classify subjects with depression and identify features with the greatest discriminatory power. PCA and logistic classification were performed within the cross-validation loop where a model is trained on all subjects but one, and then tested on the held-out subject with each subject held-out in turn. We report mean accuracy (balanced to group-size) across the cross-validation iterations. Models without PCA were also performed for comparison (L1, L2, elastic net, random forest). To further asses our model validity, we repeated our classification

pipeline on a null model obtained from randomly permuting the target class labels 1,000 times and used a permutation test to assess significance between the true and null model accuracy distributions. In order to control for possible differences in epileptiform activity residual to data-cleaning across the modules we calculated mean line-length, a commonly utilized measure for the detection of epileptiform activity (Guo et al., 2010), of the electrodes within each module and used a logistic regression model to determine if line-length across the six modules was a significant predictor of depression status.

Hierarchical Clustering to Identify Depression Networks

We reasoned that we could utilize the group-level network to identify common features that defined depression at the individual level. To do so, we mapped the principal component values (feature loadings ≥ 0.2) back to the original feature space weighted by the logistic regression coefficients. Specifically, we computed the dot product between the loading weights for each spectral-spatial feature and the coefficient weighting from the classifier. Performing this operation provided the log-odds impact of each original feature and enabled us to show the direction of change of each power band and module in relation to depression diagnosis. We then tested the distribution of feature impact on depression classification probability across depressed participants by grouping similar log-odds impact covariates (thresholded at 0.15) utilizing an agglomerative hierarchical clustering algorithm (Ravasz et al., 2002; Rihel et al., 2010; Drysdale et al., 2017; Grisanzio et al., 2018). A log-odds threshold of 0.15 was selected because it retained classification results for 98% of subjects while isolating the most contributory spectral-spatial features (see **Supplementary Figure 3A** for non-thresholded model for comparison). The clustering yielded both patient and feature groupings that defined neurophysiological network expression patterns (NEPs) of depression. We quantified the impact of these NEPs on each participant's probability of being classified as depressed by performing a sensitivity analysis where we withheld each NEP and then attributed the probability decrement from the total classification probability to the withheld activity pattern. We also ran this analysis on the boundary patients who had mild symptoms of depression but did not reach threshold (PHQ-9 < 10) for depression (**Supplementary Figure 3B**).

Model Utilization: Connectivity Analysis

In addition to alterations in the spectral content of network activity in depression, previous studies have observed distinct deficiencies in connectivity across depression networks (Sun et al., 2011; Zhang et al., 2011; Lord et al., 2012; Korgaonkar et al., 2014; Chen et al., 2017). A fundamental interest in neuroscience is the relationship between the brain's neural activity and its underlying functional and structural connectivity, which remains unknown. The graph of our whole-brain iEEG model defines correlational relationships between electrodes across our total population. We thus examined these correlational relationships across control and depressed groups independently in order to measure the relative differences of functional network organization between the two groups. First, inter- and intramodular connectivity strengths were assessed by looking at the correlations between all electrodes within the same module (intramodular) and the correlations between electrodes across all pairs of modules (intermodular). Next, to assess whether the effect of connectivity differences between groups is a network-wide characteristic of the depressed brain or whether the effect is localizable to specific modules, we used a Cohen's d effect size metric and compared the distribution of correlation strengths across depressed and control groups for each possible module pair. To assess significance across these connections we generated a null distribution of Cohen's d values for each module pair and retained the true Cohen's d values that survived multiple comparisons testing ($p < 0.001$).

RESULTS

Derivation of Functional Modules

Using leave-one-patient out validation of the correlational model, we found that the distribution of correlations (mean $r = 0.38$) was similar to the prior reconstruction accuracies (Owen et al., 2020) and centered well above shuffled correlational models (mean $r = 0.00$) suggesting the algorithm estimates activity patterns substantially better than chance. The distribution of patient level fisher transformed correlation coefficients was significantly different than 0 ($t = 13.94$, $p = 1.04e^{-25}$, **Figure 2F**). We observed that our whole-brain iEEG model was optimally parcellated into 6 stable modules (Jaccard index, $p < 0.05$, permutation test) and that these modules were spatially distributed and spanned multiple anatomical structures (**Figure 3A**). A graph of the network and its subdivision into modules is shown in **Figure 3B**, where module membership is indicated by the color of nodes (iEEG electrodes) and edges (inter-electrode correlation from whole-brain model). These modules included the left dorsolateral prefrontal cortical (L-DLPFC), left occipitotemporal (L-OT), left orbitofrontal cortical (L-OFC), right frontotemporal (R-FT), right medial frontal (R-MF), and mid-hemispheric modules. **Figure 3C** shows hub locations by their mean Montreal Neurological Institute (MNI) (Cammoun et al., 2012) coordinates and associated Brodmann Areas.

Relationship of Functional Network Identification to Depression Status

In accordance with literature-derived rates of depression in this population (Hermann et al., 2000; Gilliam et al., 2003; Swinkels et al., 2005; Hermann and Jones, 2006; Fuller-Thomson and Brennenstuhl, 2009; Rai et al., 2012), 43% of our population had self-reported depression (defined by PHQ-9 ≥ 10, $n = 23$), and 33% had mild or no symptoms of depression, which defined our control group (PHQ-9 ≤ 5, $n = 18$). The two groups did not vary in age, sex, type of epilepsy, antidepressant usage, or anti-epileptic drug class (t-test, X^2, $p > 0.4$, **Supplementary Table 1**). In order to determine the spectral-spatial neural activity features that discriminated the depressed from the control group, we used a standard leave-one-out cross validated machine learning pipeline

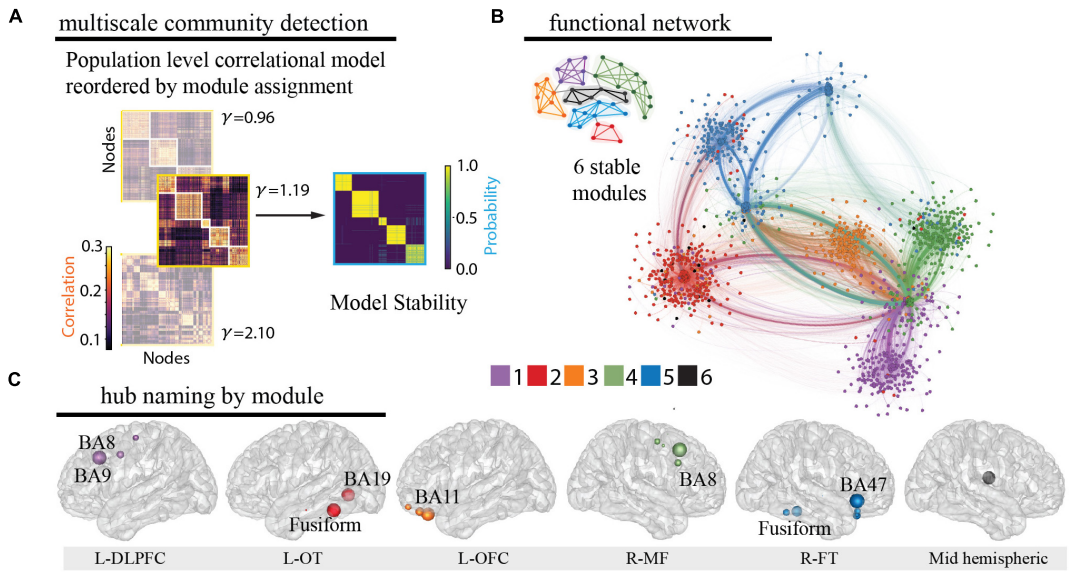

FIGURE 3 | Identification of functional modules. **(A)** Multiscale community detection was applied to the whole-brain model to group electrodes (nodes) into non-overlapping modules (communities) by their correlational relationships (Newman, 2006; Blondel et al., 2008). First, the population-level correlational model was reordered by the module assignment according to the modularity cost function. Network modules were identified at different levels of granularity by varying the tuning parameter (Garcia et al., 2018; He et al., 2018). Increasing partitions the brain into increasing numbers of modules with a limit equal to the number of electrodes, as shown here for 3 values of (left). Next, the stability of this clustering at each value of was assessed by calculating module allegiance, which describes the probability that any two electrodes occupy the same module on repeated module detection (Bassett et al., 2015) (right). A value of 1.19 was selected by comparing the similarity of partitions generated by values of with those of a commonly used brain atlas (Cammoun et al., 2012), resulting in 6 modules. Of note, one of the modules is small and difficult to resolve in the figure. **(B)** The graph of the large-scale network with module membership delineated by the color of the nodes and edges for selected of 1.19 is shown along with a schematic representation of the 6 modules. **(C)** Hubs for each module were identified by selecting electrodes with the lowest 10% participation coefficients. Values were then averaged for each Lausanne brain region per module and weighted by the distribution of electrodes across Lausanne regions in all modules. Hub weight is indicated by the size of hub, and module assignment is indicated by hub color. Module 5 contained insufficient number of electrodes for hub identification (0.3% of total sample) and coefficients across all electrodes were utilized to name this module. L-DLPFC, left dorsolateral prefrontal cortex; L-OT, left occipitotemporal cortex; L-OFC, left orbitofrontal cortex; R-MF, right medial frontal cortex; R-FT, right frontotemporal cortex.

(PCA followed by logistic regression, **Figure 4A**) (Arbabshirani et al., 2017). We found that a combination of four principal components had the strongest predictive ability to detect depressed from non-depressed subjects. Their loading weights represent their contribution toward likelihood of depression (**Figure 4B**). Utilizing the four most discriminative components alone, we achieved a mean classification accuracy of 77.4% (p = 0.002). The same classification pipeline applied to a null model obtained from randomly permuting the target class labels 1,000 times and retraining the classifier with each permutation led to an accuracy of 50.0%. Alternate classification models without PCA also performed better than chance (L1 0.68; L2 0.77; Elastic Net 0.75; Random Forest 0.60). Furthermore, a logistic regression model showed that epileptiform activity residual to data-cleaning across the modules was not a significant predictor of depression status (R^2 = 0.15, p = 0.13). Together, these data suggest that a parsimonious model with four principal components, which capture major sources of variance in spectral-spatial features, can detect subjects with depression from the control group significantly better than chance.

