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Perspectives of Implementation of Closed-Loop Deep Brain Stimulation: From Neurological to Psychiatric Disorders

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Abstract
Background: Deep brain stimulation (DBS) is a highly efficient, evidence-based therapy to alleviate symptoms and improve quality of life in movement disorders such as Parkinson's disease, essential tremor, and dystonia, which is also being applied in several psychiatric disorders, such as obsessive-compulsive disorder and depression, when they are otherwise resistant to therapy. ***Summary:*** At present, DBS is clinically applied in the so-called open-loop approach, with fixed stimulation parameters, irrespective of the patients' clinical state(s). This approach ignores the brain states or feedback from the central nervous system or peripheral recordings, thus potentially limiting its efficacy and inducing side effects by stimulation of the targeted networks below or above the therapeutic level. ***Key Messages:*** The currently emerging closed-loop (CL) approaches are designed to adapt stimulation parameters to the electrophysiological surrogates of disease symptoms and states. CL-DBS paves the way for adaptive personalized DBS protocols. This review elaborates on the perspectives of the CL technology and discusses its opportunities as well as its potential pitfalls for both clinical and research use in neuropsychiatric disorders.

Introduction

Deep brain stimulation (DBS) is a highly efficient, evidence-based therapy, which enables targeted neuromodulation for neurological and psychiatric disorders using stimulating electrodes implanted in the brain. State-of-the-art applications of DBS include symptom alleviation in movement disorders such as Parkinson's disease (PD) and essential tremor, other neurological disorder such as epilepsy, as well as mental disorders such as obsessive-compulsive disorder (OCD). It is being further explored as a therapeutic option for depression, pain syndromes, and other neuropsychiatric disorders. Therefore, DBS is an intervention that alleviates the symptoms caused by a spectrum of disorders and may significantly modify disease courses.

Currently, DBS is clinically applied in the so-called open-loop approach, with electrical pulses delivered continuously at a fixed amplitude, frequency, waveform, and pulse width (see Frey, Cagle [1] and Gilbert, Mason [2] for recent reviews on the topic), irrespective of the patients' clinical state(s). Back to the early 2000s, there were reports showing that adverse motor symptoms induced by continuous DBS on the subthalamic nucleus (STN) can be reversed by adapting the stimulation settings [3, 4] during subsequent clinical visits, and this reprogramming had a positive impact of long-term DBS outcomes [5, 6]. DBS reprogramming of the stimulation parameters has become the gold standard in clinical DBS practice, with the disadvantage of requiring time-consuming, recurrent visits to an expert clinician. Under this framework, researchers have continuously aimed at identifying suitable pathologic markers for adapting DBS parameters. Moreover, the DBS hardware has greatly improved over the years, including, but not limited to, higher electrode density and the existence of directional leads. Additionally, the DBS systems have also evolved, increasing the interest in and capabilities for CL-DBS [7], but also increasing the complexity of DBS programming strategies. More recent advances in CL-DBS have already highlighted the potential of machine learning algorithms and artificial intelligence methods to advance DBS and may facilitate the optimization of stimulation parameterization by combining information of tissue substrates (brain integrity and activity), clinical status, medical therapy levels, and patient-reported outcomes. Recently, systems with sensing capabilities have received FDA approval in USA and CE mark approval in Europe.

From a hardware perspective, in the most basic sense, a CL system evaluates an output to regulate a forthcoming input such that the system can achieve a desired state. If we break down the process slightly further, a CL system has a sensor that measures its own output and then compares this to a pre-defined desired reference output. If a disparity between the actual outcome and the reference is detected, the system adjusts the new input signal in such a way that the difference between the actual outcome and the reference is minimized. Such systems offer efficiency and control of output through regulation of signals. These CL feedback systems are ubiquitous in everyday life and exist in many different forms. A common example would be a thermostat, where the thermometer probe measures the temperature in a room and adjusts the cooling/heating apparatus to bring the room to a temperature desired by the room occupant(s). Moreover, slightly more complex everyday examples would include a driver steering their vehicle or a pedestrian maintaining their walking speed. The driver assesses the angle the car is heading and constantly uses this input information to adjust the steering wheel, which keeps the vehicle at a desired angle and hence on the desired path. Similarly, the pedestrian constantly assesses their walking speed and adjusts to keep at a comfortable or desired pace. In terms of the brain, CL relies on the detection and measurement of a biomarker (termed informed feature) which is associated with or predictive of target symptom presence and severity. The informed biomarker could be a feature of brain activation but also a functional peripheral parameter, or even a measurement of brain anatomical status (i.e., neurodegeneration). Depending on the coherence between the symptom severity and the magnitude of the corresponding biomarker, a stimulation can be regulated.

