Brain Stimulation 14 (2021) 1238–1247

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Clinical perspectives of adaptive deep brain stimulation

Matteo Guidetti [a, b], Sara Marceglia [c], Aaron Loh [d, e], Irene E. Harmsen [d, e], Sara Meoni [a, f, g], Guglielmo Foffani [h, i], Andres M. Lozano [d, e], Elena Moro [f, g], Jens Volkmann [j], Alberto Priori [a, k, *]

[a] Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, Via Antonio di Rudinì, 8, 20142, Milan, Italy
[b] Department of Electronics, Information and Bioengineering, Politecnico di Milano, Piazza Leonardo da Vinci, 32, 20133, Milan, Italy
[c] Department of Engineering and Architecture, University of Trieste, 34127, Trieste, Italy
[d] Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada
[e] Krembil Research Institute, University Health Network, Toronto, Ontario, Canada
[f] Movement Disorders Unit, Division of Neurology, CHU Grenoble Alpes, Grenoble, France
[g] Grenoble Institute of Neurosciences, INSERM U1216, University Grenoble Alpes, Grenoble, France
[h] HM CINAC (Centro Integral de Neurociencias Abarca Campal), Hospital Universitario HM Puerta del Sur, HM Hospitales, Madrid, Spain
[i] Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain
[j] Department of Neurology, University of Wurzburg, Germany
[k] ASST Santi Paolo e Carlo, Milan, Italy

ARTICLE INFO

Article history:
Received 8 December 2020
Received in revised form
1 June 2021
Accepted 31 July 2021
Available online 8 August 2021

Keywords:
Deep brain stimulation
Closed-loop
Neuromodulation
Local field potentials
Movement disorders

ABSTRACT

Background: The application of stimulators implanted directly over deep brain structures (i.e., deep brain stimulation, DBS) was developed in the late 1980s and has since become a mainstream option to treat several neurological conditions. Conventional DBS involves the continuous stimulation of the target structure, which is an approach that cannot adapt to patients' changing symptoms or functional status in real-time. At the beginning of 2000, a more sophisticated form of stimulation was conceived to overcome these limitations. Adaptive deep brain stimulation (aDBS) employs on-demand, contingency-based stimulation to stimulate only when needed. So far, aDBS has been tested in several pathological conditions in animal and human models.

Objective: To review the current findings obtained from application of aDBS to animal and human models that highlights effects on motor, cognitive and psychiatric behaviors.

Findings: while aDBS has shown promising results in the treatment of Parkinson's disease and essential tremor, the possibility of its use in less common DBS indications, such as cognitive and psychiatric disorders (Alzheimer's disease, obsessive-compulsive disorder, post-traumatic stress disorder) is still challenging.

Conclusions: While aDBS seems to be effective to treat movement disorders (Parkinson's disease and essential tremor), its role in cognitive and psychiatric disorders is to be determined, although neurophysiological assumptions are promising.

1. Introduction

Deep brain stimulation (DBS) is an important form of neuromodulation that involves the electrical stimulation of specific brain structures to modulate dysregulated neural circuitry. Over the last three decades, DBS has become a mainstream surgical procedure for the treatment of movement disorders such as Parkinson's disease and essential tremor [1,2]. Increasingly, DBS is being applied to a range of motor, mood, or cognitive circuit disorders [3]. DBS systems are programmed to deliver the ideal amount of energy to

* Corresponding author. Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, via Antonio di Rudinì, 8, 20142 Milan, Italy.
E-mail addresses: matteo.guidetti@unimi.it (M. Guidetti), smarceglia@units.it (S. Marceglia), aaron.loh@mail.utoronto.ca (A. Loh), irene.harmsen@mail.utoronto.ca (I.E. Harmsen), smeoni@chu-grenoble.fr (S. Meoni), gfoffani.hmcinac@hmhospitales.com (G. Foffani), andres.lozano@uhnresearch.ca (A.M. Lozano), emoro@chu-grenoble.fr (E. Moro), volkmann_j@ukw.de (J. Volkmann), alberto.priori@unimi.it (A. Priori).