As our primary goal was to uncover the underlying biology of depression, we next turned to an examination of the individual spectral-spatial features contained within the four components. These features comprise the circuit activity that distinguishes depression in our population (for full component loadings see **Supplementary Table 4**). To better interpret the biological meaning of this distributed network activity in terms of recognized brain regions and our similarly scaled network modules, we spatially projected the four components back onto the brain (**Figure 4C**). On visual inspection two gross patterns of spectral activity across the modules emerged. The first was high alpha power across the L-OT, R-FT, and mid-hemispheric modules (attention and default mode regions, modules 2,5, and 6 in **Figure 4C**). The second was high delta and low alpha and theta power in the L-DLPFC and OFC modules (executive and limbic regions, modules 1 and 3 in **Figure 4C**). These results suggested that low- and mid- frequency activity across broad networks characterize depression at the group level and motivated the subsequent statistical analysis to define the two patterns quantitatively.

Distinct Network Expression Patterns Define Depression

To further examine the observed inter-individual heterogeneity in expression of the group-level depression network features, we tested the distribution of feature impact on depression classification probability across participants using an

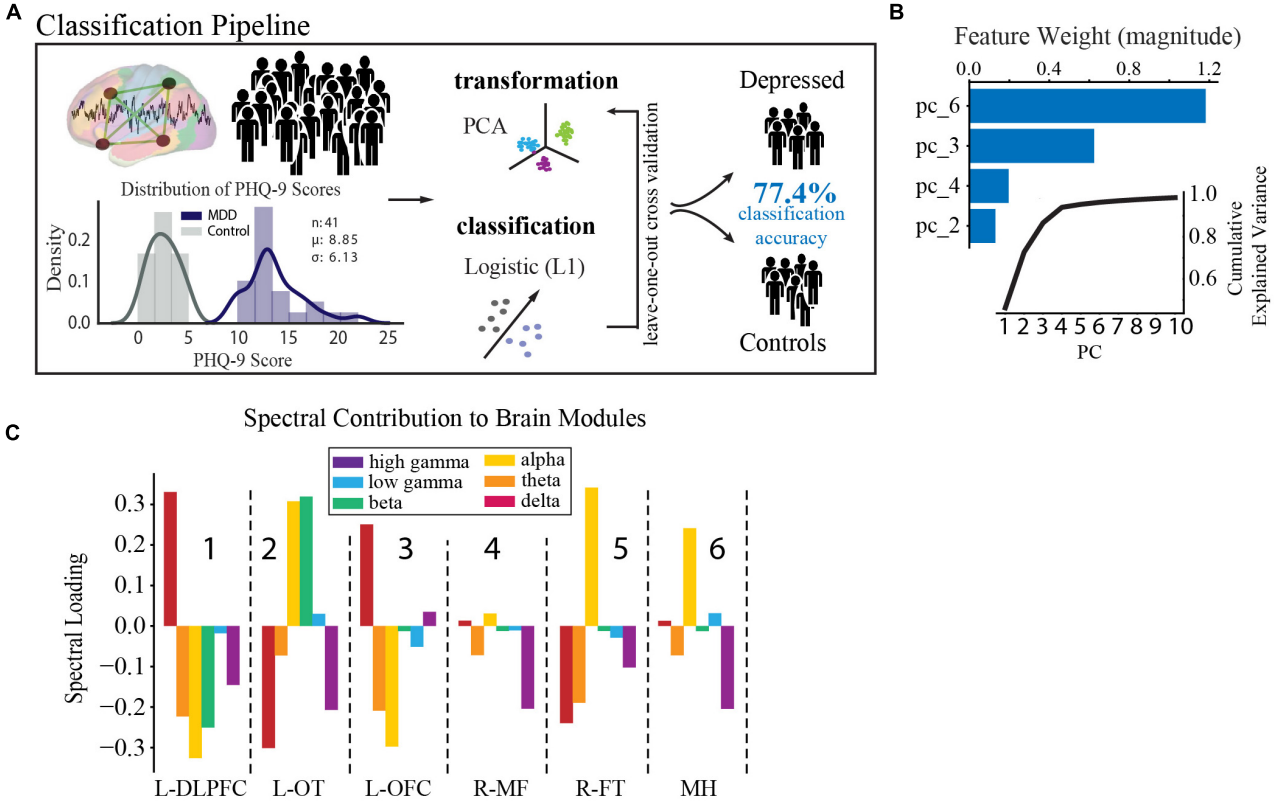

FIGURE 4 | Spectral-spatial features that discriminate depression at group level. **(A)** Activity analysis pipeline showing steps including power feature extraction, dimensionality reduction, transformation, and classification. The distribution of PHQ-9 scores across the depression (n = 18, purple) and control groups (n = 23, gray) is shown bottom left (mean PHQ-9 score 8.85, standard deviation 6.13). Power was extracted from the reconstructed time-series using the Morlet transformation in 30 s intervals across 6 frequency bands (delta = 1–4 Hz, theta = 5–8 Hz, alpha = 9–12 Hz, beta = 13–30 Hz, low gamma (gammaL) = 31–70 Hz, high gamma (gammaH) = 71–150 Hz). This process yielded 25,464 spectral power features from our model (6 frequency bands × 4,244 electrodes × 2 h). Z-scored relative power was calculated and averaged within each band across each of the 6 network modules. Power was then further averaged across time to yield 36 spectral-spatial features per participant. Principal component analysis was then used to transform the full spectral-spatial feature set, followed by logistic classification yielding 4 features that identified depression with 80.0% accuracy on the training set and 77.4% on the test set. **(B)** The component weights of the four features with cumulative explained variance across the first 10 principal components shown in the inset. **(C)** Spectral distribution of the 4 components was obtained by calculating the dot product between the loading weights (>0.2) for each spectral-spatial feature in the four principal components and the coefficient weighting from the classifier. Bars show the direction of change of each power band and module in relation to depression diagnosis and relate changes in spectral power associated with depression across spatially distributed brain networks. These spectral-spatial features represent the circuit activity that distinguishes depression in our population. DLPFC, dorsolateral prefrontal cortex; OT, occipitotemporal; OFC, orbitofrontal cortex; MF, medial frontal; FT, frontotemporal; MH, mid-hemispheric.

agglomerative hierarchical clustering algorithm (Ravasz et al., 2002; Rihel et al., 2010; Drysdale et al., 2017; Grisanzio et al., 2018). We found two distinct subnetwork activity patterns (network expression patterns (NEPs)) that strongly impacted depression and subdivided our depressed population into two groups (**Figure 5A**). The first subnetwork (NEP1) was marked by increased beta power in the L-OT module, and increased alpha and decreased delta power over the L-OT and R-FT modules. The second subnetwork (NEP2) was marked by decreased theta in the L-DLPFC, L-OFC, and R-FT modules, and decreased alpha, beta power together with increased delta power within the L-DLPFC and L-OFC modules. The presence of two subnetworks importantly demonstrated that different core features were relevant in different subjects.

We next used a sensitivity analysis to quantify the impact of each NEP on each participant's probability of being classified as depressed. **Figure 5B** shows the probability contribution of each NEP for each subject in the depressed group (top plot) and control group (bottom plot). While we anticipated that each individual would exhibit several NEPs with differing contributions to their depression classification, an alternate pattern emerged from the data. We found that increased activity in either NEP was correlated with depression, but that each patient exhibited activity in only one of the two NEPs. Thus, depressed participants fell into two groupings based on NEP activity. Classification for the first group (37% depressed subjects) was largely driven by NEP1 (n = 7, mean probability contribution = 0.38, SD = 0.13) alongside usually modest opposing contributions form NEP2, while classification for the second group (53% depressed subjects) was largely driven by NEP2 (n = 10, mean probability contribution = 0.39, SD = 0.18, **Figure 5C**), alongside more modest opposing contributions from