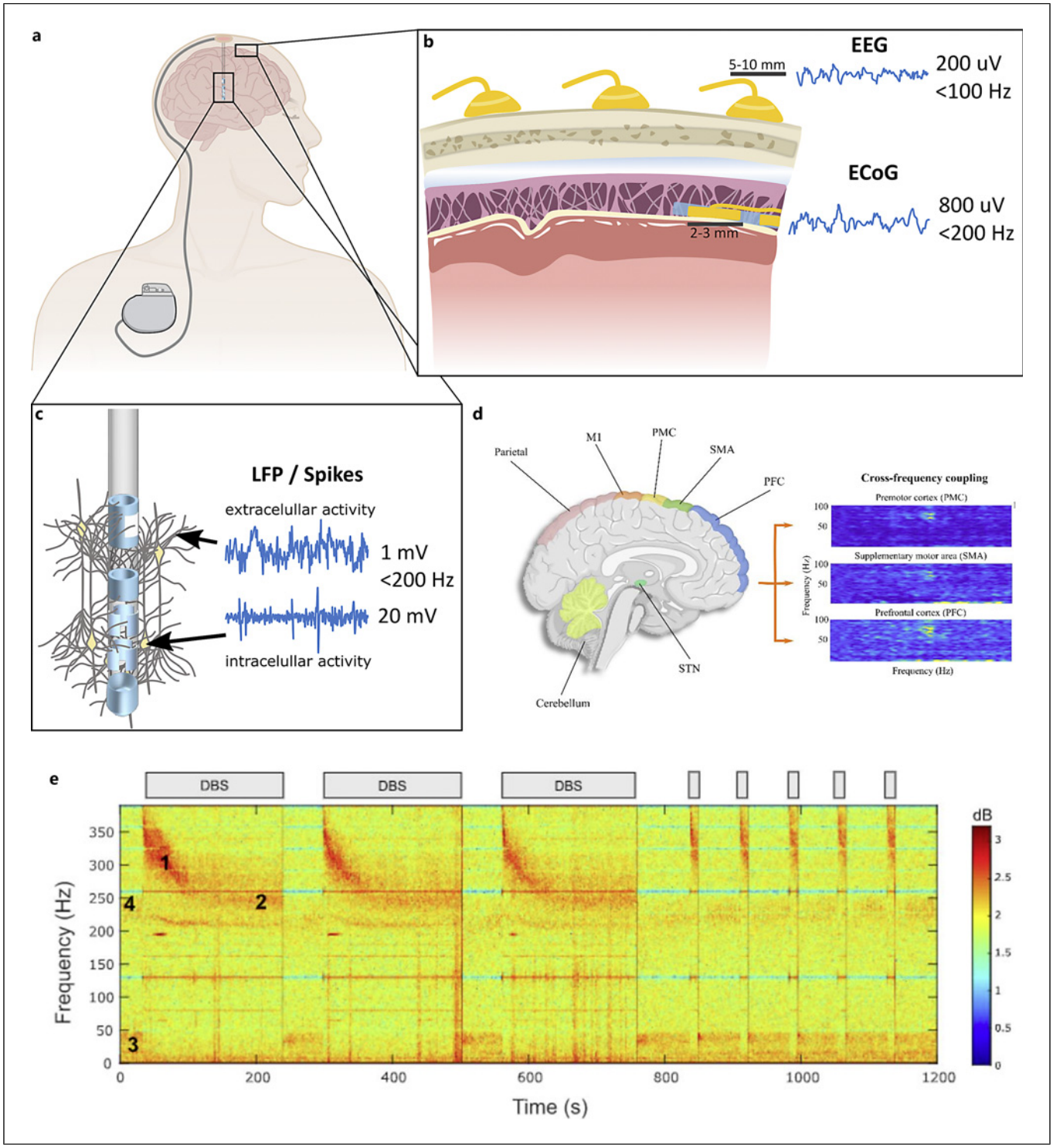
In this direction, also known as adaptive DBS, CL-DBS is aimed at dynamically modifying stimulation according to brain, symptom, and disease states, which is currently achieved by sensing their electrophysiological surrogates. Such experimental biomarker-based neural approaches can then be adapted to respond by delivering a modified stimulation pattern depending on the patient responses, which may vary across diseases. These constitute major advances towards an individualized improvement in patient outcomes with DBS and opens new avenues for advanced models for targeting individual symptoms or pathological brain states as in neuropsychiatric disorders.

Importantly, in the development of CL-DBS for motor disorders it is important to not only focus on the optimization of motor symptoms. Optimal well-being of the patient does not only depend on optimal and objective control of motor symptoms but also on the symptom severity of non-motor symptoms as well as the *subjectively* experienced symptom burden. At settings where optimal motor control is achieved, these other contributing symptoms may be differentially affected, which may lead to patients experiencing less wellbeing at these settings. The patients' subjective experiences, as measured with, for instance, "ecological momentary assessments," should therefore be explicitly considered in the development of clinical applications of CL-DBS [8]. Therefore, adapting DBS parameters according to fluctuating symptom severity while considering current and target brain states may achieve better response (increase its efficacy) and potentially reduce induced side effects, at lower energy use. For this aim, DBS can be also utilized as a research instrument to precisely investigate physiological and pathological bases of brain functioning in already implanted patients. This dual utility of DBS, as a brain-circuitry sensor and a modulator, has emerged in the recent years and has been exploited for the development of CL-DBS approaches.

Under the assumption that an overlapping neural circuitry may drive similar motor and non-motor symptomatology in neurological and psychiatric disorders, the advent of CL-DBS may be translated across disease indications. In this paper, we integrate the current knowledge of CL-DBS approaches in distinct neuropsychiatric diseases. First, we describe the clinical states that can be targeted by CL-DBS, including quantification of brain networks and disease states from brain imaging and simultaneous electrophysiological recordings with stimulation. Then, we discuss the current opportunities and considerations of such biomarker-based approaches regarding their association with both symptoms and DBS outcomes as well as the potential for their development into novel approaches for the treatment of neuropsychiatric disorders in which the symptoms are similarly driven by pathological network activity. Finally, we present some examples of cross-fertilization between invasive and non-invasive brain stimulation, the development of neurofeedback (NF), and the relevance of neuroimaging in DBS network studies to fill the gaps of CL-DBS.

