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Deep brain stimulation: is it time to change gears by closing the loop?

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Abstract

Objective. Adaptive deep brain stimulation (aDBS) is a form of invasive stimulation that was conceived to overcome the technical limitations of traditional DBS, which delivers continuous stimulation of the target structure without considering patients' symptoms or status in real-time. Instead, aDBS delivers on-demand, contingency-based stimulation. So far, aDBS has been tested in several neurological conditions, and will be soon extensively studied to translate it into clinical practice. However, an exhaustive description of technical aspects is still missing. *Approach.* in this topical review, we summarize the knowledge about the current (and future) aDBS approach and control algorithms to deliver the stimulation, as reference for a deeper undestending of aDBS model. *Main results.* We discuss the conceptual and functional model of aDBS, which is based on the sensing module (that assesses the feedback variable), the control module (which interpretes the variable and elaborates the new stimulation parameters), and the stimulation module (that controls the delivery of stimulation), considering both the historical perspective and the state-of-the-art of available biomarkers. *Significance.* aDBS modulates neuronal circuits based on clinically relevant biofeedback signals in real-time. First developed in the mid-2000s, many groups have worked on improving closed-loop DBS technology. The field is now at a point in conducting large-scale randomized clinical trials to translate aDBS into clinical practice. As we move towards implanting brain-computer interfaces in patients, it will be important to understand the technical aspects of aDBS.

1. Introduction

Deep brain stimulation (DBS) involves the implantation of electrodes in the brain to emit signals that modify abnormal brain activity that cause motor, mood, or cognitive disturbances underlying neurological and psychiatric disorders. To achieve symptom relief, conventional DBS (cDBS) systems are individually programmed and deliver continuous energy to the brain. Since its advent in the late 1980s to treat essential tremor (ET) and Parkinson's disease (PD), DBS may be beneficial in a range of disorders such as obsessive-compulsive disorder, Tourette syndrome, treatment-resistant depression, drug and alcohol addictions, and Alzheimer's disease [1]. Advances in DBS hardware have similarly expanded the available parameter space to optimize therapeutic outcomes for patients. This includes the development

of directional leads to steer energy delivery [2], and software capable of delivering stimulation at kilohertz frequencies [3]. Despite using DBS for novel indications and with more parameter options, DBS is still clinically applied using conventional open-loop stimulation techniques that rely on continuous stimulation. Stimulation-related side effects, such as dysarthria and postural instability [4, 5], can be reversed by reprogramming, thus suggesting that continuous delivery of energy to the brain is non-optimal and may limit patients' therapeutic potential while also increasing battery consumption. In addition, it has been hypothesized that continuous stimulation may impair response inhibition [6], possibly leading to stimulation-induced impulsivity [7–10].

The use of closed-loop or adaptive deep brain stimulation (aDBS) can, at least in theory, overcome the disadvantages of cDBS by delivering the ideal amount of energy to the brain based on clinically relevant biofeedback signals in real-time [11]. Through the reliance on feedback variables (e.g. brain signals) that correlate to a patient's clinical state, aDBS systems respond to deliver stimulation that is optimized and only when needed, thereby avoiding unnecessary stimulation. First developed in the mid-2000s, early work on aDBS focused on identifying which signal to use for controlling the device. At the time, technology was already being used to record signals from implanted DBS electrodes post-operatively [12], which showed that local field potentials (LFPs) correlated with the motor state of the patient. As an important first step in the development of aDBS, the first prototype to filter the DBS artefact in LFP recordings during ongoing stimulation was developed in 2007 [13]. Since the first attempts to record peri-electrode signals during stimulation, technology has rapidly evolved to provide new devices (implantable and non-implantable) that allow for varying degrees of automatic adaptation of DBS parameters. Thus far, several papers have reported on the clinical application of aDBS in animal models of movement disorders and human movement disorder patients [14]. Although further exploration is warranted, cognitive and psychiatric disorders have recently been targeted for aDBS implantation [15, 16]. This review provides a comprehensive overview of the technology and approaches to aDBS, which is important given the forthcoming translation of aDBS into clinical practice.

2. Technological building blocks of aDBS

DBS is a form of neuromodulation in which electrical energy is delivered to targeted brain regions to control and improve patient symptoms. In control theory, an open-loop system occurs when the output does not affect the input. cDBS is an open-loop system since stimulation is delivered continuously, regardless of the patient's clinical state. Alternatively, a closed-loop system is characterized by a relationship between the output and the input, such that the controlling action depends on the generated output of the system using a feedback loop. aDBS (figure 1) is a closed-loop system in which the patient's state is estimated using a measurable variable that is changed by the therapeutic effect of DBS (control variable). A control algorithm takes the control variable as input and, using a reference input (i.e. the desired value of the variable that should correspond to the desired patient's state), calculates the stimulation parameters (manipulated variable) that will be applied to the patient. Therefore, the system output influences the system input, thus closing the loop [17]. This closed-loop model of aDBS is based on three conceptual, functional modules that represent the building blocks of the adaptive technology: (a) sensing block that measures the feedback variable, (b) control block that analyses the variable and calculates the new stimulation parameters, and (c) stimulation block that controls the delivery of stimulation (figure 1).