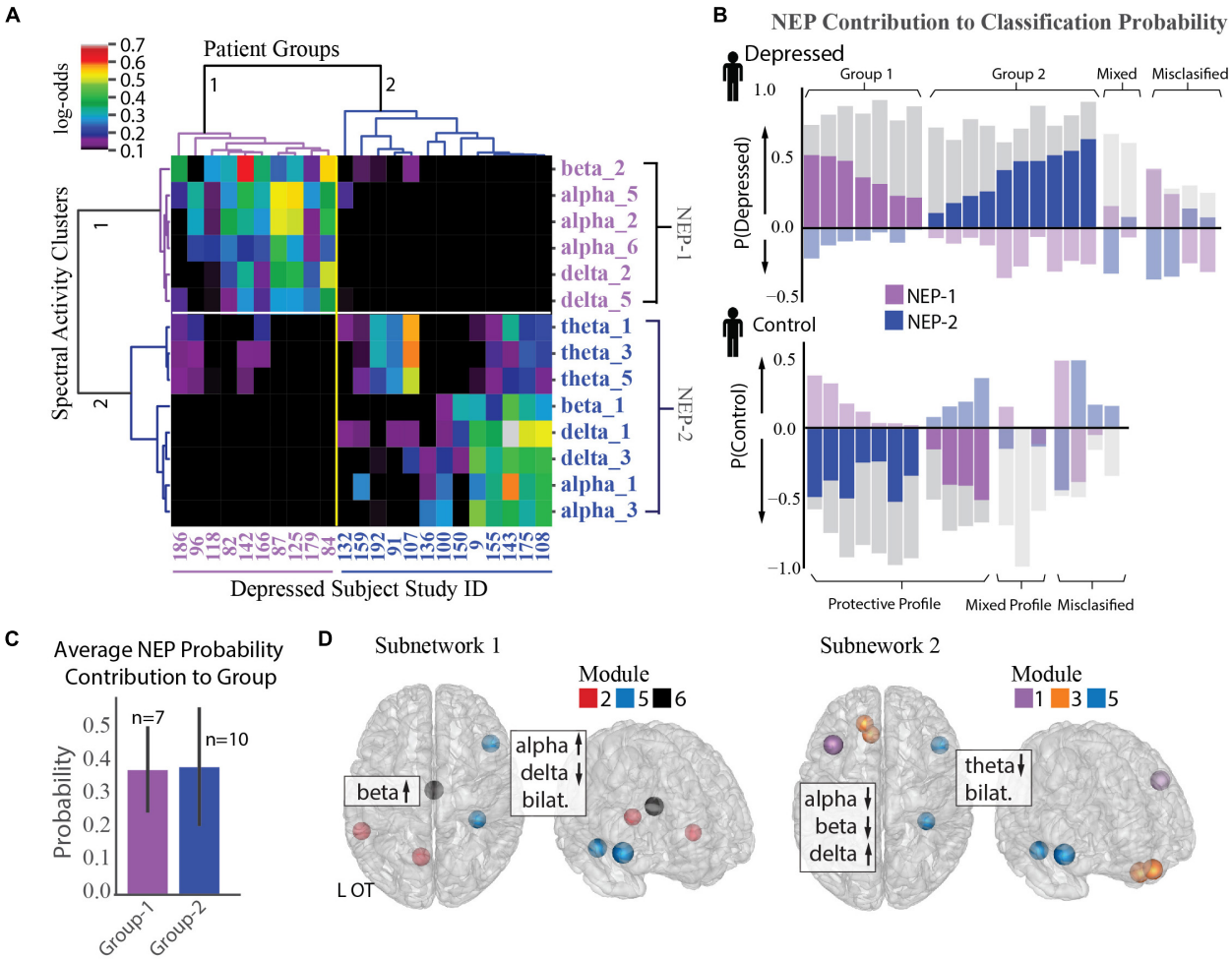

FIGURE 5 | Identification of two depression subnetworks. **(A)** Hierarchical clustering on log-odds of spectral-spatial features at the individual patient level showing 2 patient groups (horizontal groupings) and 2 network expression patterns (NEPs) (vertical groupings). Columns represent individual patients with patient study number shown at bottom, and rows represent spectral power across one frequency band and module (ex. alpha_1 = alpha power across module 1). Magnitude of log-odds represented by color of corresponding boxes (color-bar legend top right). Spectral-spatial features associated with NEP-1 represented in purple text and those associated with NEP-2 represented in blue text. **(B)** NEP probability contribution for the depressed group (top plot) and control group (bottom plot) derived from a sensitivity analysis where the probability of depression for each individual was calculated in total and with a perturbation where each NEP was held out. The probability difference was attributed to the presence of the NEP. This probability contribution is represented by the colored bars overlaid over each patient's total probability of being depressed as derived from the machine learning classification model (gray bars, probability > 0.5 leads to classification of depression). The perturbations do not sum to produce the total classification probability; rather each quantifies the relative importance of that NEP toward depression. Bars in the positive direction indicates a positive contribution toward depression, and those in the negative direction indicate a protective contribution toward depression. Subjects where one of the two NEPs did not drive classification probability are shown in muted colors (mixed profile). Subjects classified incorrectly shown on far right of each plot (misclassified). **(C)** Mean probability contribution of each NEP to two patient groups is shown. NEP-1 (purple bars) contributed most strongly to the probability of depression in the first group (mean = 38% probability contribution, SD = 0.13) and NEP-2 (blue bars) contributed most strongly to a second group (mean = 39% probability contribution, SE = 0.18). Number of participants who exhibit each NEP shown above each bar. Error bar = standard deviation. **(D)** Direction of activity and spatial distribution of activity changes within NEP shown on glass-brain in several orientations. Hubs for each module within the NEP are designated by hub color.

NEP1. Classification of the remaining 11% of participants was either driven by mixed effects of both NEPs or there was little contribution from either NEP and may be evidence of additional subnetworks that were not resolved in our dataset. Two distinct groups also emerged from the control participants with NEP activity contributing here as well, but with distinct contribution profiles compared to the depressed participants. Classification for the first group (21% control patients) was driven either by mixed effects of both NEPs or little contribution of either NEP, as we anticipated. Classification for the second group, was driven by one of the two NEPs with a more modest contribution of the opposing NEP (79% of control group). We might speculate that relative NEP activity could represent either risky or conversely, protective activity profiles, and that NEP activity could be modulated in either direction to treat depression. The anatomical distribution of the two depression

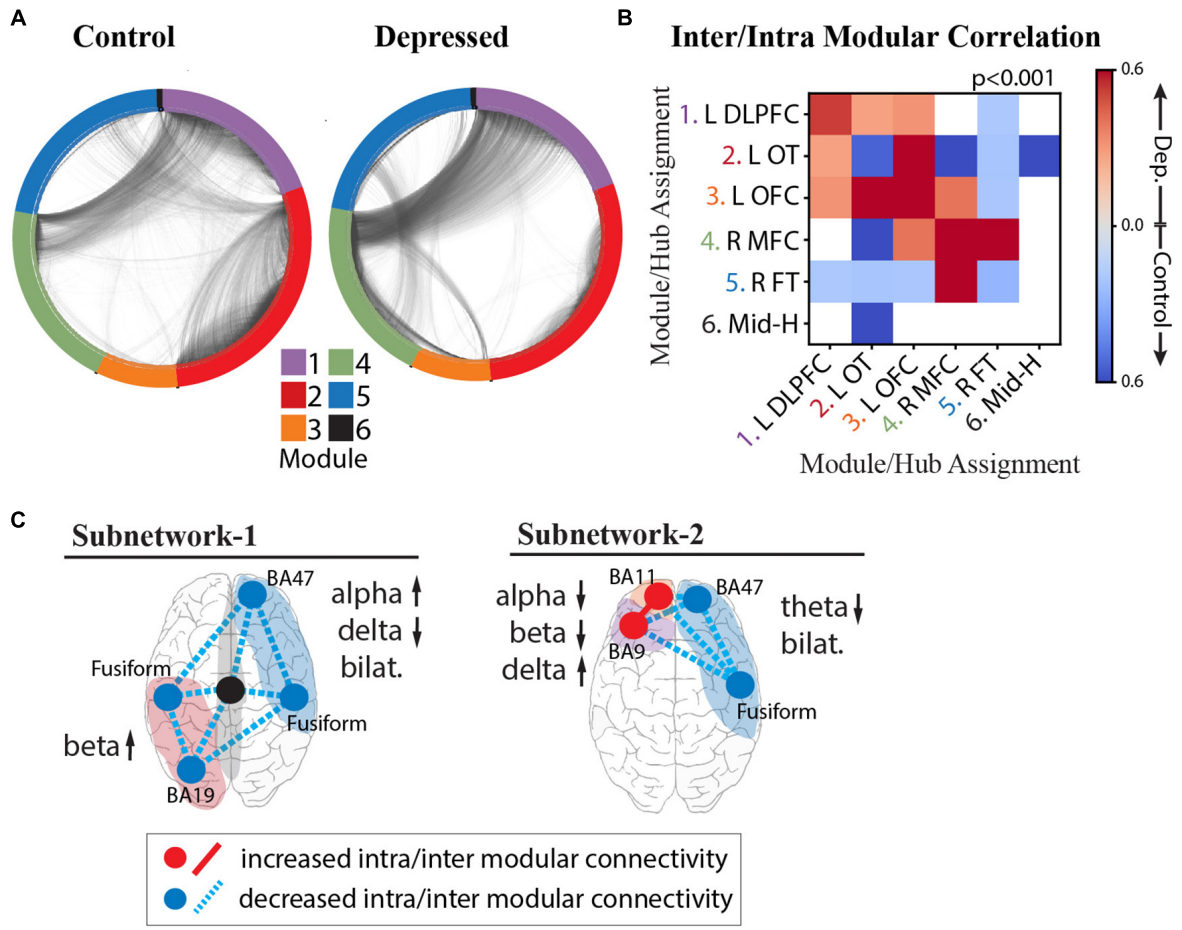

FIGURE 6 | Intra- and Inter-modular connectivity signatures of depression and control groups. **(A)** Connectivity structure derived using whole-brain iEEG model recalculated for the control group (left) and depressed group (right) with module membership delineated by the color of the nodes (electrodes), and edges (connections between electrodes) delineated by the black interconnecting lines. **(B)** Heatmap of significant Cohen's *d* values calculated from the distribution of correlation strengths between depressed and control groups for each possible module pair and compared to Cohen's *d* values for a null distribution derived from permuted nodal module assignment. Those that survived multiple comparison testing ($p < 0.001$) were retained (red: increased connectivity for depressed group; blue: increased connectivity for control group; white: not significant). **(C)** Schematic of NEP-1 (left) and NEP-2 (right) showing both connectivity and spectral power underlying each pattern. Increased connectivity strength shown in red, and decreased connectivity shown in blue (hub = intramodular, line = intermodular connectivity). Color of shaded area refers to module number as shown in color legend in **(A)**.

subnetworks and the associated changes in spectral activity are shown in **Figure 5D** and **Supplementary Figure 3C**.

Network Organization Is Disrupted Across Depression Subnetworks

We expected that alterations in functional network topology would also be present in our depressed population and that we could delineate new relationships between activity and functional connectivity with our high-resolution dataset to more comprehensively characterize depression subnetworks. We performed a connectivity analysis using correlation of local field potential activity across modules as an estimate of functional connectivity between electrodes. **Figure 6A** shows the two-dimensional representation of the functional network structure for control (left) and depressed (right) groups. In comparison to the control group, we qualitatively observed an overall reduction in the segregation between modules in the depression network.

To quantify these differences and test whether the effect of connectivity differences between groups is a network-wide characteristic of the depressed brain or whether the effect is localizable to specific modules, we calculated the inter- and intra-modular connectivity strength. **Figure 6B** shows the heatmap of significant Cohen's *d* values, where a greater effect of connectivity for the depressed group is indicated in red, and lower effect of connectivity for the depressed group is indicated in blue. The results demonstrate strong evidence that, indeed, there are module-specific differences in the effect of connectivity between depressed and non-depressed individuals suggesting that modules may express hyperconnectivity or hypoconnectivity in depression depending on their anatomical localization in the brain. In the depressed group, there was overall greater

frontal connectivity and weaker cross-hemispheric connectivity. Specifically, we observed greater intra-modular connectivity within L-DLPFC, L-OFC, and R-MFC modules, weaker intra-modular connectivity within L-OT and R-FT modules, and greater inter-modular connectivity between L-DLPFC, L-OFC, and L-OT modules. Hubs in the insula, amygdala, temporal pole and fusiform gyrus drove the cross-module connectivity (top 10% participation coefficient, see section "Materials and Methods"). We also observed a decrease in cross hemispheric connectivity in the depressed group compared to the control group (L-DLPFC/L-OFC to R-FT modules, and L-OT to R-FT/R-MFC modules), with hubs in the insula, temporal-parietal region and amygdala responsible for this decreased connectivity. The L-OFC module showed greater connectivity with the R-MFC module, and R-MFC module exhibited stronger connectivity with the R-FT module.