The Role of Electrophysiological Signals in DBS

Assessment of the neural substrates of brain function in the timeframe in which they occur is possible with non-invasive techniques such as electroencephalography (EEG), or invasive, including microelectrode recordings,



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local field potentials (LFPs), single-unit activity, and other electrophysiological measures (Fig. 1a–c). EEG signals reflect the electrical activity of neural networks over a specific period of time. Electrophysiological recordings do not only allow real-time access to brain activity but also to evaluate effects of stimulation, thus opening a window to

evaluate the input-output relationship of the brain regions and networks.

One interesting capability of modern DBS systems is that they can measure depth of brain activity at non-stimulating contacts on the DBS electrode [9], which has allowed the exploration of subcortical neural dynamics, through LFP recordings. Two possibilities exist to acquire LFP signals, namely, patient externalization directly after surgery or the use of sensing technology on chronically implanted patients. At the edge between current open-loop DBS approaches and CL-DBS, electrophysiological LFP recordings are highly valuable post-implantation as they can be used to fine-tune the stimulation parameters or for the long-term monitoring of implanted patients.

Electrophysiological recordings have further value during the characterization of movement patterns. For example, information about the quality of executing a fine-granular hand motor task under varying DBS conditions [10]. It is important to highlight that the oscillatory activity and synchronization is different across brain networks or systems [11]. Further, based on the assumption that the interaction between oscillations can also happen at different frequency bands [9], the so-called cross-frequency coupling can be used as a meaningful measurement of the brain state (Fig. 1d). Cross-frequency activity is modulated by clinically relevant high-frequency (above 100 Hz) DBS stimulation frequencies, particularly at gamma frequencies [12], which have allowed to determine that not only increased beta power is clinically relevant but also an increase in the coupling between beta in the STN and broadband gamma (~50–200 Hz) amplitude in the motor cortex [13]. Other approaches include spectral power measurements, coherence (for instance, phase-amplitude coupling), and measurements of synchronization of oscillatory activity at specific frequencies, phase, and waveform, as well as oscillatory activity bursts. The combination of LFPs recordings from the basal ganglia, recorded at the tip of a stimulation electrode placed deep in the brain, and recordings from the cortex of PD patients have helped characterize the temporal dynamics of DBS-evoked activity (Fig. 1e), showing that DBS inhibits beta activity (13–30 Hz) while increasing gamma rhythm (60–90 Hz [12, 14]). Further, using such LFP measurements, it has been recently demonstrated that despite control of decision and movement speed shares some commonalities, the causal contribution of the STN to both processes can be disentangled [15]. Thus, electrophysiological recordings have successfully been utilized for characterizing brain network and behavioural responses to DBS.

In PD, the possibilities of CL-DBS for the management of clinical symptoms, mostly based on LFP measurements, have already been shown and recently reviewed [16]. These studies have evidenced that delivering high-frequency stimulation only when increased beta-band power is detected at a patient-specific threshold improved PD motor symptoms with higher clinical efficacy than continuous DBS [17–20].

In summary, the role of electrophysiological recordings in current DBS strategies involves (1) substantiation of the optimal target identification within the brain by analysing the pathological neural activity associated with the particular disorder. In this sense, by recording neural signals from the target region and surrounding areas, clinicians can determine the most effective site for electrode implantation. (2) Intraoperative guide for the neurosurgeons during DBS electrode implantation surgery. (3) Neural circuit mapping via analysis of the (ab)normal firing patterns and communication between brain regions, which in turn allows a deeper understanding of particular brain disorders. Therefore, by leveraging electrophysiological techniques, clinicians can enhance the precision,

Fig. 1. Analysing electrophysiological brain data. **a** Schematic representation of the implanted electrodes in deeper brain structures. The squares serve to depict different invasive and non-invasive electrophysiological techniques. **b** Electroencephalography (EEG) and electrocorticography (ECoG). EEG that allows to register the activity of groups of neurons that is volume conducted to the surface of the head, while ECoG records activity using electrodes inserted on the subdural space. **c** Deep into the brain, stimulation electrodes or microelectrodes are inserted surgically, allowing to register extracellular and intracellular activity, respectively; DBS electrodes have a dual function, stimulation, and recording of deep brain structures. **d** Example of analysis of electrophysiological signals in which extraction of the signal sources from the EEG in the time domain can be achieved and combined with LFP recordings to evidence interregional connectivity (e.g., through cross-frequency coupling). **e** Spectral features over time evidence that during stimulation, an evoked activity (ERNA) appears between 300 Hz and 350 Hz (label 1) and its power attenuates while dropping in frequency until it reaches a steady state centred around 260 Hz (label 2). Stimulation blocks are denoted by the grey rectangles at the top of the trace. In addition, during stimulation, there is a prompt suppression of beta and low gamma power (label 3) and a modulation of the HFO frequency (label 4) is present before stimulation. Note that line noise artefacts are visible throughout the recordings at 50 Hz and its harmonics, along with the stimulation artefact at 130 Hz and its harmonics, despite being reduced by notch filters. Movement artefacts, affecting mostly lower frequencies, are particularly visible in the third stimulation block.

effectiveness, and long-term outcomes of DBS, ultimately improving the quality of life for individuals suffering from neurological and psychiatric conditions.