Depending on the type of aDBS being developed, there are different implementations of each block. First, the sensing block has to be implemented according to the type of feedback variable chosen to adapt DBS, which can be measured while DBS is ON to adjust parameters moment-by-moment [18, 19], or when DBS is OFF to provide on-demand stimulation [20]. To date, numerous studies have employed various electrophysiological techniques to find a reliable signal that can be used to control stimulation. Possible feedback variables for aDBS include neurochemical signals representing dopamine fluctuations [21, 22], external variables such as surface electromyography or wearable accelerometers, and neurosignals recorded from implanted deep brain electrodes (LFPs) or cortical electrodes (electrocorticograms (ECoG)).

The choice of the best feedback variable depends on several factors already highlighted in early works on aDBS [17]. They include the (a) correlation between the chosen variable and the symptoms that stimulation has to address, (b) feasibility of the recording, (c) learning curve necessary to introduce the new technology (e.g. the need to change neurosurgical practice to implant other electrodes, or the need for family/caregivers to deal with wearable sensors), (d) possibility to improve therapy personalization using aDBS, and (e) battery consumption for the implantable pulse generator (IPG) with sensing and control hardware [18, 22].

Neurochemical signals are still in their infancy. Despite promising results [23, 24], there is still no strong evidence on the correlation between neurochemical signals and PD symptoms, thus limiting the present feasibility of the approach. The neurochemical approach would also likely require additional implants to allow for sensing, thus significantly altering current neurosurgical practices [21]. Similarly, despite external variables being accurate in

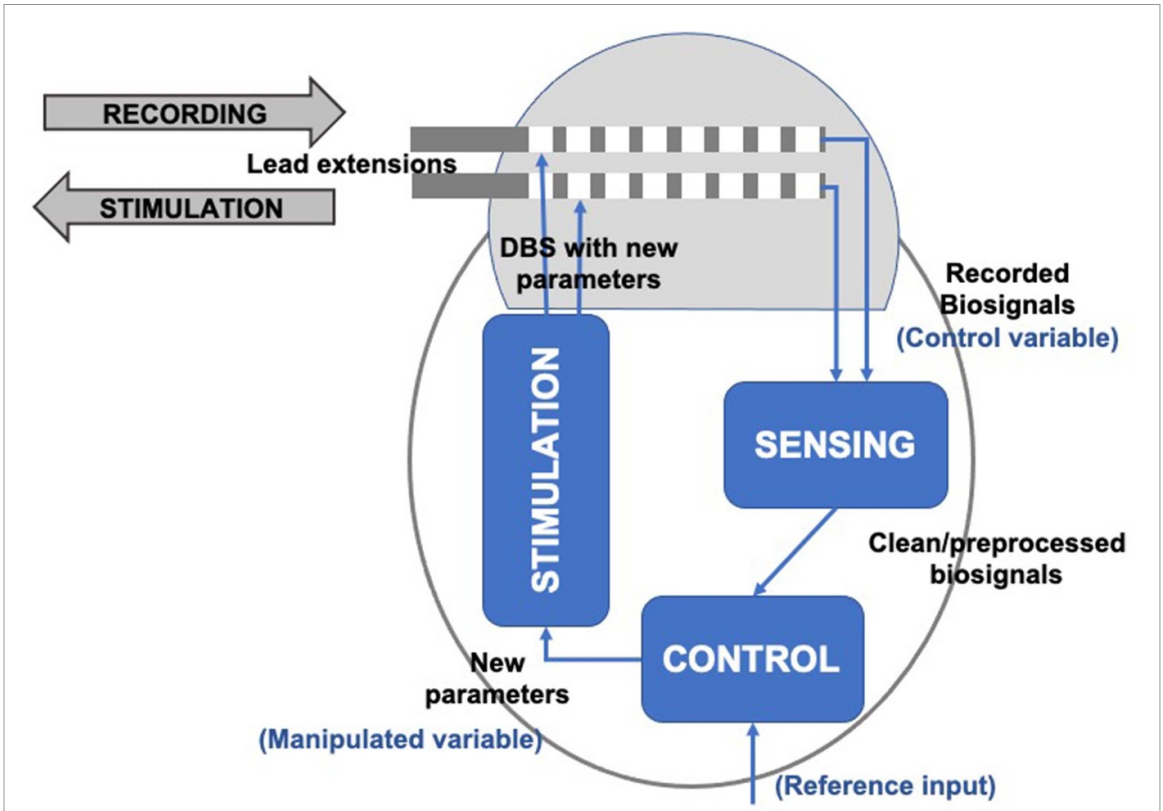

Figure 1. Adaptive DBS building blocks. Closed-loop technology consists of a (a) sensing block that measures the feedback variable, (b) control block that analyses the variable and calculates the new stimulation parameters, and (c) stimulation block that controls the delivery of stimulation.

capturing several symptoms, especially tremor [25], bradykinesia [26, 27], dyskinesias [28], and freezing of gait (FOG) [29], they are limited in practice by the need to wear additional sensing equipment. For these reasons, some literature reviews suggest that closed-loop aDBS based on neurosignals from implanted electrodes is a promising choice at the current stage of development [11, 21, 22].