On the basis of the above analyses we were able to parse specific connectivity components that characterize the two depression subnetworks (**Figure 6C**), unifying both activity and connectivity analyses across cortical and deep structures with a level of specificity that has not previously been possible. In the first subnetwork characterized by NEP1 we observed increased beta power in the L-OT module, and right-left asymmetry in the alpha and delta bands over right frontal/L-OT modules with weaker intra- and inter-modular connectivity throughout. In the second subnetwork characterized by NEP2 we observed a hyperactive left frontal cortex that was more highly connected within itself but more weakly connected to R-FT module. Lower theta bilaterally was observed in this subnetwork.

DISCUSSION

In this report, we present a large study of direct neural recordings aimed at identifying depression networks, made possible by multi-day iEEG recordings paired with a depression measure. The opportunity to directly record semi-chronically from cortical and subcortical structures in this manner enabled us to estimate whole-brain neural activity and incorporate both activity and connectivity analyses to resolve new subnetworks underlying depression. We found that depression is associated with a complex distributed pattern of network activity and two distinct depression subnetworks were expressed in 89% of depressed patients. These included a poorly connected occipitotemporal network characterized by heightened beta activity, and a hyperconnected frontal cortical subnetwork characterized by low alpha and theta power.

Our ability to delineate the functional organization and spectral activity patterns of depression networks with high spatiotemporal resolution relied on the application of a network neuroscience framework to the output of the SuperEEG model. Recently, Betzel and colleagues successfully applied a similar correlational network model to multi-subject iEEG recordings, followed by community detection, and found network organization to be representative of that obtained from DTI and fMRI (Betzel et al., 2019). We further extended these findings, by applying the iEEG model to the study of disease status for the first time. The two depression subnetworks we identified are supported by previous fMRI and EEG studies of depression that have found individual components of the subnetworks in different studies including limbic alpha power that correlates with depression severity (Neumann et al., 2014), disruptions in frontal theta, temporal beta (Newson and Thiagarajan, 2018), and alpha asymmetry (Henriques and Davidson, 1990, 1991; Tomarken et al., 1992; Wheeler et al., 1993; Gotlib et al., 1998). Decreased connectivity in the occipital, temporal, and right medial frontal regions (Veer et al., 2010) and higher frontal connectivity has also been observed (Nofzinger et al., 2005; Greicius et al., 2007; Frodl et al., 2010; Sheline et al., 2010; Alexopoulos et al., 2012; Cheng et al., 2016). Our findings of two dichotomously expressed subnetworks may provide a partial explanation for the inconsistent findings across prior EEG studies that have predominantly focused on single frequency band or brain regions and have lacked rigorous cross-validation as noted by a recent meta-analysis (Widge et al., 2019).

Prior analyses of neuropsychiatric-related iEEG features have been made using components of the patient dataset used in this study (Kirkby et al., 2018; Sani et al., 2018; Scangos et al., 2019a). These efforts (Kirkby et al., 2018; Sani et al., 2018) have focused on studying a broad emotion state rather than depression and took region-based approaches using low subject numbers due to the problem of heterogenous electrode coverage across individuals. The computational approach developed here was motivated by limitations of this prior work, enabling us to incorporate parallel information from all of our subjects despite differing electrode coverage, perform group level analyses of depression, and uncover distributed circuit activity. While our aim was to capture network dysfunction associated with depression, the two distinct ways in which activity within the NEP networks combinatorically relates to disease classification also suggest the possibility of their reflecting depression biotypes. Deeper exploration of these putative biotypes awaits further study.

Functional connectivity informs longer time-scale organization of neural populations whereas functional activity informs moment-to-moment behavior of neural populations. Our finding that some brain regions show distinct changes in both activity and connectivity, while other regions, such as the right medial frontal region (module 4), demonstrate connectivity differences alone suggests that depression is both a state-invariant connectivity disorder and a state-dependent activity disorder. This relationship might explain why traditional antidepressant medications can take 6–8 wks to start working, yet ketamine can improve symptoms on the same day of administration (McGirr et al., 2015). It is possible that the presence of aberrant activity over long periods of time could shape network connectivity via plasticity or that changed connectivity patterns can impact the timing and flow of normal neural activity. Future work using high temporal resolution iEEG could inform how symptom-states and depression traits are integrated at the level of distributed neural circuits.

We acknowledge some weaknesses in the results presented. Depression in epilepsy is thought to arise from similar

origins to primary depression [ex. stress (Wulsin et al., 2016), inflammation (Vezzani et al., 2011), circuit dysfunction (Gleichgerrcht et al., 2015)], and is responsive to antidepressants (Kanner, 2003) suggesting it can provide valuable insight into depression more broadly. It remains unknown whether the depression networks we identified are related to the presence of epilepsy. Our categorical approach using the PHQ-9 to identify depressed patients was straightforward to apply in the context of complex data and has direct clinical relevance. However, it also selects inherently imperfect diagnostic boundaries and limited our capacity to examine variation in depression among subjects. Furthermore, as this was a cross-sectional investigation, some patients in the control group had a history of depression treated with ongoing antidepressant use but were not depressed per the PHQ-9 at the time of the study. Future analyses could explore how neural signatures vary with symptom severity in addition to alternative dimensional approaches which have the potential benefit of mapping neural features onto symptom profiles (Drysdale et al., 2017; Grisanzio et al., 2018). Furthermore, assumptions about the number of communities are a limitation of the community detection method (Betzel et al., 2019). Future studies could explore changes in network structure across depressed and non-depressed individuals at different levels of resolution.

While our whole-brain iEEG model was extensive in coverage, we did not have electrodes placed in all brain regions, including some regions implicated in depression (Mayberg et al., 1997; Malone et al., 2009; Hamani et al., 2011; Marchand et al., 2012; Riva-Posse et al., 2018) and the density of electrode sampling varied across brain regions leading to uncertainty in the accuracy of estimation in sparsely sampled areas (Owen et al., 2020). We dealt with this constraint by discounting the effect of each individual node degree before running community detection and comparing network measures to a null model that accounted for overall node density. Furthermore, our prior work has shown no reliable correlation between reconstruction accuracy and density (Owen et al., 2020). SuperEEG relies on accurate reconstruction of held-out activity patterns. While accuracy of this algorithm is significantly above chance and similar to the test-retest reliability of fMRI in redetecting estimated activity (Bennett and Miller, 2010), improved reconstruction is an important area for future work. The SuperEEG approach reconstructs just a portion of the verum iEEG signal – the remaining unexplained portion may stem from subject-specific variation in connectivity (Mueller et al., 2013; Finn et al., 2015), state-dependent variability in connectivity (Hutchison et al., 2013a,b) within subjects, or statistical noise. It follows that of this faithfully reconstructed portion of the iEEG signal, we found that higher-order principal components of spectral-spatial iEEG activity were most important for identifying patients with depression. Taken together, we speculate that depression may in fact have a low-dimensional network representation that is widely pervasive in the iEEG signal but represents just a small portion of iEEG signal dynamics. Importantly, we found that alternate machine-learning pipelines converged on these same low-dimensional features. Thus, there is high likelihood that the neural features we have found reflect circuit physiology that is stereotyped to depression.

With advancements in data processing capabilities and accessibility we may be able to reduce assumptions and the estimation burden, extend coverage to more brain regions, and utilize larger samples. Indeed, work to integrate our findings with network features from high spatial resolution MRI is already underway by our group. Finally, while ideally we would have independent test and training datasets for the machine learning used for classification, we utilized leave-one-out cross validation due to our sample size.

Through the current study, we identified two novel subnetworks of depression. The results have important implications for disease subtyping, diagnosis, treatment planning, and monitoring of depression status. These subnetworks could form the basis for interventions at many different potential control points along each subnetwork and suggest that interventions that change both connectivity and spectral power could be promising. For example, they provide a mechanistic rationale for practitioner's choice between right and left DLPFC vs. OFC targets for repetitive transcranial magnetic stimulation (Drysdale et al., 2017; Feffer et al., 2018). Evidence of high activity in one network pattern, countered by an anti-weighting of the other pattern further suggests the existence of protective or high-risk profiles and the possibility of preventative treatments. A library of new treatment targets and frequency-specific treatment parameters (Chanes et al., 2013; Cocchi and Zalesky, 2018) could enable a new wave of interventional therapies that personalize treatment based on neurophysiological signals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The electrophysiological whole-brain atlas (correlational model) has been uploaded to zenodo (https://zenodo.org/record/5540172#.YVUn9WZKjzc).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board at University of California, San Francisco. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KS, AKh, EC, and AKr conceived the study. KS, AKh, and PD analyzed and interpreted the data. JA and EA contributed to data collection. JM and LO contributed to data analysis methods. KS wrote the manuscript with significant input from all authors. All authors reviewed and approved the manuscript.

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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.2021.746499/full#supplementary-material

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Conflict of Interest: AKr consults for Eisai, Evecxia, Ferring, Galderma, Harmony Biosciences, Idorsia, Jazz, Janssen, Merck, Neurocrine, Pernix, Sage, and Takeda. EC has patents related to brain stimulation for neuropsychiatric conditions, brain mapping, and speech neuroprosthesis and also given talks related to epilepsy treatment for Neuropace and Cyberonics/Livanova.

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Safety and Tolerability of a Wearable, Vibrotactile Stimulation Device for Parkinson's Disease

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Background: Resting tremor is a cardinal symptom of Parkinson's disease (PD) that contributes to the physical, emotional, and economic burden of the disease.

Objective: The goal of this study was to investigate the safety, tolerability, and preliminary effectiveness of a novel wearable vibrotactile stimulation device on resting tremor in individuals with PD.

Methods: Using a randomized cross-over design, subjects received two different vibrotactile stimulation paradigms (high amplitude patterned and low amplitude continuous) on two separate laboratory visits. On each visit, resting tremor was video recorded for 10 min at baseline and while the vibrotactile stimulation was applied. Tremor severity was scored by a blinded clinician.