Transient States of Synchronization and CL-DBS

As mentioned above, CL-DBS represents a tool to optimize the delivery of stimulation in the temporal domain and a thorough understanding of the temporal dynamics of neuronal oscillations is critical for the implementation of this technology [21]. Currently, basal ganglia beta activity is the best-characterized symptom biomarker in PD [22–25]. The amplitude of beta activity is not sustained over time but is characterized by a fluctuating nature that can arbitrarily be segregated into transient states of synchronization (i.e., beta bursts ~200 ms duration) [25, 26]. After the withdrawal of dopaminergic medication in PD (off state), beta bursts tend to become longer and reach higher amplitude levels. Length and amplitude of beta bursts are related to the overall level of motor impairment [25, 27–30]. In addition, beta bursts may also elicit a more instantaneous impact on motor performance as their occurrence prior or during ongoing movements may slow down movement velocity [31–33]. These observations are consistent with the hypothesis that the increased synchronization denoted by beta bursts compromises the information coding capacity in the basal ganglia-cortical networks and may negatively affect upon motor performance [34].

In summary, the evidence is accruing that such transient states of synchronization represent clinically relevant periods for temporally targeted stimulation. In fact, beta-burst-driven CL-DBS algorithms have already been successfully piloted [35, 36] and are currently further validated in on-going CL-DBS clinical trials (NCT04547712, NCT05402163). Alternative and promising CL-DBS algorithms may target slower amplitude dynamics fluctuating over minutes, which, for instance, can index the ON-OFF medication transitions known in PD [20, 37, 38]. Future efforts for the optimization of CL-DBS may include objective electrophysiological processing techniques for feedback signal selection [39, 40], as well as the combination of multiple feedback signals [41, 42] in implantable devices to better address the variety of individual symptoms states.

Notably, beta oscillations have mainly been studied in the STN. However, beta oscillations occur ubiquitously throughout the brain including cortical and subcortical structures [43, 44]. Of particular interest for DBS, the pallidum expresses beta oscillations, which have been linked to movement slowness in dystonia [45] and to drug-induced dopamine depletion [46]. Thus, similar to subthalamic beta power, pallidal beta oscillations might be a valuable feedback marker for improving motor impairment using closed-loop (CL-)DBS. This supports our initial hypothesis that overlapping neural circuitry may drive similar motor and non-motor symptomatology in brain disorders, which may be translated to deploy CL-DBS across disease indications.

A further alternative fingerprint to be used for CL is gamma oscillations. Gamma oscillations from both cortical and subcortical motor regions contralateral to movement are linked to motor control. Specifically, gamma synchronization is considered as an oscillation that promotes movement and encodes vigour of motor output [47, 48]; it is encountered when movement is successfully stopped [49] and changes according to the alertness levels [50]. For a detailed overview of gamma activity, please see Wiest, Torrecillos [51]. Interestingly, a narrowband gamma, particularly within the range of 60–90 Hz, has been linked to therapy-induced dyskinesias. These results suggest the existence of different gamma oscillations. Because narrowband gamma is primarily an induced activity by either dopaminergic medication or DBS and is minimally affected by voluntary movements in patients with PD [52, 53], it represents a promising biomarker for dyskinesia in CL-DBS. Noteworthy, a thalamic gamma narrowband has been detected in several neurological disorders including ET, dystonia, and myoclonic epilepsy [54, 55], despite not being related to dopaminergic medication in such diseases.

CL-DBS for Movement Disorders: Opportunities in Patients with Acutely Externalized Leads

While sensing-enabled implantable DBS systems allow for the recording of neural signals from chronically implanted electrodes during unconstrained activity and in naturalistic environments, perioperative subcortical sensing with DBS electrodes temporally externalized in a laboratry environment has been performed for more than 20 years. Despite limitations of the latter, including limited recording time, a constrained testing environment, potential stun effects, and long hospitalization time for the patients, working with externalized electrodes still offers unique advantages for research. Indeed, this setting allows for a better signal-to-noise ratio, a higher sampling rate, and the possibility of accurately synchronized recordings of other signals such as EEG, magnetoencephalography, and EMG. This approach could thus offer new insights into the underlying circuit pathophysiology and how cortical and

subcortical neural oscillations translate into muscle activities in behaviour. It also offers a unique opportunity to test new algorithms and hardware, without being limited by what is feasible with an implantable device.

In PD, gait difficulties, including freezing of gait (FoG), remain a clinical challenge, with the effect of dopaminergic medication and conventional STN DBS often insufficient and variable. There have been important research efforts towards better understanding of FoG. Anil, Hall [56] used an experimental, implanted, sensing neurostimulator (Activa® PC + S, Medtronic, Inc.) to measure synchronous STN LFPs, shank angular velocities, and ground reaction forces in freely moving patients. They observed that patients with FoG showed greater sample entropy in the alpha (8–12 Hz) frequency band during periods of FoG than during walking without FoG. Later on, Subramanian, Morris [57] reported that prolonged beta burst durations in the STN differentiated patients with freezing from those without freezing, and these prolonged beta bursts were shortened during DBS that improved gait. Meanwhile, recording with externalized leads either during the surgery inside the operation theatre or during the interval between staged operations also offers new insight on the pathophysiology of FoG, related to the above-mentioned technical characteristics. For example, Subramanian, Hindle [58] performed intraoperative recordings, and found that increases in multi-unit activities, and beta/theta rhythms in the STN are associated with freezing onset in PD.