https://doi.org/10.1016/j.brs.2021.07.063

the brain to achieve symptom relief. Currently, conventional DBS (cDBS) settings employ constant, uninterrupted stimulation that is independent of functional status and need. Associated disadvantages of chronic stimulation include stimulation-induced adverse effects and increased battery consumption. For example, the constant stimulation of the subthalamic nucleus (STN) in Parkinson's disease (PD) has been associated with speech impairments and increased risk of falls [4–6]. At least, in theory, stimulation should be delivered only when needed. This on-demand or contingency-based stimulation would be active intermittently (in an "adaptive mode") to optimize current delivery and improve therapeutic outcomes while reducing adverse effects. Comparable to cardiac pacemakers, adaptive DBS (aDBS) relies on feedback variables (e.g., brain signals) that correlate to a patient's clinical state to determine the amount of stimulation that is to be delivered at a certain point in time. Historically, aDBS was driven by cDBS adoption and started being implemented and tested in movement disorders, particularly PD and Essential Tremor (ET), that represent the indications with higher level of application and knowledge, whereas cognitive and psychiatric disorders, despite being promising, still remain a future challenge (Fig. 1). In addition, aDBS is applicable also to non-conventional stimulation approaches (Fig. 1) most of which were conceived and simulated as intrinsically closed loop, even though not tested yet in patients. Here we will review current preclinical and clinical data on aDBS in movement disorders, and, in order to provide a full perspective on aDBS, we will provide insights on the hypotheses grounding its adoption in cognitive and psychiatric disorders.

2. aDBS technology

Considering the current DBS clinical practice, the concept of aDBS is based on a closed-loop model in which the feedback variable, representing the clinical state of the patient, is measured and processed to automatically optimize the stimulation parameters to treat the current condition and symptoms [7]. This closed-loop model of aDBS is based on three conceptual modules, that are usually implemented in three different technological components: (1) a *sensing module* that measures the feedback variable, (2) a *control module* that processes the feedback variable to extract biomarkers and updates stimulation parameters using specific control algorithms, and (3) a *stimulation module* that delivers stimulation to the brain.

The sensing module, being mostly represented by the hardware necessary to measure the chosen feedback signal, depends on the timing required for sensing. If the patient requires continuous stimulation, sensing must also be performed when stimulation is ON, but this requires artifact rejection strategies [8–10]. Artifact rejection can be done either via hardware [9] or software [10]. 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, therefore, the sensing block does not need any artifact rejection technology. The sensing module captures the feedback variable (i.e., a reliable signal that can be used to control stimulation). To date, the two neurosignals that have been tested the most are local field potentials (LFPs) recorded directly from the implanted DBS electrodes in the target, and electrocorticography (ECoG) signals recorded from cortical strips implanted in the cortex. Both types of neurosignals have the advantage of being captured through implanted sensors and have both been shown to correlate to patients' motor state in different pathologies (e.g., PD, dystonia, Tourette syndrome) [7,11–13]. Other possible feedback variables include neurochemicals (e.g. dopamine fluctuations) [14], surface electromyographic signals [15] or recordings from wearable accelerometers [16].

The control module includes two functional building blocks, one dedicated to biomarker extraction from the feedback signal, and one dedicated to the calculation of the stimulation parameters. Biomarker extraction consists of signal processing algorithms and data analysis, including for example filtering, pattern detection, and so on. After biomarker extraction, the control can be implemented according to three distinguishable major strategies: (1) ON/OFF responsive mode, (2) state machine, and (3) adaptive mode. In ON/OFF mode, the control block switches the stimulation from OFF to ON according to the patient's need as estimated from the calculated biomarker ("on-demand" stimulation [17–21]). State machine means the control block has several possible "states" or configurations (e.g., the patient is moving, sleeping, has dyskinesias, etc.),