Results: Both vibration paradigms were well safe and well tolerated and resulted in a reduction in resting tremor severity with a moderate effect size ($n = 44$, $p < 0.001$, $r = 0.37$–0.54). There was no significant difference between the two vibration paradigms ($p = 0.14$).

Conclusion: Short durations of vibrotactile stimulation delivered *via* wearable devices were safe and well tolerated and may attenuate resting tremor severity in individuals with PD. The sample size as well as the potential preliminary effectiveness revealed by two arms of the study could not eliminate the potential for a placebo effect.

Keywords: Parkinson's disease, resting tremor, wearable technologies, vibration, UPDRS, vibrotactile, Parkinson tremor, wearables acceptance

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INTRODUCTION

Resting tremor is a highly prevalent and burdensome symptom of Parkinson's disease (PD) (Hughes et al., 1993; Louis et al., 1997; Kowal et al., 2013). With no available cure for PD, current therapies target the symptoms of the disease. Responses of resting tremor to pharmaceutical intervention vary widely between individuals (Kalia and Lang, 2015; Pasquini et al., 2018) and variations in tremor intensity accompany medication "off" periods that occur even with extended release formulations (Ramirez-Zamora and Molho, 2014). Surgical interventions may provide more pronounced and consistent alleviation of resting tremor (Deuschl et al., 2006), but have limited clinical indications (Morgante et al., 2007; Kestenbaum et al., 2015). Therefore, auxiliary therapies for resting tremor remain highly desirable. Whole body vibration such as vibrating chairs and platforms has been investigated as a potential means

to reduce resting tremor, however, results have been inconsistent (Haas et al., 2006; King et al., 2009; Kapur et al., 2012; Gaßner et al., 2014).Regardless of efficacy, such interventions do not represent a practical solution for many individuals as they are immobile, expensive and not highly customizable. If effective at lessening resting tremor, wearable vibrotactile stimulation devices may represent an attractive solution to PD patients. The aim of this pilot study was to evaluate the safety and tolerability of vibrotactile stimulation delivered *via* wearable devices on Parkinsonian resting tremor. We also aimed to collect preliminary effectiveness data on each study arm.

MATERIALS AND METHODS

Subjects

Participants with a diagnosis of PD and resting tremor in one or both hands were enrolled in the study. All subjects provided written informed consent. The study was approved by the local Program for Protection of Human Subjects (IRB 17-00555). All study procedures took place at the Abilities Research Center at Mount Sinai Hospital between July 2017 and January 2018. Individuals with moderate to severe cognitive impairment, pre-existing essential tremor, deep-brain stimulation implant, or sensory impairments that would make their response to sensory stimulation unpredictable were excluded from the trial.

Study Design

This feasibility study was a randomized cross-over clinical trial. Each individual was assessed on two different occasions,

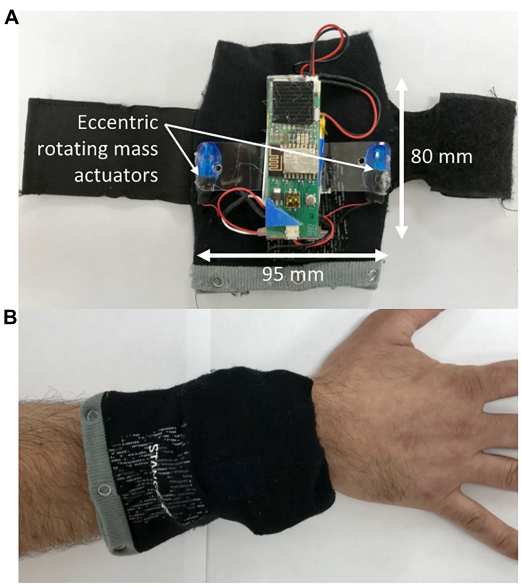

FIGURE 1 | The wearable vibrotactile stimulation device. Each vibration unit powered two eccentric rotating mass actuators from which the vibrotactile stimulation was delivered **(A)**. The vibration units were housed in cloth pouches that were attached to the subject's wrists and ankles using a Velcro strap **(B)**.

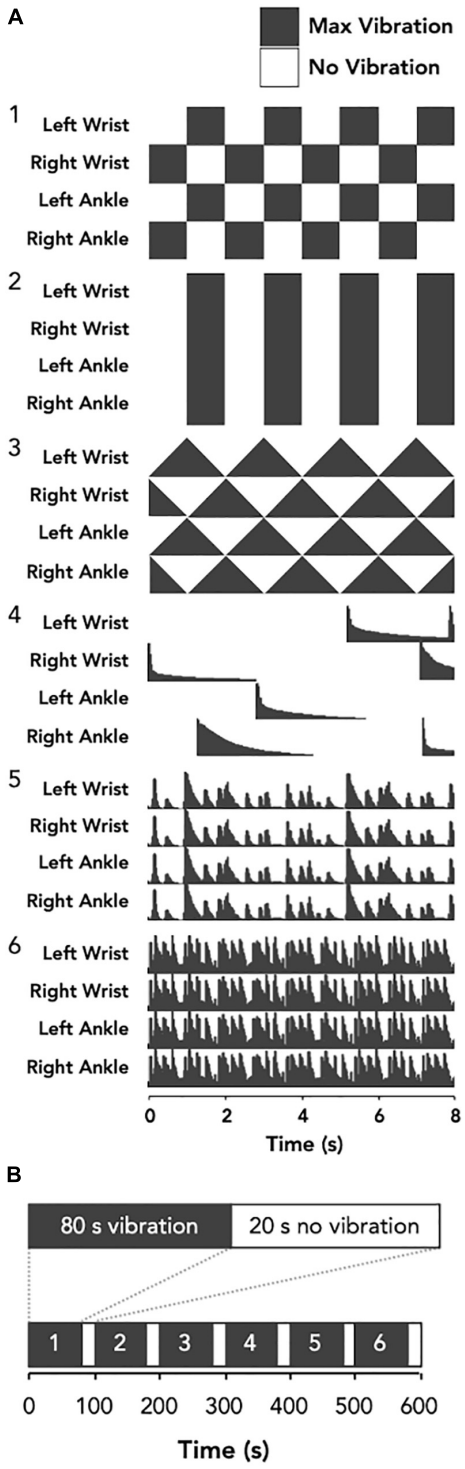

FIGURE 2 | Schematic representation of the vibrotactile stimulation protocol. The vibration patterns for the HA-P vibration trial **(A)** were three crafted waveforms; left-right oscillating (1), on-off oscillating (2), and sawtooth (3), and three audio extracted waveforms; random chimes (4), slow ternary monophonic music track (5), and fast electronic music track (6). Conversely, for the LA-C vibration trial the stimulus was constant (not shown). Each bout of vibration was delivered for 80 s with 20 s off-periods separating each bout **(B)**.

TABLE 1 | Vibration paradigm, intensity, and comments during study visits.

	Visit 1				Visit 2			
Patient ID	**Vibration paradigm**	**Wrist intensity level**	**Ankle intensity level**	**Comments**	**Vibration paradigm**	**Wrist intensity level**	**Ankle intensity level**	**Comments**
1	HA-P	Full	Full		LA-C	–	–	
2	LA-C	–	–		HA-P	Full	Full	
3	HA-P	Full	Full		LA-C	–	–	
4	LA-C	–	–		HA-P	Medium	Full	
5	LA-C				HA-P	Full	Full	Protocol #3 "It will put me to sleep," "Sounds like a car motor"; #5 "Normally when I listen to music the tremors are better"
6	HA-P	Full	Full		LA-C	–	–	
7	HA-P	Full	Full		LA-C	–	–	
8	LA-C	–	–		LA-C	–	–	
9	HA-P	Full	Full		LA-C	–	–	
10	HA-P	Full*	Full*		–	–	–	
11	LA-C	–	–		LA-C	–	–	
12	HA-P	Medium*	Full		HA-P	Full	Full	
13	LA-C	–	–		LA-C	–	–	
14	LA-C	–	–		HA-P	Full	Full	
15	HA-P	Full*	Full*	Protocol #1:"Feels like arm is being massaged" #2: "There's a pleasant sensation through the arm" #3: "Pleasant feeling"; "I feel like I can open my hand easier" #4 "Feels less effective" #5: "Better than 4" # 6: "More relief" "I like the beat better" "Feels some relief after going through the whole protocol"	LA-C	–	–	"My arm does feel better with device on"
16	HA-P	Full*	Full*		LA-C	–	–	
17	HA-P	Full	Full		LA-C	–	–	
18	HA-P	Full	Full		LA-C	–	–	
19	LA-C	–	–	"Staying stationary in the same position is uncomfortable"	HA-P	Full	Full	
20	HA-P	Medium	Full		LA-C	–	–	
21	HA-P	Full	Full		LA-C	–	–	
22	HA-P	Full	Full		LA-C	–	–	
23	HA-P	Full	Full		LA-C	–	–	
24	LA-C	–	–		HA-P	Full	Full	
25	LA-C	–	–		HA-P	Full	Full	
26	LA-C	–	–		HA-P	Full	Full	
27	HA-P	Full	Full		LA-C	–	–	
28	LA-C	–	–		HA-P	Full	Full	
29	LA-C	–	–		HA-P	Full	Full	
30	LA-C	–	–	"With jolt stops tremors for 1–2 s"	HA-P	Full	Full	
31	LA-C	–	–		HA-P	Full	Full	
32	HA-P	Full*	Full		LA-C	–	–	Protocol #6: "The noise tended to take away from the shaking; it was a slight distraction" "Didn't seem to be doing much"
33	HA-P	Full	Full		LA-C	–	–	
34	LA-C	–	–		HA-P	strong	Full	

(Continued)

TABLE 1 | (Continued)

	Visit 1				Visit 2			
Patient ID	**Vibration paradigm**	**Wrist intensity level**	**Ankle intensity level**	**Comments**	**Vibration paradigm**	**Wrist intensity level**	**Ankle intensity level**	**Comments**
35	HA-P	Full	Full	"It is disconcerting to draw spirals with the device on"	LA-C	–	–	
36	LA-C	–	–		HA-P	Full	Full	
37	LA-C	–	–		HA-P	Full	Full	
38	HA-P	Full	Full		LA-C	–	–	
39	HA-P	Full	Full		LA-C	–	–	
40	LA-C	–	–	"It feels like the vibration is stronger in the right wrist than in the left wrist"; "I got used to the vibrations at the end"	HA-P	Full	Full	
41	LA-C	–	–		HA-P	Full	Full	
42	HA-P	Full	Full	"The sound and the rough form factor is too much for the whole day"	LA-C	–	–	
43	HA-P	Full	Full		LA-C	–	–	
44	LA-C	–	–		LA-C	–	–	

*HA-P, high amplitude patterned vibration; LA-P, low amplitude continuous vibration. *Requested decrease in intensity.*

with a 1–14-day interval between visits. Baseline assessments involved a 10-min video recording of baseline resting tremor. The wearable vibrotactile stimulation devices were then placed over the subject's wrists and ankles and another 10-min video recording was collected while vibrotactile stimulation was delivered. During recordings, subjects were seated with their knees and feet together, with forearms positioned on the armrests of the chair so that their hands hung unobstructed from their wrists. Subjects were instructed not to alter their medication schedule but significant effort was made to ensure that both study sessions occurred at the same time of day, under the same medication parameters for all participants. Both visits were scheduled at a similar time of day when their tremor was thought likely to be present.