Recording STN LFPs from patients with externalized electrodes during gait-like tasks has delivered a better understanding of the role of the STN in normal gait control [59]. Here, an observation of rhythmic modulation of activities in the beta frequency band in STN LFPs in tandem with stepping movements increased beta activities during the stance phase of the contralateral leg and reduced beta activities during the active movement phase of the contralateral leg including propelling, swinging, and touching down. The STN modulation across the two hemispheres shows an anti-phase pattern, mirroring the alternating movements of the two legs in walking. This alternative modulation pattern captured in the STN LFPs can be enhanced with an auditory stimulus and increases the regularity of the stepping movements [60]. In another study, a similar modulation pattern in the pedunculopontine nucleus, which also has an important role in locomotion and gait control, was observed [61]. Previous studies have found that continuous high-frequency stimulation suppresses the beta activity in the STN LFPs [14, 62, 63]. A new biomimetic stimulation pattern, which mimic the modulation pattern observed in normal walking, has been shown to lead to entrainment in the stepping movements [64] and is currently being tested in patients during free walking. To drive adaptive DBS for gait difficulties forward, continuous efforts are required to advance the investigation about the activity changes in the STN during FoG, to better understand its pathophysiology, as well as identifying biomarkers for the switching of stimulation protocols that better suit the pathophysiological and movement status.

A further example comes from essential tremor, in which patients experience tremors only when they are performing a voluntary movement or maintaining a specific posture. Continuous DBS is a very effective therapy; however, many patients experience the loss of the DBS effect due to habituation and/or the progression of the disease [65]. Therefore, the concept of stimulation on demand for essential tremor developed almost parallel to DBS itself [66]. In recent years, there has been an increased research effort on CL-DBS for essential tremor, using either accelerometer [67], EMG, or electrocortical (electrocorticography) measurements as feedback signals [60, 64, 67–70]. Thalamic LFPs recorded from the same electrode implanted for stimulation provide further information about voluntary movements with an average decoding accuracy of 80% at the false-positive rate of around 20% [69]. Real-time CL-DBS based on movement decoding using thalamic LFPs has been tested in patients with externalized electrodes, and can achieve similar effects in tremor suppression as conventional DBS, but with only a fraction of the total energy delivered to the brain [61]. Here, deep learning convolutional neural networks may further improve decoding accuracy if based on particular brain states, but the testing of more sophisticated methods is currently not be feasible in patients with chronically implanted devices due to technical constraints.

As such, lead externalization offers the opportunity to test and compare different signal processing and control algorithms, as well as hardware design for adaptive DBS for PD [66]. We are also taking advantage of the high frequency of sampling and of the precise synchronization of different measurements to test the effect of stimulation timing on motor function and decision-making [8]. This will help us better understand the mechanisms of DBS in terms of changes in both behaviour and neural signals. Research in acutely externalized electrodes will probably provide proof of concepts and speed up the clinical translation of new algorithms and protocols for CL neuromodulation.

Besides novel hardware, recent proposals for open-source platforms for CL-DBS research have been developed [71]. This will enhance the development of new algorithmic approaches to decode disease- or

symptom-specific brain states and to learn CL control strategies are important building blocks to drive the research on CL-DBS. Providing exchangeable modules for recording hardware, decoding, user tasks, stimulation strategies, and stimulation hardware, this experimental platform comes with extensive monitoring functionality and will support reproducible research in the field.

Considerations regarding CL-DBS Approaches in Psychiatric Disorders

Most previous CL-DBS studies have focused on PD and essential tremor. However, since the general goal of CL-DBS is to improve efficacy and reduce side effects by tailoring stimulation to individual patients and changes in their clinical states, we are convinced that CL stimulation will have implication beyond these disorders. For instance, any condition, in which electrical stimulation has demonstrated clinical efficacy, might ultimately benefit from novel CL approaches.

As mentioned earlier, targeting oscillatory responses in movement disorders, namely PD, is already making strides for CL-DBS [16, 72], but similar oscillatory features are proving useful for other diseases, such as Tourette syndrome [73, 74], and both neurologic and neuropsychiatric diseases often show increased oscillatory hypersynchrony [75–77]. Further, in psychiatric diseases different networks may need to be targeted for optimal clinical outcome [78]. This supports our proposal that translation of oscillation-informed stimulation may be helpful for psychiatric disorders.

Mental illness is currently understood as a dysfunction of brain networks [10, 14, 27, 62, 79] and thus, DBS can be considered to replicate the benefits of, for example, movement disorders. OCD has been the only accepted indication for DBS in psychiatry, but its efficacy remains to be proven against other techniques. Recently, the CE mark was lost for OCD and at this moment in Europe there remains no established indication in the psychiatric disorders [80]. Targeted stereotactic lesions can be remarkably effective even in refractory cases of depression and OCD [63, 65]. CL-DBS may provide an avenue to shift this balance more towards the neuromodulatory approach. The challenge for CL-DBS in OCD, depression, as well as other psychiatric disorders is to identify relevant neural signatures of mental illness and its fluctuating symptoms that provide meaningful feedback to stimulator devices [2]. Recent work has made special emphasis in the opportunities for CL-DBS in depression [81]. For some psychiatric disorders, candidate EEG markers for potential CL-DBS are currently being studied [70, 71, 82]. Overall, current approaches offer opportunities for CL-DBS by the aid of MRI modalities, for example, through personalized brain mapping and targeting [81], in which diffusion imaging may be used to identify the fibre tracts underlying the electrophysiological signals, and deliver a data-driven decision on the local target to implant the electrodes.