To date, neurosignal-based aDBS is the only feedback variable that has been studied in humans (figure 1). The two neurosignals that have been tested are LFPs recorded directly from the implanted DBS electrodes in the target and ECoG signals recorded from cortical strips implanted in the cortex. Both types of neurosignals have the advantage of being captured through implanted sensors, thus minimizing the potential stigma associated with wearable devices and maximizing the stability of the recorded signal. Moreover, both correlate with patients' motor states in different disorders (e.g. PD, dystonia, Tourette syndrome) [17, 30]. However, ECoG signals require an additional implant, which can represent a drawback when compared to LFPs.

2.1. Sensing block

The sensing building block has different implementations depending on the timing required for sensing. For example, if the patient requires continuous stimulation (as in PD) and DBS parameters are adapted moment-by-moment to the patient's state, sensing must be performed concurrently with stimulation. Simultaneous sensing and stimulation are only possible if artefact rejection strategies are implemented. Among artefact rejection strategies, the most common is the use of filtering based on the substantial band separation between the stimulus artefact (>100 Hz) and the frequency bands of interest (<50 Hz) [13, 31]. Another option is to use clamping strategies that trigger the sensing switch to turn OFF when the DBS pulse is delivered [32]. The rejection of stimulation artefact is crucial for LFP signals (recorded from the same site as stimulation) but not essential for ECoG signals (recorded far from the stimulation site). Conversely, if the patient does not need continuous stimulation, as in epilepsy or tic control for Tourette syndrome, there is no need to record while stimulation is ON, and the sensing block does not require artefact rejection technology. In this case, the sensing block continuously records the patient's signals, and when a specific pattern is detected that correlates to the onset of the abnormal symptom that is to be controlled, stimulation starts while sensing stops. Devices that implement sensing during stimulation can also be used in the case of separated sensing and stimulation. However, devices developed for separate sensing and stimulation do not allow for sensing during stimulation.

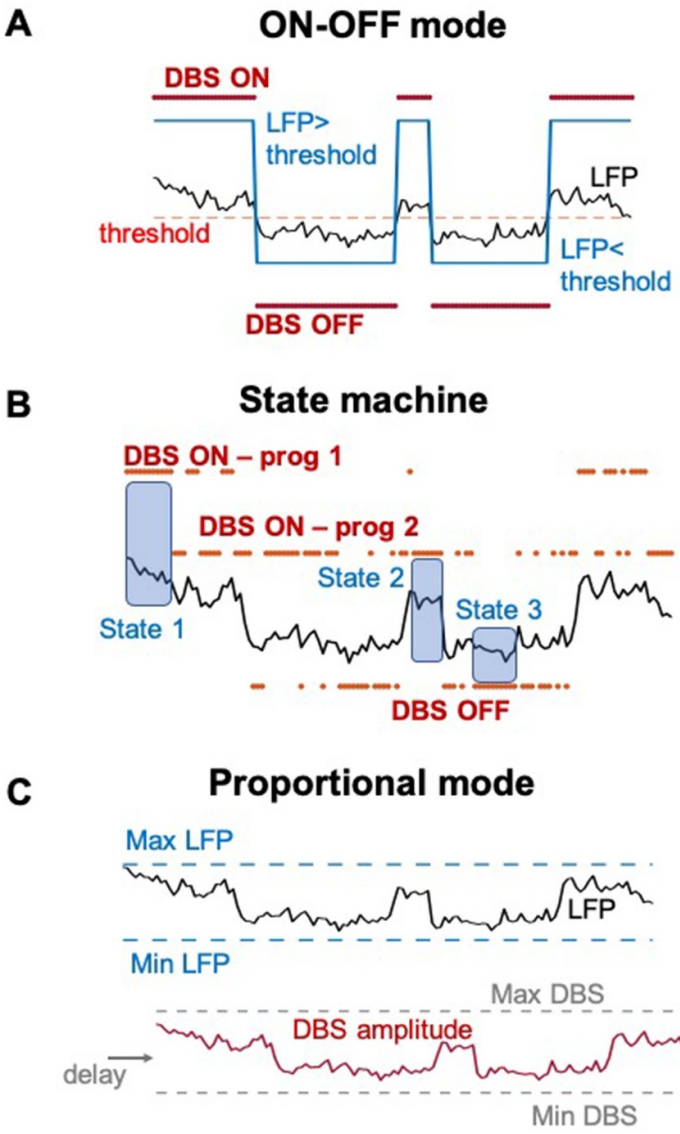

Figure 2. Implemented control strategies. The figure represents three implemented control strategies for aDBS. Each panel represents an exemplary local field potential signal (LFP, black line) and the adapted stimulation output (red line): (A) ON/OFF mode: when the LFP exceeds a pre-defined threshold (red dashed line), the control block switches the stimulation ON, otherwise stimulation is OFF; (B) state machine: a classification system associates the LFP pattern to the most probable state, and switches ON the specific DBS program, that is best suited to treat the predicted state; (C) proportional mode: LFP is continuously measured, and the stimulation parameters are changed using an algorithm that uses the variable itself as input. In this example, the linear proportional mode changes DBS amplitude linearly following the dynamic of the LFP signal, with a small delay that depends on the applied backward average.