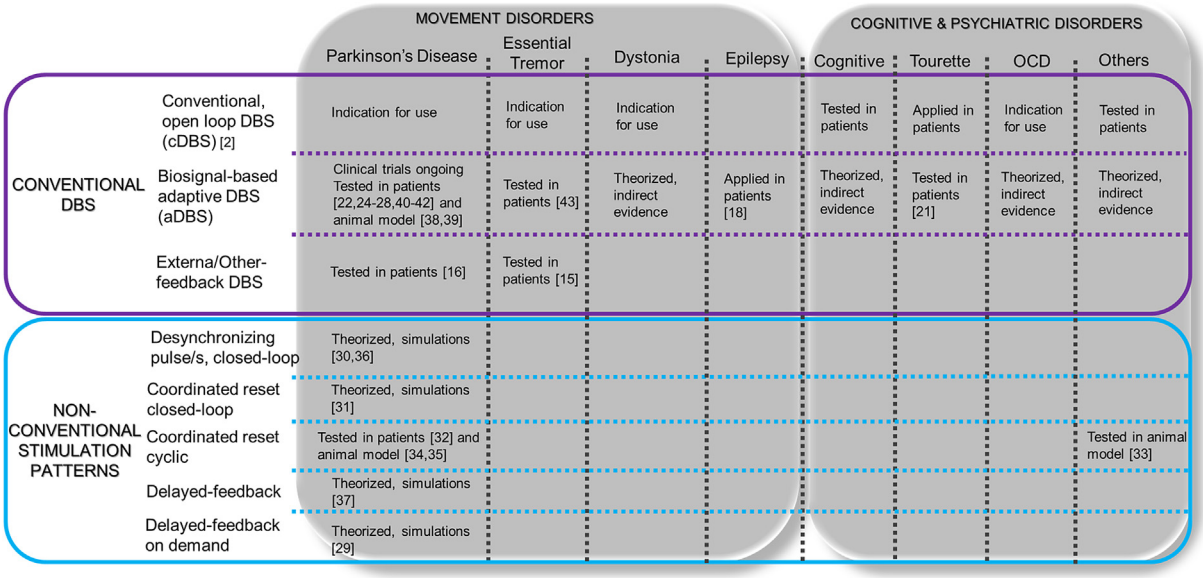

Fig. 1. Graphical representation of current DBS stimulation protocols and applications. DBS = deep brain stimulation; cDBS = conventional deep brain stimulation; aDBS = adaptive deep brain stimulation; OCD = obsessive-compulsive disorder.

in which the optimal "state" is selected by a classification algorithm based on the calculated biomarker [22]. Lastly, the adaptive mode means the control module continuously follows the dynamic of the biomarker and determines the stimulation parameters accordingly. This approach requires a closed-loop algorithm that correlates the biomarker of the patient's state and the stimulation output [23–25].

The stimulation module is already commonplace as it is embedded in most cDBS implanted pulse generators (IPGs). In principle, all possible stimulation parameters can be adapted, including amplitude, frequency, and pulse width. However, possibilities of the stimulation block may be limited in practice by software or hardware constraints (e.g., IPGs are unable to stimulate at pulse widths of <10 μs). In aDBS applications, the stimulus waveform can be either the classical biphasic, charge balanced, asymmetric waveform [22,24,26–28], or it can be more complex. For instance, different theoretical stimulation patterns - e.g., single desynchronizing pulse administered with a specific phase [29], pair of pulses, the first aimed to synchronize and reset and the second aimed to desynchronize [30], multi-site coordinated high-frequency pulse trains delivered in different sites at different times (coordinated reset stimulation, CRS [31–35]), linear or nonlinear delayed feedback [29,36,37] – were all originally modelled to be administered when LFP signals, as representative of the degree of synchronicity of a neuronal population, and can be also applied using an on-demand ON/OFF approach [29].

aDBS technology was initially exploited in external devices [23,27] that allowed to test the concept in preclinical and clinical studies especially in movement disorders (see Section 3). The only available implantable device implementing aDBS is the RNS Neuropace used in epilepsy [18], and tested in Tourette Syndrome [21], both not requiring artifact rejection. To date, there are two commercial devices (CE-marked) providing LFP sensing during stimulation, but their application as aDBS devices still requires clinical investigation.