To effectively treat a disorder such as depression with CL approaches, a system needs to automatically evaluate a biomarker for the individual's mood. Clinical evidence shows that affect can fluctuate within minutes [83] to days [84] and such fluctuations must be captured by a reliable assessment or biomarker. In principle, it should be irrelevant if such fluctuations of affect occur in a diseased or a physiological brain. Assessment using rating scales is not adequate to capture quick fluctuations since they usually apply a time frame of 1 or 2 weeks. At present, there is no biomarker which unequivocally corresponds to the individual's experience of his/her acute mood state. There are other approaches, which probe multiple sites of the subcortical networks with multiple depth electrodes, in order to isolate the ideal hub region as well as to extract readings of mood and its fluctuations [85–87] in depressed patients (see Widge [88] for a recent parallel perspective). However, stereo EEG is invasive and a potential scalability of such an approach is likely improvable. Less invasive approaches try to combine implanted DBS electrode recording with additional prefrontal cortical surface electrodes recordings to assess mood and anxiety in PD patients [89]. The results of such practices are promising and might point to standard regions for biomarker detection (beta frequency range) in the prefrontal region with respect to mood and anxiety. Additionally, translational research has recently identified hints for depression readings at a different low gamma frequency range [90] in the prefrontal cortex of rodents.

If and how such biomarker readings can effectively be manipulated with DBS is a yet unsolved question and amongst others dependent on the target region for stimulation. Multiple target regions are under research for antidepressant efficacy. Two of the most researched regions are the subgenual cingulate gyrus [91, 92] and the superolateral branch of the medial forebrain bundle [59, 93] with dramatically different response dynamics of days to a few weeks (superolateral branch of the medial forebrain bundle) to months (subgenual cingulate gyrus). These dynamics might influence the usability of a certain target region in a CL setting.

At this moment, there is only one approved system with CL capacity, which may, in principle, drive DBS. The NeuroPace responsive neurostimulation (RNS®) system is

Table 1. Available devices and software suitable for CL-DBS

Device	Manufacturer	Key features
Newronika AlphaDBS and FilterDBS	Newronika	Rechargeable pulse generator with sensing technology to record noise-free LFPs while electrical stimulation is delivered
Medtronic AdaptiveStim (Activa Percept™ PC + S)	Medtronic	Neurostimulator with sensing electrode, widely available
CLOVER-DBS – sensor-based optimization for Boston Scientific Vercise	Boston Scientific	Semi-automatic, CL iterative computer algorithm facilitating the initial programming of DBS settings for PD patients
SceneRay harmony DBS+	SceneRay	Adaptive stimulation technology, primarily for Parkinson's
G102RS device	PINS Medical	Dual channel rechargeable implantable pulse generator with sensing technology
Picostim™	Bioinduction®	Skull-mountable DBS device; LFP recordings during and post-implantation, with real-time display of the frequency components of the signal
*Abbott Infinity DBS+	Abbott	Directional leads, rechargeable neurostimulator
NeuroPace RNS® System[a]	NeuroPace	Approved treatment for adults with drug-resistant focal epilepsy. Recognizes and responds to patient-specific iEEG patterns

*Suitable hardware for CL-DBS but not yet available. [a]CL device already approved, despite not for DBS.

FDA approved in the indication of focal epilepsy [94] and recently its potential use for depression has been shown in a proof of principle study [86]. Two further available systems (Newronika's Alpha-stim DBS and Medtronic's Percept™ PC) are currently undergoing clinical trials for their safety and efficacy in CL-DBS for PD (Medtronic's NCT04547712 and Newronika's NCT04681534), but other implantable sensing technologies exist (e.g., G102RS device – PINS Medical, China; Picostim™ – Bioinduction®), as well as ongoing clinical trials evaluating the performance of programming methods (NCT03037398; CLOVER – Closed Loop Programming Evaluation Using External Responses for Deep Brain Stimulation). Table 1 summarizes available devices and their differential technical features. However, because of the previously mentioned reasons (distinct frequency ranges, cumbersome clinical mood detection, and others), these systems need to be specifically equipped for CL in specific indications.

Insights from NF Experiments for CL Systems

Some limitations for implementing DBS-based CL-based therapies in new patients and patient populations include the invasive nature of DBS implantation procedure carrying with it all the associated risks and demanding long-term follow-up. This highlights the interest in a non-invasive methodology, which can operate on similar principles to achieve similar success. On the contrary, a self-adapting system would lower the workload of the clinicians by diminishing the need for control or reprogramming visits.

The application of feedback systems in medicine is observed in the CL-DBS systems [95]. NF is a CL methodology that allows for the training of the self-regulation of brain regions or networks using real-time feedback of neural signals, as obtained, for example, by non-invasive functional MRI (fMRI) [81]. Particularly, using fMRI for NF applications gives access to deeper brain regions when compared to other brain imaging modalities such as EEG and functional near-infrared spectroscopy [27]. In real-time fMRI (rt-fMRI) NF training, participants receive a measure of their brain activity or connectivity from pre-defined region(s) and use this information to regulate the selected region(s) using cognitive strategies. This enables participants to develop personal strategies that are most effective in self-regulation, thereby providing an individually tailored intervention [27]. NF is a highly sustainable form of non-invasive neuromodulation, which, once learned, can be applied by patients whenever needed to overcome disease symptomatology.