2.2. Control block

The control block has two sub-blocks. One is dedicated to analysing the control variable to estimate the patient's state. The other is dedicated to defining new stimulation parameters based on comparing the control variable and the reference input. The first block can implement various signal processing algorithms, from simple band power estimations to more complex machine learning-based algorithms. To date, the human implementations of aDBS are based on the analysis of the feedback variable based on *a priori* knowledge of the correlation between the variable itself and the patient's state. However, approaches based on computational models or machine learning models were proposed [33–35]. For instance, Mohammed *et al* proposed an approach that combines machine learning techniques with fuzzy logic to improve the ability of the classifier to discriminate the patient's status [34]. The estimation of the patient's state through the analysis of the control variable serves as input to the second block that compares it to the desired patient's state or patient's state estimation (reference input) and provides new stimulation parameters. In general, the feedback control may be digital or proportional. The digital approach consists of selecting a state from a definite number of states (two or more), according to a classification of the control variable. The proportional approach is based on the calculation of an error signal (i.e. the difference between the reference input and the control variable

measured) that guides the definition of the stimulation parameters.

Among these general strategies, three were implemented up to now (see figure 2). The first strategy is an ON/OFF mode (digital) in which the control block switches the stimulation between OFF and ON according to the patient's needs. This represents the classical control strategy for applications requiring on-demand stimulation, such as in epilepsy [36] or Tourette syndrome [20, 37]. It has, however, also been used for PD [38, 39] and recently in PD patients at battery replacement [8]. The second strategy is a state machine (digital) in which the control block has several possible states or configurations (e.g. the patient is moving, the patient is sleeping, the patient has dyskinesias, etc), and the optimal state is chosen according to the recorded signal. This requires a classification algorithm aimed at establishing the patient's most probable state among those defined [40]. The third strategy is a proportional mode in which the control variable is continuously measured and analysed, and the stimulation parameters are changed using an algorithm that uses the variable itself as input [18, 19].

In PD, the ON/OFF mode was first proposed by Little *et al* [38], who developed a stimulation paradigm guided by the amount of beta activity recorded. The control law was based on a threshold that was selected for each patient and optimized to decrease the stimulation time by 50%. Stimulation was turned ON when beta activity exceeded the threshold and turned OFF when beta activity returned below the threshold. The ON/OFF strategy was also applied in Tourette syndrome using a responsive stimulation paradigm in which a 10 s stimulation and 2 min refractory period followed tic detection [41]. The state machine control is based on a classifier (support vector machine) to distinguish between a high (therapeutic) value and a low (non-therapeutic) value. This control block exists in the Activa™ PC + S device (Medtronic Inc. Minneapolis, MN, USA) coupled with ECoG recordings [40]. The state machine switches DBS parameters between two or more states that must be previously defined to match the patient's therapeutic stimulation. Lastly, the proportional mode was applied by Rosa *et al* [42] and was based on a linear adaptation of DBS amplitude according to the power of LFP beta (13–35 Hz) activity. This approach produces a smooth change in DBS amplitude without transients between states and requires only the definition of the maximum amplitude applicable to the patient.

2.3. Stimulation block

Finally, the stimulation block is the component that is embedded in most cDBS IPGs. In principle, all possible stimulation parameters can be adapted, including amplitude, frequency, and pulse width. Although present applications only use amplitude modulations (AMs), emerging evidence suggests the potential use of all other parameters in adaptive algorithms, as discussed in the section 5. However, the capabilities of the stimulation block may be limited by software or hardware constraints (e.g. some IPGs are not able to reduce the pulse width <10 μs).

As an alternative strategy to cDBS delivery, Tass *et al* [43] proposed a stimulation algorithm based on the coordinated reset (CR) technique. In this paradigm, weak high-frequency pulse trains are delivered to different electrode contacts at different times. They are used to reset the phase of the targeted neurons, thus reversing pathological synchronization.

3. Historical perspective

As a general concept, adaptive stimulation was first patented by Michael S John in 1996 as a system and method to rehabilitate patients from traumatic brain injury, coma, and movement disorders (US Patent 6066163A, 2 February 1996). Almost a decade later, LFP-based aDBS was conceptualized by Priori *et al*. This initial research focused on aDBS techniques that simultaneously record and stimulate. A major challenge was the rejection of stimulation artefact in LFPs when recorded during stimulation [31]. A device called FilterDBS was designed to provide continuous artefact-free recordings when DBS was ON [13]. FilterDBS was used to study the response of LFPs during stimulation in PD patients, thereby collecting indirect evidence of the feasibility of LFP-based aDBS [44, 45]. Following this technology, an industry-sponsored patent by Medtronic described a closed-loop DBS architecture, which further spurred the development of adaptive DBS [46].