Vibrotactile Stimulation

The vibrotactile stimulation was applied to both wrists and ankles using four custom-built wearable devices to promote an optimal full body vibrotactile stimuli. Each device involved a vibration unit with two eccentric rotating mass actuators approximately 75 mm apart (**Figure 1A**), which was housed in a cloth pouch that was fastened to the limb using a Velcro strap (**Figure 1B**). On one visit, the devices provided six distinct vibration patterns to evaluate the overall tolerability of strong, noticeable vibrotactile stimulation paradigms (**Figure 2A**). The frequency of vibrations during these patterns ranged from 40 to 200 Hz. Each pattern was 80 s in duration, with 20 s separating each pattern; making a total of 10 min, and participants were given the opportunity to provide feedback about each pattern of vibrotactile stimulation (**Figure 2B**). During the other visit, the devices provided a continuous vibration at approximately 48 Hz to evaluate the overall tolerability of a weak, barely noticeable vibrotactile stimulation paradigm. This vibration was also applied for six 80 s blocks, with a brief pulse of vibration marking the start and end of each block, and 20 s separating each block. These two vibration paradigms are hereon referred to as high amplitude patterned (HA-P) vibration and low amplitude continuous (LA-C) vibration, respectively. Vibration intensity (full, strong, medium, or weak) was set up initially at full and adjusted according to subject's tolerance throughout each session.

Quantification of Tremor

Subjects were video recorded (30 Hz) using the Microsoft Kinect 2 throughout both visits. Resting tremor severity was scored according to item 20 of the Unified Parkinson's Disease Rating Scale (UPDRS) by a clinician who was blinded to vibration status. Resting tremor severity was scored on a minute-by-minute basis throughout the four 10-min resting tremor assessments; both the baseline and vibration periods of the HA-P vibration and LA-C vibration trials.

Statistical Analyses

We used multilevel modeling to test for within- and between-subject differences in tremor severity while accounting for the within-subject non-independence of the repeated measures. Baseline tremor scores were similar between visits, and were therefore averaged to simplify these models. Gender, age, time since diagnosis, whether the participant was currently taking Parkinsonian medication, and time since last medications dose showed no significance as covariates and were therefore removed from the model. Final analyses used three-level models with tremor severity scores at level 1, experimental condition (averaged baselines, HA-P vibration, and LA-C vibration) at level 2, and subjects at level 3. Effect sizes were computed using the standardized regression coefficients.

RESULTS

Subjects

Fifty-two subjects were enrolled in the study. One subject dropped out after the first visit due to inability to tolerate the seated position, and another opted out for personal reasons not given. Six subjects did not exhibit a resting tremor in both the baseline and vibration recordings in one or both of the laboratory visits and were subsequently excluded from the analysis. Thus, data analysis was performed on the remaining 44 subjects (33/11 males/females; age: 67 ± 10 years; time since diagnosis: 6 ± 4 years). All resting tremor severity scores ranged between 0 and 3. Most participants (93%) were undergoing pharmacological treatment for Parkinsonian symptoms at the time of the study, including levodopa, dopamine agonists, and antidepressants. Time between study session and last medication dose was 4.9 ± 4.0 and 5.4 ± 4.9 h for the LA-C and HA-P vibration trials, respectively.

Safety and Tolerance

All subjects tolerated the vibrotactile stimulation well, with no reported adverse events. Five (11%) requested decrease in vibration intensity. No subjects reported discomfort in response to the stimulation or requested early termination of the vibration. Comments and setting preferences are detailed in **Table 1**.

Effect of Vibrotactile Stimulation

Figure 3 provides an overview of the changes in resting tremor severity score between baseline and during application of the vibrotactile stimulation. For the HA-P vibration trial, 16 subjects exhibited a decrease in median resting tremor severity compared to four subjects showing an increase, while 24 subjects exhibited no change. Similarly, for the LA-C vibration trial, 26 subjects exhibited a decrease in median tremor severity compared to three subjects exhibiting an increase, while 15 subjects displayed no change.

The multilevel models identified significant differences in tremor severity between baseline and HA-P [$t_{(88.0)} = 3.39$, $p < 0.001$, $r = 0.54$], and baseline and LA-C [$t_{(88.8)} = 4.80$, $p < 0.001$, $r = 0.37$]. No difference was identified between HA-P and LA-C with [$t_{(42.0)} = 2.04$, $p = 0.16$] or without controlling for each subject's baseline tremor severity score [$t_{(89.5)} = 1.50$, $p = 0.14$].

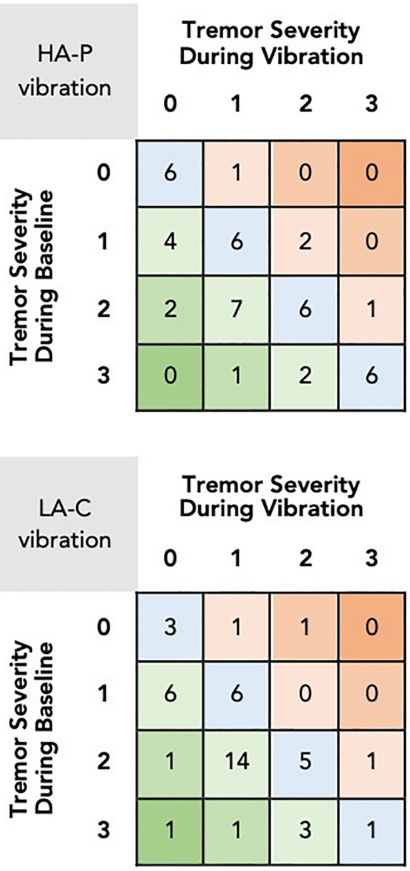

FIGURE 3 | Changes in median resting tremor severity scores between baseline and during vibration for the HA-P (top) and the LA-C (bottom) vibration trials. The rows and columns of the grid refer to the tremor severity scores during baseline and vibration, respectively, with each square displaying the number of subjects who received these scores. Squares in the lower left corner of the grid represent the number of subjects that exhibited reductions in tremor severity with the vibrotactile stimulation, squares in the upper right represent increases in tremor severity, and squares in the main diagonal represent no change.

DISCUSSION

Our results demonstrated that two different paradigms of 10 min of vibrotactile stimulation of the wrists and ankles using a novel set of wearable devices was safe and well tolerated by individuals with Parkinsonian resting tremor. The associated effect sizes were moderate in both the HA-P and LA-C vibration paradigms, with only a small number of subjects exhibiting an abolition of resting tremor (HA-P: $n = 5$; LA-C: $n = 6$) or a reduction of more than one point (HA-P: $n = 3$; LA-C: $n = 3$). These effects were not as pronounced as those frequently observed by pharmaceutical or surgical intervention (Bejjani, 2000), however, as patients often abandon Parkinson's medications due to side effects, the demand for well-tolerated auxiliary therapies remains considerable.

The neurological mechanism by which vibrotactile stimulation may relieve motor symptomology of PD is not fully described, but may be related to the pathophysiology of PD. Dopamine depletion leads to pathologically increased neuronal synchronization in the beta frequency (15–30 Hz) band throughout the basal ganglia, thalamus and sensorimotor cortex (Brittain and Brown, 2014). Disruptions in synchronization in this frequency band are associated with improvements in motor symptoms (Kuhn et al., 2008). Tactile stimulation of the skin causes a decrease in synchronous beta band activity in the sensorimotor cortex (Gaetz and Cheyne, 2006). Therefore, it is plausible that vibratory input to the skin may be capable of disrupting the pathological beta activity observed in PD and relieving the accompanying motor symptomology (Sharififar et al., 2014; Syrkin-Nikolau et al., 2018).

The main limitation of the current study was the sample size and also the potential for a placebo effect given that both stimulation paradigms revealed clinical benefits. The inclusion of an adequate sham condition is pertinent in PD as expectations of benefit can lead to dopaminergic activation (de la Fuente-Fernández et al., 2001) and this pilot trial was important as it revealed that the two conditions were active stimulation and therefore could not be considered a sham for future trials. An additional limitation of the current study was that the duration of the safety and tolerability evaluation was quire short and therefore does not provide us with information regarding safety and tolerability of this technology in an extended home use context. Further investigation of the current wearable devices is therefore required to determine how the moderate benefits observed in the current investigation compare to placebo responses, and to evaluate safety and tolerability of the technology in a home environment.

CONCLUSION

In conclusion, this pilot study demonstrated that short durations of vibrotactile stimulation delivered *via* wearable devices is a safe and feasible intervention stimulus in individuals with PD, and may confer a mild to moderate relief of resting tremor severity. Future research should examine the effects of extended home use of wearable devices on a broader range of motor impairments.

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 human participants were reviewed and approved by the Program for Protection of Human Subjects at Icahn School of Medicine at Mount Sinai (IRB 17-00555). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DP conceptualized the study. AF and TP organized and executed the project. SB designed and executed statistical analysis. DP, LT, and AF prepared the first manuscript draft. All authors reviewed and approved the final version of the manuscript.