To explore applications where NF can supplement DBS (e.g., at earlier stages of disease, or for patients who would not fulfil criteria for DBS, or in conditions for which efficacy of DBS has not yet been established), PD can serve as a good starting point. One of the most common brain regions targeted for training is the supplementary motor area (SMA), which is relevant for motor initiation and has been implicated both in the

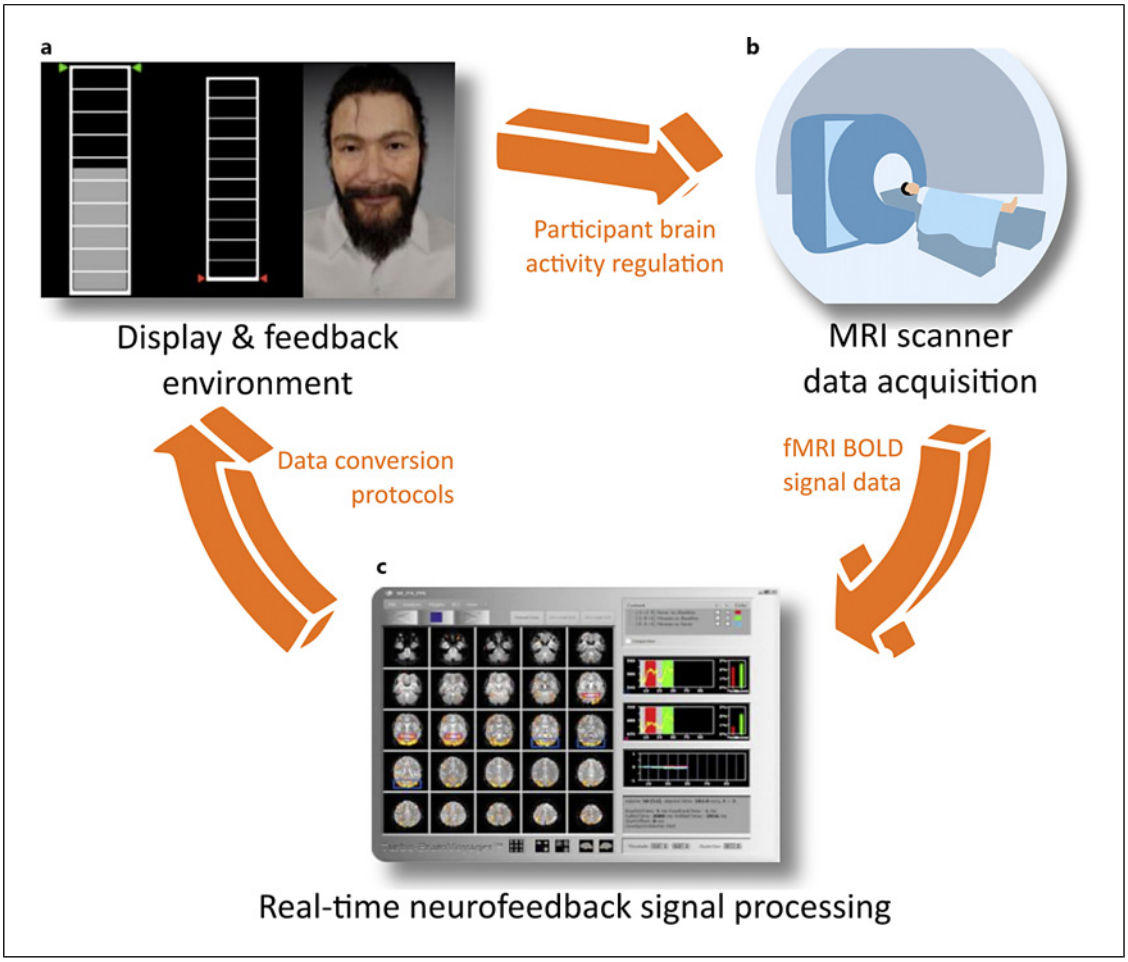

Fig. 2. rt-fMRI-based CL NF. **a** The participant lies in the scanner and views their own brain activity as feedback to apply cognitive strategies and achieve a predefined regulation goal. **b** The brain activity is measured and acquired in real time by the MRI scanner. **c** MRI data are sent to a software package where the signal is processed and converted in real time. The processed signal is then displayed on a screen in a form easily understood by the participant (feedback image created using Unreal Engine 4 [Epic Games, Inc., Cary, NC, USA]-based application).

pathophysiology of PD and in possible compensatory processes [56]. Proof of concept of fMRI-NF targeting the SMA has been demonstrated in PD [57, 58], but the target selection has so far been rather generic, such as average activation level of the SMA, and the clinical effects have been limited (and not significantly superior to an active control intervention).

Deep areas of the brain can also be reached by fMRI-NF and, thus, the basal ganglia areas associated with the motor network that is primarily affected in PD are targeted. This opens up opportunities to train upregulation of specific parts of the basal ganglia in PD and potentially even mimic some of the effects of DBS (Fig. 2), which have been investigated in a number of studies with concomitant fMRI [68]. Exploring such a transfer of concepts and targets from DBS to fMRI-NF is the topic of the ongoing work of the Neuripides Consortium (https://neuripides.eu/).

Current Challenges of CL-DBS

There are various challenges that need to be addressed for implementing CL-DBS not only in well-controlled research environments but in real-life clinical settings. First, the optimal feedback biomarkers need to be stable over time and detectable in the target patients. For example, STN beta power can be recorded years after the DBS operation and is present in a majority of, albeit not all, PD patients [72, 96, 97]. This problem is less clear for

other proposed feedback markers. A second challenge imposed by CL-DBS is that the system needs to learn a control strategy to adaptively deliver stimulation depending on the ongoing brain signal recordings. Due to the large number of potential states that are reflected in electrophysiological recordings, learning an optimal strategy for an individual may require a large number of interactions with a particular patient, i.e., probing the effect of small variations of the stimulation parameters. To reduce this time to a minimum, the pre-training of control algorithms in simulated CL environments could represent a practical option [82, 98].

Furthermore, if electrophysiological feedback markers are applied, CL system can be affected by stimulation artefacts (e.g., Herz, Little [99]) or other sources of electrical activity such as electrocardiography activity in subclavicular implants [100] requiring appropriate online artefact correction procedures.