In 2010s, the first device implementing closed-loop DBS (with continuous sensing separated from stimulation delivery) was approved for epilepsy [47, 48] and is currently being applied for Tourette syndrome [41].

At the same time, aDBS for PD was being developed. In 2011, the first proof-of-concept of aDBS guided by cortical signals was conducted in a non-human primate model of parkinsonism [49]. Soon after that, Medtronic published the architecture of an implantable aDBS device for application in humans [50]. This design was embedded in Medtronic's Activa® PC + S research device, allowing LFP sensing and recording while delivering targeted DBS therapy.

Meanwhile, LFP data were obtained from chronic recordings and in long-term DBS patients at the time of battery replacement [45, 51]. These data were essential to overcome the limitation of all prior neurophysiological studies that were based on LFPs recorded immediately after DBS electrode implantation and before the connection with the implanted IPG. However, the latter condition is characterized by

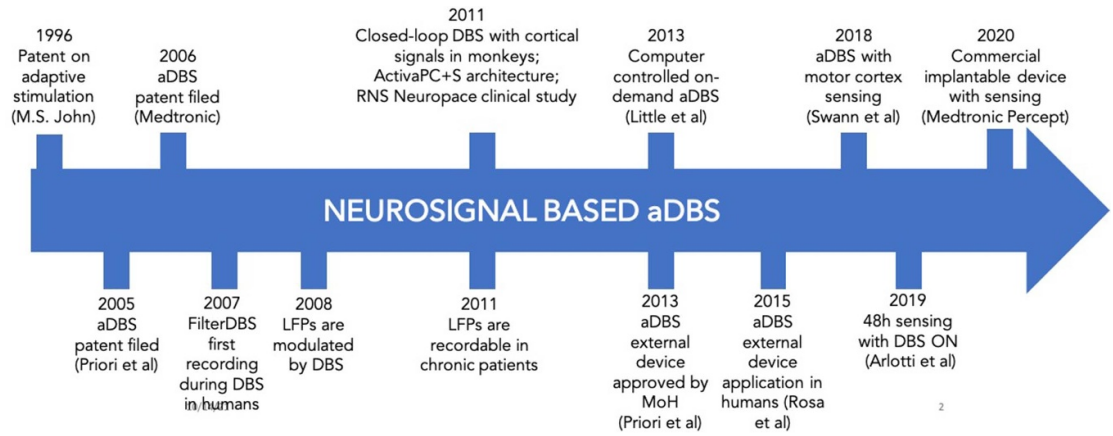

Figure 3. History of adaptive DBS technology. Timeline of significant aDBS milestones since 1996. aDBS, adaptive deep brain stimulation; LFPs, local field potentials; MOH, Ministry of Health (Italy).

dynamic changes in the electrode-tissue interface and often by the presence of oedema [52], which makes it challenging to generalize findings to the effects of chronic stimulation.

From 2013 onwards, aDBS experiments rapidly evolved. Little *et al* developed the first custom-made closed-loop DBS device that applied stimulation, albeit for a short period, and used an external computer mimicking the control block [38]. The first external device that embedded sensing, control, and stimulation was also CE-marked and subsequently used for experimentation in patients with PD [42]. Since then, experiments have been conducted using the external aDBS device, custom-made computer-based aDBS system, and PC + S IPG [53, 54]. These studies allowed a more in-depth understanding of aDBS, not only from a clinical viewpoint but also from a technological perspective. For instance, some reports showed that sensing from implantable IPGs may be limited by the presence of electrocardiographic (ECG) signals superimposed to the LFP trace artefact [55], thus necessitating the improved design of electronics to prevent the ECG signal from being recorded by IPGs [55]. In addition, while most reports demonstrated that aDBS provides comparable [19], or even superior [39], motor control in PD than cDBS, and delivers significantly lower amounts of energy to the tissue (up to a 73% reduction of the total electrical energy delivered to the tissue [19]), the energy used to power the sensing and the control module is not insignificant. Finally, the feasibility of aDBS years after DBS and its superiority with respect to cDBS was recently demonstrated [8], thus confirming previous indirect evidence of LFP recordings and DBS-induced suppression in chronic patients [44]. At the present stage of development, future implantable systems should use a rechargeable system, instead of a primary cell, in order to leverage the full potential of aDBS. Recently, an implantable device with the ability to record LFPs while DBS is ON (Medtronic Percept™) has received the CE mark [56]. However, it does not allow aDBS delivery and utilizes a primary cell which negatively impacts battery life. Figure 3 provides an overview of important historical time points in the development of aDBS.

4. Control biomarkers for aDBS in PD

4.1. Local beta oscillations

LFP studies have a long history, with the earliest experiments dating to the late 1990s and early 2000s [57]. Oscillatory activity was identified in the human thalamus and basal ganglia that correlated with motor and non-motor aspects of PD, dystonia, Tourette syndrome, obsessive-compulsive disorder, and other pathologies treated with DBS [58, 59]. Among these, the beta band (13–35 Hz) was identified as the most promising for aDBS in PD, considering its strong relationship with motor aspects of the disease [12, 44]. Currently, LFP-based aDBS devices for PD research are based on AMs of subthalamic nucleus (STN)-LFP beta activity. The use of beta activity as a feedback control biomarker is supported by several direct and indirect findings from studies aimed at decoding basal ganglia pathophysiology [60]. PD patients tend to have abnormally high beta synchrony in the STN, which decreases following levodopa administration (especially in the lower portion of the band, from 13 to 20 Hz) [12, 61].