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CASE REPORT
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Effect of Deep Brain Stimulation on Cerebellar Tremor Compared to Non-Cerebellar Tremor Using a Wearable Device in a Patient With Multiple Sclerosis: Case Report

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Tremor of the upper extremity is a significant cause of disability in some patients with multiple sclerosis (MS). The MS tremor is complex because it contains an ataxic intentional tremor component due to the involvement of the cerebellum and cerebellar outflow pathways by MS plaques, which makes the MS tremor, in general, less responsive to medications or deep brain stimulation (DBS) than those associated with essential tremor or Parkinson's disease. The cerebellar component has been thought to be the main reason for making DBS less effective, although it is not clear whether it is due to the lack of suppression of the ataxic tremor by DBS or else. The goal of this study was to clarify the effect of DBS on cerebellar tremor compared to non-cerebellar tremor in a patient with MS. By wearing an accelerometer on the index finger of each hand, we were able to quantitatively characterize kinetic tremor by frequency and amplitude, with cerebellar ataxia component on one hand and that without cerebellar component on the other hand, at the beginning and end of the hand movement approaching a target at DBS Off and On status. We found that cerebellar tremor surprisingly had as good a response to DBS as the tremor without a cerebellar component, but the function control on cerebellar tremor was not as good due to its distal oscillation, which made the amplitude of tremor increasingly greater as it approached the target. This explains why cerebellar tremor or MS tremor with cerebellar component has a poor functional transformation even with a good percentage of tremor control. This case study provides a better understanding of the effect of DBS on cerebellar tremor and MS tremor by using a wearable device, which could help future studies improve patient selection and outcome prediction for DBS treatment of this disabling tremor.

Keywords: DBS, cerebellar tremor, accelerometer, multiple sclerosis, case report

INTRODUCTION

Tremor of the upper extremity is one of the major causes of disability in multiple sclerosis (MS). Although the exact prevalence is unknown, one study found that 58% of participants had tremor, and of these, 27% had a tremor-related disability, and 10% had incapacitating tremor (Alusi et al., 2001). MS tremor is complex, in that it contains a postural and kinetic tremor as in essential tremor (ET) and an additional ataxic intentional tremor component of cerebellar dysfunction in many cases (Koch et al., 2007), which is likely due to the involvement of the cerebellum and cerebellar outflow pathways by MS plaques (Alusi et al., 2001). MS tremor is often poorly responsive to medications commonly used for ET, such as primidone and propranolol (Roy and Aziz, 2014). The effect of deep brain stimulation (DBS) of a ventral intermediate nucleus (VIM) on the control of hand tremor in patients with MS is highly variable and, in general, the tremor is less responsive than those associated with ET or Parkinson's disease (PD; Roy and Aziz, 2014), even in DBS targeting posterior subthalamic area (PSA) or caudal zona incerta (cZi; Xie et al., 2012a; Ramirez-Zamora et al., 2016), or combined targets (Oliveria et al., 2017). Even in those with improved tremor following surgery, the improvement does not always translate to improved functional status (Roy and Aziz, 2014).

We hypothesized that patients with MS with a tremor of the cerebellar ataxic component could still have a good response to DBS in tremor suppression as in rhythmic postural and action tremor of ET type, except that the distal oscillation would prevent transformation into a functional benefit. We would test this hypothesis through the use of a wearable accelerometer on the index finger approaching a target with a subsequent waveform analysis of amplitude and frequency to quantitatively characterize the different tremors in each individual hand at the beginning and end of the target approaching movement at DBS Off and On status. The hand function is also captured in the **Supplementary Video Clips**. This study could help decipher the effect of DBS on cerebellar tremor and function control and help future studies to improve patient selection and outcome prediction in patients with MS undergoing DBS.

METHODS

Case Description

The subject was an 18-year-old man with a 7-year history of relapsing-remitting MS and stable MS symptoms for more than 1 year on Natalizumab 300 mg IV every month for ≥6 months when he visited us in 2015. He had severe tremor on the right hand, with prominent postural tremor and kinetic tremor for more than 3 years, which had a significant cerebellar component of distal oscillation. He also had moderate postural and kinetic tremor on the left hand without significant distal cerebellar oscillation. He virtually lost hand function (worse on the right than the left) for at least 1 year prior to his visit to us due to the gradual worsening of his tremor. He had severe truncal ataxia as well for which he had been wheelchair-bound for years. His hand tremor failed to respond to primidone 125 mg po tid and propranolol 30 mg po tid. He had no MS plaques in VIM and PSA/cZi areas and no evidence of enhancing lesions in brain MRI with contrast. A decision was made to implant bilateral VIM/cZi DBS (Medtronic 3387, MN, USA) by our team to improve his hand tremor.

Prior to the DBS procedure, a CT and MRI of the brain were fused, and the Schaltenbrand atlas was superimposed over the imaging to help plan the trajectory to the anatomical target of VIM/cZi. The intraoperative microelectrode recordings were used to define the electrophysiological target. The macrostimulation test was applied to assess the clinical effectiveness and adverse effect profile and further refined the target with minor intraoperative adjustments of the DBS leads. Fusion of MRI with intraoperative CT demonstrated that macroelectrode tips located at the border of VIM and cZi, with stereotactic coordinates of (−12.4, −4.8, +1.6) on the left and (+11.9, −4.9, +2.7) on the right (medial-lateral, anterior-posterior, and superior-inferior coordinates, respectively, given in mm relative to the midcommissural point and midsagittal plane). The ventral contacts yielded best tremor suppression, with the settings of C+/0–, amplitude 4.2 V, pulse width 60 μs, and frequency 180 Hz for the left lead, and C+/8–, amplitude 3.8 V, pulse width 60 μs, and frequency 180 Hz for the right lead at 1 year after the DBS placement.

The finger trajectories were captured as follows: Motion was encoded by an accelerometer embedded in a cardboard tube (5 cm long, 2 cm diameter), which was placed over the index finger of the subject. A small shielded cable was dressed up the arm to the shoulder, allowing unencumbered movement. The three X, Y, and Z channels were fed into electroencephalogram amplifiers (0.1–50 Hz) and averaged, yielding a single movement trajectory over time. The quantitative amplitude and frequency were automatically transformed into conventional power spectrums.

The Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) was used to assess the overall tremor score, right upper extremity tremor score (rest, posture/intention), left upper extremity tremor score, right hand function score (in drawing A, B, C, and pouring water) and left hand function score at DBS On state (for 15 min) compared to DBS Off (for 15 min) state. The Scale for the Assessment and Rating of Ataxia (SARA) was also used to assess the overall ataxia score, right upper extremity ataxia score (finger chase, nose-finger test, and fast alternating hand movements), and left upper extremity ataxia score at DBS On state compared to DBS Off state.

The timeline of events is demonstrated in **Figure 1**. Finger trajectories are displayed in **Figure 2**, and the quantitative amplitude and frequency are displayed in **Figure 3**.

RESULTS

Hand Movement Trajectories With DBS Off and On

By visual inspection (**Figure 2**), the left hand in a non-MS non-DBS normal person as a control and the left hand in the patient with MS had no significant change in waveform (amplitude and

Abbreviations: DBS, deep brain stimulation; MS, multiple sclerosis; VIM, ventral intermediate nucleus; PSA, posterior subthalamic area; cZi, caudal zona incerta.

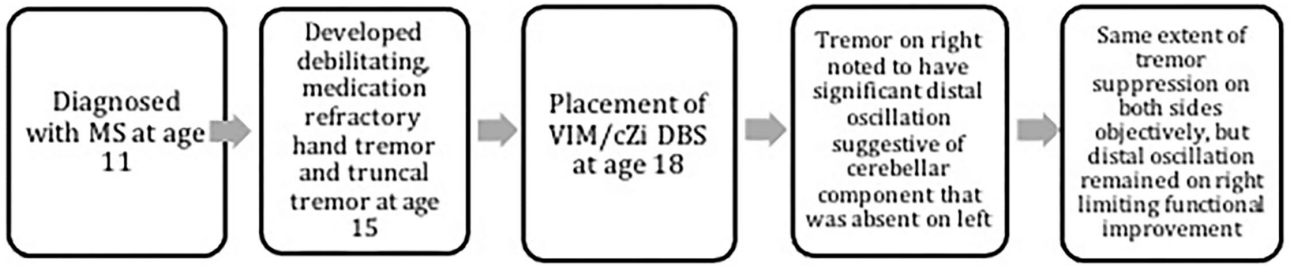

FIGURE 1 | The timeline of events. The timeline of the events is depicted in the flowchart.

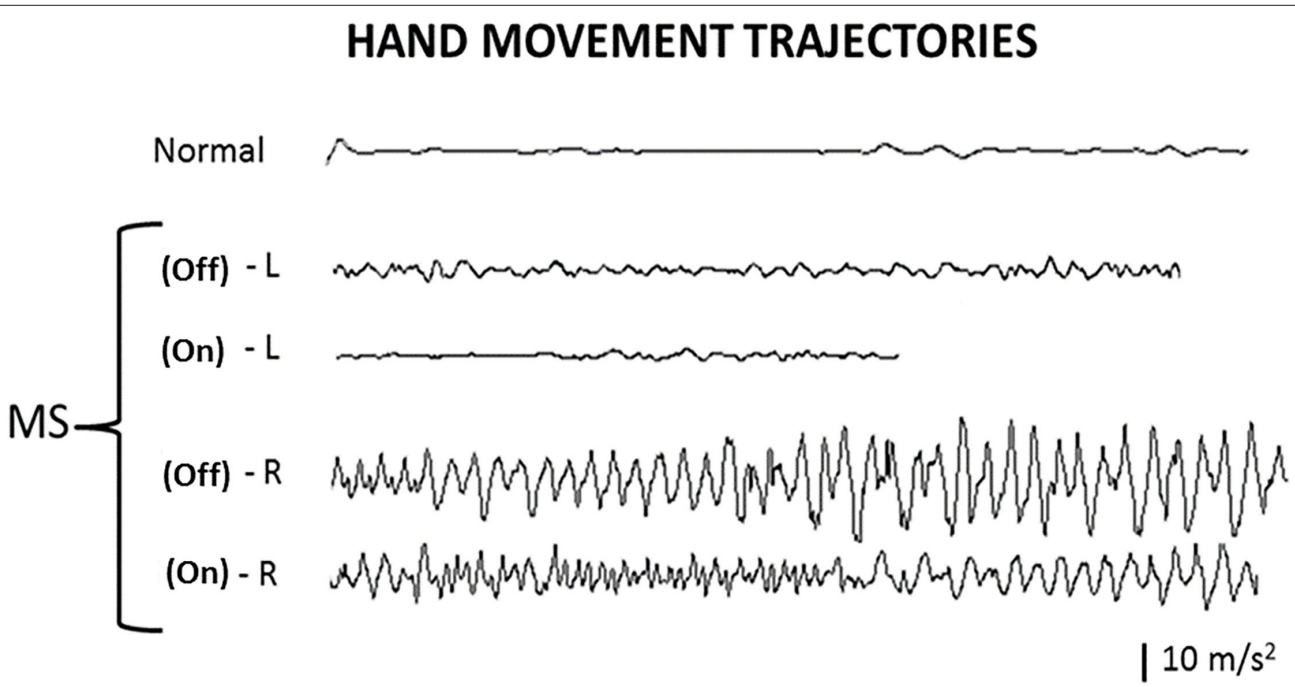

FIGURE 2 | Hand movement trajectories. Index finger movement trajectories in the finger-to-finger task illustrate the tremor amplitudes and frequencies of the hands, with deep brain stimulation (DBS) Off and On. Normal, normal healthy person; L, left hand; R, right hand; Off, DBS Off; On, DBS On.