As previously highlighted, it is very likely that single electrophysiological markers is not sufficient to achieve optimal outcomes from CL-DBS. Thus, CL-DBS may need a combination of electrophysiology/brain activity markers with brain integrity (locally and at the network level), clinical and medication status, and patient's ecological momentary assessments. This end up into a real-time adjustability problem. Further, DBS effects are not only determined by stimulation amplitude, but optimizing clinical effects can require simultaneous adjustments of contact selection, stimulation frequency, and pulse width. For optimizations in such high-dimensional spaces, more complex machine learning algorithms might be required rather than a single feedback marker [21, 41]. Finally, despite some studies exist on patient-specific, electrophysiology-informed CL-DBS, and clinical trials are undergoing, CL-DBS can be considered on their earliest stages. Such studies are opening new insights into the biology of brain diseases but also demonstrate the scalability challenges for CL-DBS to highly heterogeneous disease populations.

MRI Applications Relevant for CL-DBS

Additionally to the methods already mentioned, further opportunities for CL-DBS are offered by structural and fMRI, which are widely used to characterize tissue properties non-invasively in humans. For example, magnetic field strengths of 1.5 and 3 Tesla currently provide means for clinicians and surgeons for the preoperative detailed characterization of patients and surgery planning for DBS implantation. The standard workup can include 3D-T1 magnetization-prepared rapid acquisition gradient-echo, fluid-attenuated inversion recovery/T2, susceptibility-weighted imaging, diffusion images, and gadolinium-enhanced MRI as part of the perioperative protocol.

In addition to their utility for current clinical practice, MRI techniques can provide important information about local and global brain properties, herby supplementing clinical routine tests such as neuropsychological assessment or functional impairment evaluation that are not designed to detect such events [101]. Recent evidence exists that the atrophy in the central brain areas accurately predicts the post-operative clinical outcome in PD patients undergoing STN DBS [102, 103]. Similarly, the connectivity of the brain networks (e.g., through graph theory or diffusion imaging) can unmask motifs of the brain that are strongly correlated with clinical outcomes following DBS [102, 104] or guide parametrization of the stimulation [105]. Further, and bearing in mind automatic DBS programming, information from morphometric or network properties can be fed into a single-subject characterization of the brain integrity or the brain pathological state, which may be considered for the initiation and adaptation of CL stimulation parameters. Here, we envision a vast opportunity for machine learning approaches to include structural and functional information for the adaptation of stimulation paradigms. As a recent example, it has been reported that besides electrophysiological (e.g., LFPs) measurements providing a neural signal for clinically effective CL-DBS, MRI markers, particularly those informing about the preoperative degree of structural and functional damage within the targeted network, can provide an early and objective signal of the disease status as well as the time needed to achieve the aimed DBS outcomes in depression patients [106].

Overall, MRI can be used as means (1) to provide a basis on the tissue integrity status during planning DBS targeting; (2) to provide information on the initial parameter setting and programming according to the properties of targeted network; (3) to facilitate data-driven, individualized, and optimized localization of the spot to perform sensing; (4) to allow longitudinal monitoring of disease-related pathological progression that interferes with DBS functioning.

Conclusions

Despite current advances in DBS technology, further research is needed to succeed in the development and application of CL-DBS. Such evaluation should utilize the temporal dynamics of imaging and electrophysiological

biomarker signals, as well as their evoked and induced responses to DBS and the relevant clinical state of the patients, including their monitoring with peripheral devices. Importantly, patient's ecological momentary assessments should be considered for the development of CL-DBS applications. This integrative information may provide a window for increasing DBS efficacy and be further developed into CL applications that translate into clinical settings. Moreover, studies involving larger sample sizes or chronic recordings would allow translating the current understanding of motor-system-related electrophysiology CL-DBS mechanisms for different brain conditions and lastly may help to deliver individualized therapy to patients with neurological and neuropsychiatric diseases.

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Conflict of Interest Statement

Maria Fiorella Contarino is a member of the Advisory Board (all fees to institution) of Abbvie and Inbrain, has consultancies (all fees to institution) with Medtronic (independent consultant for research and educational issues) and Inbrain (independent consultant for research), and has received speaking fees from Abbvie (fees to institution), ECMT (CME activity), and Boston Scientific (fees to institution). The rest of the authors have no conflicts of interest to declare.

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Author Contributions

Authors Gabriel Gonzalez-Escamilla, Sergiu Groppa, Gerd Tinkhauser, Halim Ibrahim Baqapuri, David E.J. Linden, Huiling Tan, and Volker Arnd Coenen were responsible for conceptualization, literature search, investigation, data curation, writing – original draft, writing – review and editing, visualization, and made agreement 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. Authors Bastian Sajonz, Damian M. Herz, Christoph Wiest, Joana Pereira, Matthias R. Dold, Manuel Bange, Dumitru Ciolac, Viviane Almeida, Neuber John, Daniela Mirzac, Juan Francisco Martín-Rodríguez, Christian Dresel, Muthuraman, Astrid Daniela Adarmes Gomez, Marta Navas, Gizem Temiz, Aysegul Gunduz, Lilia Rotaru, Yaroslav Winter, Rick Schuurman, Maria Fiorella Contarino, Martin Glaser, Michael Tangermann, Albert F.G. Leentjens, Pablo Mir, Cristina Virginia Torres Diaz, and Carine Karachi were responsible for writing – review and editing, made the final approval of the version to be published, and made agreement 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. Authors Gabriel Gonzalez-Escamilla, Sergiu Groppa, and Volker Arnd Coenen were responsible for supervision and project administration.

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