Beta power has been used to characterize the human STN and subsequently refine DBS targeting [62]. Subthalamic beta oscillations are localized in the motor area of the STN (dorsal STN), with a decreasing gradient from the dorsolateral to the ventromedial areas [63]. Importantly, beta activity is stable over time, as demonstrated in beta recordings performed in chronic DBS patients over 24 h [45, 64]. Rosa *et al* also showed that the beta frequency of LFPs can be modulated by DBS [51]. Moreover, beta power correlates with motor symptoms in PD, as measured by the Unified Parkinson's Disease Rating Scale - III (UPDRS-III) scale [54, 65]. Resultingly, beta activity

was selected as a biomarker for use in early aDBS experiments. Known beta dynamics facilitated the feedback algorithm setup as well as the interpretation of the results. However, several factors limit the ability of beta oscillations to be used as a biomarker for aDBS. First, abnormal beta activity is not observable in all patients [44], thus requiring the identification of other biomarkers for these patients. Second, beta activity has not been correlated with tremor, FOG, or dyskinesia, all of which may benefit from a closed-loop approach. These symptoms may be better represented by other frequencies (e.g. theta, alpha, gamma activity) or signals (e.g. cortico-subthalamic phase coupling [66]). Further research is warranted to identify other biomarkers—or combinations of biomarkers—to better represent the patient's state and optimize aDBS [67].

4.2. Other network biomarkers

The complexity of network dynamics cannot be solved using a beta-only feedback model. The inclusion of other frequency bands should be considered to target a patient's state, which often consists of mixed symptoms. For instance, low frequency (2–7 Hz) STN activity correlates to dyskinesias [68] and non-motor aspects of basal ganglia functioning [69]. Cortical narrowband gamma (70–90 Hz) activity has also been associated with dyskinesias [70] and used in recent ECoG signal-based aDBS applications [40]. Furthermore, cortical involvement in the modulatory effects of DBS suggests that a shift from local oscillatory activity to network dynamics should be adopted to address many neurological and psychiatric disorders now classified as circuitopathies [71]. Nonlinear synchronizations within the low and high beta band were observed in dopamine-depleted patients, suggesting that low beta activity is involved in bradykinesia and rigidity and high beta is involved in movement execution and planning [72, 73]. This corresponds with recent evidence suggesting a role for high beta in the communication between STN and muscle activity [74]. A more complex communication mechanism in the basal ganglia-thalamocortical loop based on frequency modulations (FMs) instead of AMs was demonstrated by Foffani *et al* during movement preparation, execution, and recovery [75]. Although low and high beta activity both showed a shift of the central frequency during movements, only the low beta band was regulated by the dopaminergic system [75]. Furthermore, beta power alone cannot explain the occurrence of complex phenomena, such as FOG. FOG is characterized by impaired cortical-subcortical network communication represented by cortical-STN decoupling in the lower frequencies (7–13 Hz) [66]. De Hemptinne *et al* also showed that broadband gamma phase-amplitude coupling was modulated by DBS in patients with PD [76]. Collectively, these observations suggest that AMs are too simplistic to explain the complex scenario of cortical-subcortical dynamics involved in PD and DBS mechanisms. Therefore, future adaptive DBS may be designed to use multi-frequency oscillatory activity to re-establish the physiological network dynamic.

Other techniques that do not rely on beta amplitude include using the beta phase as a feedback variable to trigger stimulation preceding the beta AM [77]. Another possibility is represented by the evoked resonant neural activity observed at very high frequencies [78], which may underlie DBS mechanisms of action. Using resonant activity as a feedback variable could help design aDBS approaches capable of fine-tuning stimulation to re-establish the physiological network resonant activity [79]. Nonlinear dynamics, or even fractal- or entropy-based approaches, may also be useful for representing the clinical state in adaptive strategies [73, 80].

4.3. External biomarkers

Since biomarkers that control stimulation must reliably correlate to patients' states moment-by-moment, external variables (i.e. signals recorded non-invasively) have also been studied, with promising results. In one study, aDBS controlled by electromyographic activity recorded from the deltoid muscle significantly reduced intention tremor in patients with ET [81]. Similarly, the amplitude of resting tremor measured by a wearable watch was used as feedback for aDBS and suppressed tremor by up to one-third in five tremor-dominant PD patients [82]. These studies, however, did not establish aDBS superiority over cDBS for tremor control, nor has feasibility been demonstrated in clinical practice. The use of external devices also requires patients to adhere to their consistent wear with minimal displacement, which may increase stigma and social burden.