frequency pattern) at the end of the test (when the finger of the patient was getting close to the finger of the examiner, <3 cm away) compared to that at the beginning of the test (when the patient was holding up a finger 30 cm away from the finger of the examiner), during both the DBS Off and DBS On states. In contrast, the right hand in the patient with MS had a significant change in the waveform at the end of the trajectory or movement compared to that at the beginning of the trajectory, during both the DBS Off and DBS On states. Notably, the overall tremor amplitudes were reduced on both hands at the DBS On state compared to the DBS Off state.

Power Spectrum of the Hand Trajectories With DBS Off and On

By the amplitude and frequency analysis (**Figure 3**), the left hand had no significant change in amplitude and frequency at the end of the test compared to that at the beginning of the test, at both DBS Off and On states (**Figure 3**, left upper panel), although the amplitude was reduced by about 60% at DBS On state (**Figure 3**, left lower panel). In contrast, the right hand had a significant change in amplitude and frequency at the end of the trajectories compared to that at the beginning, with doubled amplitude and doubled peaks of different frequencies at the end of the test, at both DBS Off (**Figure 3**, right upper panel) and On states (**Figure 3**, right lower panel), although the amplitude was reduced by about 60% at DBS On state.

Hand Function With DBS Off and On

Although the tremor is improved on both hands after the DBS surgery (DBS On compared to DBS Off), a better functional improvement is observed on the left hand compared to the right hand when the hand extended to the distal targets with DBS On (**Supplementary Video Clips**). FTMTRS for the overall

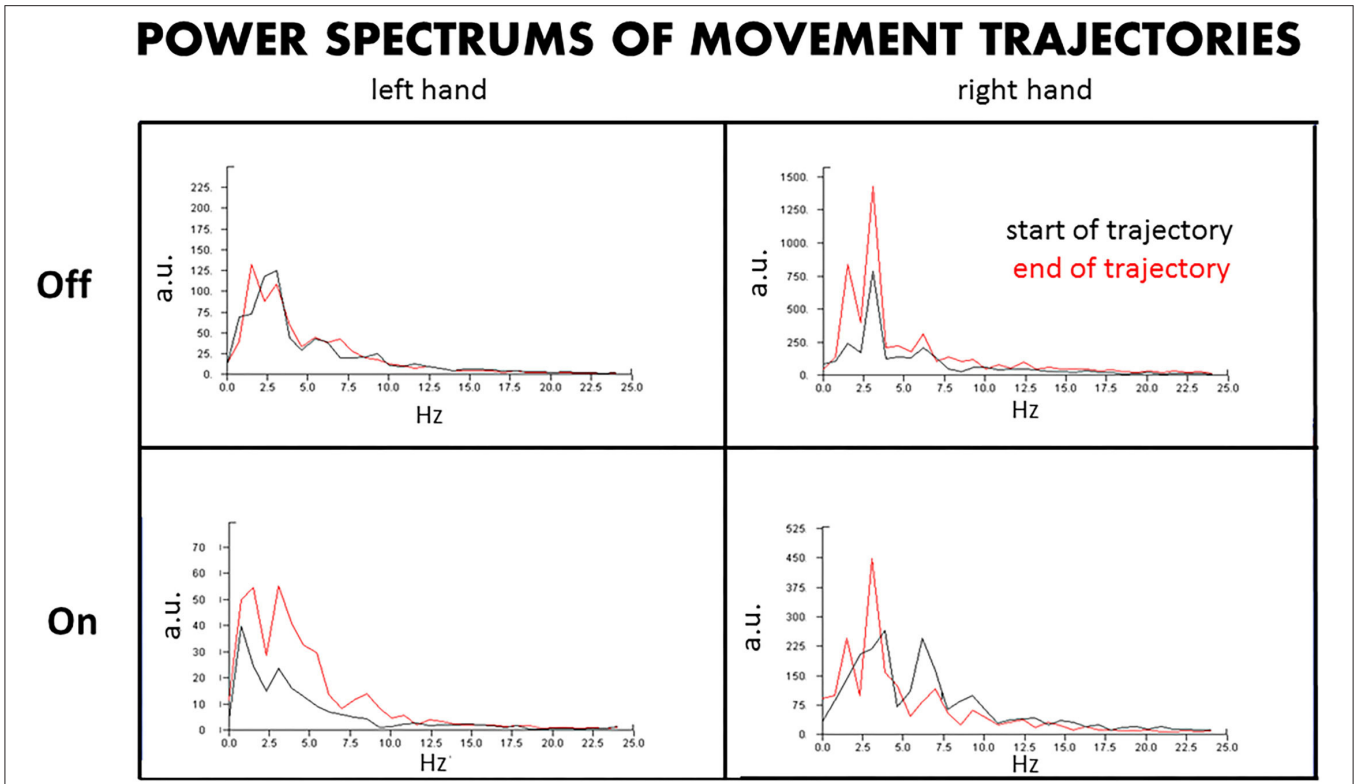

FIGURE 3 | Power spectrum of the hand trajectories. The power spectrum of the hand trajectories reveals the amplitudes and dominant frequencies of the tremors at the beginning and end of the movements approaching the target, with DBS Off and On. L, left hand; R, right hand; Off, DBS Off; On, DBS On; a.u., arbitrary units.

tremor score was improved by 40%; right upper extremity tremor score (rest, posture/intention) was improved by only 37%, but left upper extremity tremor score improved by 66%; the right hand function score (in drawing A, B, C, and pouring water) improved by only 25%, but the left hand function score improved by 50%, all at DBS On state compared to DBS Off state. SARA for the overall ataxia score was improved by 23%; the right upper extremity ataxia score (finger chase, nose-finger test, and fast alternating hand movements) improved by only 33%, but the left upper extremity ataxia score improved by 62% at DBS Off state compared to DBS On state.

DISCUSSION

In the patient with MS, undergoing bilateral VIM/cZi DBS, reduction in tremor amplitude was similar regardless of the absence or presence of cerebellar-type tremor, but the functional benefit was limited by the presence of cerebellar-type tremor. The cerebellar ataxia component was observed in the right hand, with the distal oscillation of reduced frequency and increased amplitude when the hand approached the target. Although the suppression of the tremor by DBS was similar (by 60%) at both the beginning and the end of the finger-to-nose test on both types of tremors as captured by the accelerometer, the hand function was significantly different, with much worse function on the right hand with cerebellar ataxia compared to the left hand without significant cerebellar ataxia component, as shown by the **Supplementary Video Clips** and the FTMTRS and SARA scores on distal hand function, as the distal amplitude of the right hand was much worse due to the distal oscillation of the ataxia. This could also explain why the patient with MS often holds the hand close to the trunk when they use the ataxic hand, as it could reduce the distal oscillation and make the hand steadier with a better function. It is interesting to know that in a relatively well-controlled study with detailed analysis, in this study, we found that cerebellar tremor in fact could be suppressed by DBS. It is the oscillation when approaching the target that increased the amplitude (by about 2-fold) in ataxia that makes the hand function poorly controlled compared to that without significant distal oscillation. It also suggests that ataxia is not necessarily an absolute contraindication for DBS in carefully selected cases with less distal amplitude by oscillation, as the greater amplitude would impair the hand function otherwise. Tremor with ataxia component could have a reasonable response to DBS, as reported in a patient with fragile X-associated tremor/ataxia syndrome (Xie et al., 2012b), and two other case reports as well (Cury et al., 2019; Barcelos et al., 2020), although in this study we wanted to explore more on why a nice tremor suppression by DBS is unable to be transformed to functional gain and how we can predict the responsiveness of the cerebellar tremor to DBS (such as how big the distal oscillation in cerebellar tremor could affect the function gain), which could help proper selection of DBS candidates with cerebellar tremor

and would have a more broad clinical application. The modern accelerometer could easily adapt a new program to assess the ataxia and oscillation by automatically comparing the distal to the proximal amplitude and frequency, and possibly even be able to do a three-dimensional comprehensive analysis as well. Given the overall limited functional control of MS tremor by DBS even in well-selected targets (Xie et al., 2012a; Ramirez-Zamora et al., 2016; Oliveria et al., 2017), the proof of the concept as demonstrated in this study by this limited case report should be further validated by a clinical trial or serial cases on MS tremor for the better selection of patients with MS and the better prediction of their outcome for DBS.

Patient Perspective

The patient provided a written consent for this study and publication. He has been happy with the improved tremor control and hand function, particularly on his left hand. His hand tremor and function remain stable as described during the 5-year follow-up, without side effects being reported so far.

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/s.

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

TX contributed to conception, design, and drafting the article. TX, MP, AJ, DS, and VT contributed to data collection, analysis, and interpretation. All authors contributed to critical revision of the article and have read and approved the final version of the article.

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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.2021.754091/full#supplementary-material

Supplementary Video Clip 1 | DBS Off.

Supplementary Video Clip 2 | DBS On.
Hand function at DBS Off and On. Although the tremor is improved on both hands after the DBS surgery (DBS On in Clip 2 compared to DBS Off in Clip 1), a better function is observed on the left hand compared to the right hand when the hand extended to the distal targets with DBS On (Clip 2).

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