5. Adaptable parameters

Although amplitude has been the only stimulation parameter used as a variable in current aDBS algorithms [19, 54, 83], theoretically, any parameter or stimulation pattern could be used. Recent advances in DBS technologies (e.g. directional leads, multiple independent current control sources) and nonconventional stimulation patterns (e.g. active symmetric square biphasic pulse, phasic burst stimulation) also mean that programming and adaptation possibilities are endless [84–87]. Thus, adaptive DBS systems could expand the therapeutic window and minimize stimulation-induced adverse effects.

5.1. Amplitude

The volume of tissue activated (VTA) by the electrical field should overlap with the targeted brain region to achieve the best clinical outcome. However, the VTA depends on several factors, including stimulation parameters, tissue anisotropy [88, 89],

Figure 4. Visual representation of the volume of tissue activated (VTA). The programming user interface of Medtronic (*left*) and Boston Scientific (*right*), showing the VTA as a virtual reproduction in 3D of the spread of current (electrical field) delivered by the DBS lead to the anatomical structures near the selected target.

and electrode design [90]. The VTA is directly related to amplitude since the voltage is directly related to current spread (total electrical energy delivered, TEED = (voltage^2 × pulse width × frequency)/impedance) [91]. Currently, commercial DBS systems provide a visual estimate of VTA (see example in figure 4) based on stimulation settings but not accounting for axons or soma adjacent to the electrodes. High amplitudes induce large VTAs, which correlate with better control of the motor symptoms in PD [92], dystonia [93], ET [94], and Tourette syndrome [95] (table 1). Conversely, a large VTA needed to improve clinical symptoms can also induce acute and chronic adverse effects due to the current spreading to brain structures adjacent to the intended therapeutic target [96]. A lower amplitude (smaller VTA) may be sufficient to achieve clinical benefit depending on the proximity of the VTA to the intended target as well as patients' activities, symptoms, and medication effects. The advantages of amplitude modulation through aDBS systems have been demonstrated in PD patients by improving dysarthria [83] and dyskinesias [20, 95], with an overall reduction in TEED. Moreover, unnecessary high-voltage stimulation is associated with negatively impacting therapeutic outcomes in some patients [97]. Amplitude control with aDBS could reduce or avoid this phenomenon and potentially extend battery life [18].

Current aDBS systems are based on constant voltage (CV) devices. Recently, constant-current (CC) stimulation instead of CV has been used in PD [98], ET [99], and dystonia [100] on the theoretical basis that CC stimulation might be more reliable and effective than CV stimulation. Although there is some evidence that the percentage of corticofugal axon activation is greater with CC stimulation compared to CV in acute DBS settings [101], the full clinical advantage remains unclear.

5.2. Pulse width

Pulse width contributes to TEED in a direct and linear fashion. However, its relationship with DBS benefits and adverse effects is much less intuitive than that for amplitude, and as such, proportional approaches may not be as suitable for pulse width. It is known that pulse width has an important relationship with chronaxie and thus with neural activation. Wider pulse widths decrease the precision in reaching neuronal targets, as exemplified by stimulating large myelinated axons and inducing more adverse effects [102]. Pulse width is usually narrow (60 μs) in STN DBS to obtain a clinical benefit. However, it can be wider in thalamic (ventral intermediate nucleus) DBS [94] and globus pallidus internus (GPi) DBS, especially in dystonia patients (table 1) [93]. Recent studies support the use of pulse widths <60 μs to improve the therapeutic window and reduce stimulation-induced adverse effects such as dysarthria and gait ataxia (table 1) [103, 104]. A

Table 1. Therapeutic DBS settings and associated stimulation-related adverse effects for Parkinson's disease, essential tremor, and dystonia.

	Symptom/ adverse effect	Effective parameter range			Neurosignal-related biomarker
		Amplitude ($V\ mA^{-1}$)	Pulse width (μs)	Frequency (Hz)	
Symptoms					
Parkinson's disease	Bradykinesia and rigidity	1.5–3.5 (STN, GPi)	60–90 (STN, GPi)	100–185 for tremor (STN, GPi, VIM) and for tremor and bradykinesia (STN, GPi)	Beta (∼20 Hz) activity (STN, GPi) [38, 54, 106]
Essential tremor	Action tremor	1.5–4.0 (VIM)	60–90 (VIM)	130–185 (VIM)	Beta (∼20 Hz) activity (cortex) [107, 108]
Dystonia	Tonic and phasic movements	1.5–4.0 (STN, GPi)	60–450 (STN, GPi)	40–185 (STN, GPi)	Alpha (∼4-12 Hz) and Theta (∼13–30 Hz) bands activity (GPi) [108, 109]
Adverse effects					
Parkinson's disease	Dysarthria	Variable, according to the other parameter changes (STN, GPi)	<60 (STN)	—	—
	Dyskinesia	Variable, according to the other parameter changes (STN, GPi)	—	—	Gamma (∼70 Hz) activity (cortex) [40]
	Capsular effects	Variable, according to the other parameter changes (STN, GPi)	—	—	—
	FOG	—	—	60–80 for FOG and gait issues (STN); 20–80 Hz for FOG and falls (PPN)	—
Essential tremor	Dysarthria	Variable, according to the other parameter changes (VIM)	<60 (VIM)	Variable, according to the other parameter changes (VIM)	—
	Ataxia	Variable, according to the other parameter changes (VIM)	<60 (VIM)	Variable, according to the other parameter changes (VIM)	—
Dystonia	Dysarthria	Variable, according to the other parameters change (STN, GPi)	Variable (GPi)	—	—
	Capsular effects	Variable, according to the other parameters change (STN, GPi)	Variable (GPi)	—	—
	Bradykinesia	—	—	<100 Hz (GPi)	—
	FOG	—	—	<100 Hz (GPi)	—

FOG, freezing of gait; GPi, globus pallidus internus; PPN, pedunculopontine nucleus; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus.

narrower pulse width could also reduce maladaptive plasticity in dystonia [105].

5.3. Frequency

Similar to pulse width, frequency provides a linear contribution to TEED. However, the effects of frequency on a patient's state are nonlinear. Therefore, FMs may be more suitable for digital strategies (e.g. different frequencies set for different states) than proportional strategies. Traditionally, the frequency necessary to improve tremor is >100 Hz [94, 110] and >50 Hz for bradykinesia [92, 111], whereas the effects of frequency on dystonia are more variable (therapeutic range is from 40 to 185 Hz) (table 1) [112–114]. Nevertheless, high-frequency stimulation is energy-consuming, and chronic high-frequency stimulation of the STN and GPi might induce FOG and speech impairment (table 1) [4, 5, 115]. The use of lower frequencies (20–80 Hz) has also been shown to be beneficial in pedunculopontine nucleus

stimulation to improve FOG and falls in some PD patients [116]. Furthermore, a recent pilot study demonstrated that simultaneous low-frequency stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the STN improved levodopa-unresponsive gait freezing in PD [117]. Although the exact mechanisms of FM on cortical and subcortical activities remain largely unknown, a frequency-based adaptive system is attractive given the variable effects of frequency according to brain target and disorder.

5.4. Nonconventional stimulation settings

Novel stimulation strategies such as narrow and biphasic pulses that create new DBS waveforms have shown potential advantages compared to standard parameters in PD, ET [118, 119], and dystonia [86] patients tested in acute settings. Similarly, polarity reversal from conventional monopolar cathodic to anodic stimulation might be superior in improving off-motor period symptoms compared to standard stimulation in PD patients with STN DBS [120].

More recently, new theoretical models are emerging to tailor the stimulation patterns according to temporal characteristics of pathological neural oscillations in a closed-loop fashion to disrupt the abnormal signal synchrony (phase-specific DBS) [84, 121]. This strategy seems to be effective in acutely suppressing tremor in ET [85]. The CR is another theoretical approach with good preliminary results in PD [122]. A similar strategy called phasic-burst stimulation has also been used by applying a burst of stimulus pulses over a range of predicted phases. This approach is superior to a single phasic stimulus pulse in suppressing pathological oscillations in ET and dystonic tremor [85]. Although encouraging, acute results of nonconventional stimulation approaches need to be confirmed in larger clinical trials and over a longer period of time. Furthermore, the value of new programming paradigms needs to be established with regard to treatment efficacy and improving ease of DBS programming and management. Undoubtedly, several electrical stimulation parameters other than amplitude might be useful in aDBS to enhance therapeutic outcomes, reduce stimulation-induced adverse effects, and lengthen battery life.

6. aDBS future challenges

One of the main advantages of implanting aDBS systems is recording brain signals while delivering electrical stimulation, representing a 'totally implantable bidirectional neural prosthesis' [123]. Given the magnitude of potential data, it is imperative to develop effective strategies to manage, store, and analyse such data and integrate it with relevant clinical information [124]. Proprietary cloud solutions could be used to transfer data from IPGs through, for instance, mobile applications. However, the use of informatics standards (e.g. HL7 FHIR) to represent information will be necessary to allow confidential data sharing. The cybersecurity threat of misusing and controlling another person's implants (known as brainjacking) [125] must also be considered. Other factors that may need to be resolved include limited data storage, bandwidth, and increased battery consumption due to constant communication between the IPG and the sensing technology.

Continued research is necessary to optimize the use of aDBS and overcome current limitations, such as the need for pre-defined thresholds or reference values of the control variable. Moreover, disease progression likely requires that the selected biomarker and/or control variable threshold changes, limiting the ability of aDBS to follow the patient's state. However, this challenge can be overcome using self-adapting algorithms, likely based on machine learning techniques, which may understand the biomarker's dynamic.

We can expect that advances in adaptive stimulation technologies will focus on using more personalized biofeedback signals that are fine-tuned to target specific symptoms and the delivery of stimulation based on the adaptation of a wide range of parameters. Overall, aDBS will improve therapeutic outcomes while reducing stimulation-induced adverse effects.

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Data availability statement

No new data were created or analysed in this study.

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Declaration of interest

M G, I E H, A L, and S Me declare no conflict of interest. A M L and J V are consultants for Medtronic, Boston Scientific, Abbott, and Newronika. E M is a consultant for Abbott, Medtronic, and Newronika. G F, S M, and A P are founders and shareholders of Newronika Spa.

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