3. Available data in movement disorders

3.1. Models and studies in animals

The first in-vivo experiment [38] on aDBS technology ("adaptive" mode) was conducted by comparing its effects with cDBS in a primate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model (MPTP model) of PD. Closed-loop stimulation was delivered to the globus pallidus internus (GPi) and was driven by neuronal activity in the primary motor cortex (M1) or GPi itself. In this experiment, aDBS was more clinically effective, resulting in the improvement of akinesia by about one third compared to conventional open-loop stimulation. From a neurophysiological viewpoint, aDBS reduced abnormal cortico-basal ganglia discharge rates and modulated the oscillatory activity of pallidal neurons, considerably more than cDBS (see Table 1).

In 2017, the clinical results from LFP beta-based, ON-OFF system aDBS were compared with conventional and sham DBS in the STN of MPTP monkeys [39]. With regards to sham stimulation, both aDBS and cDBS significantly reduced rigidity scores; however, no difference in effect was observed between the two active stimulation paradigms. This suggests that adaptive systems may not achieve superior improvement in motor control over conventional DBS, a finding similarly observed in humans (see Table 1).

3.2. Studies and clinical effects in patients

Several papers report the clinical application of aDBS on human subjects with movement disorders such as PD and ET. For this review on the clinical data in humans, we only included studies reporting quantitative clinical outcomes and followed an historical perspective (see Table 1).

The first report on aDBS guided by external feedback variables for ET considers four patients with bilateral aDBS of the thalamic nucleus ventralis intermedius (Vim) and nucleus ventralis oralis posterior (Vop) [15]. Stimulation was controlled in ON/OFF responsive mode by electromyography (EMG) activity recorded from the deltoid muscle. The authors reported that aDBS significantly reduced intention tremor. Despite the absence of a control condition (i.e., cDBS), this report highlights the possible importance of EMG-controlled on-demand approaches in ET. However, the feasibility of EMG-controlled aDBS in the clinical practice remains to be demonstrated.

A similar approach was repeated then with five tremor-dominant PD patients [16]. An aDBS system that was controlled in "adaptive" mode by the power of resting tremor, as measured using a wearable watch, was used. Results showed that tremor was suppressed by up to one third during aDBS, but whether these effects on tremor were superior to cDBS was not established.

In PD, the first report of LFP-based aDBS in humans was published in 2013 [27]. The authors compared the effects of DBS (ON/OFF mode) driven by unilateral beta LFP activity and cDBS of the STN in a group of eight patients with advanced PD. Although both DBS and cDBS improved UPDRS (subscore items 20, 22, 23), the benefit of aDBS was significantly higher by 20–30 %. Though this study was the first to report the benefit of on-demand approaches over cDBS, it was limited by a short observation period (10 min of stimulation). Moreover, a full evaluation of the motor effects on activities of daily living was not feasible since subjects were restrained by the experimental setup near the brain-computer interface.

Some of these limitations were addressed when a STN-implanted freely moving PD patient was stimulated using a portable aDBS device controlled by LFP beta power [25]. In this case the continuous "adaptive" mode was used. A 2-h stimulation paradigm showed that the clinical effect of aDBS was superior to that of cDBS in reducing levodopa-induced dyskinesia by almost 50 %. Despite the limitations of a single-case report, this study corroborated and expanded upon the findings from Little et al. [27] by reporting the feasibility and efficacy of adaptive DBS (compared to cDBS) for a longer assessment period (2 h) and in a freely moving patient.

Two subsequent studies [28,40] tested the use of bilateral on-demand ON/OFF aDBS in PD patients. The first [40] demonstrated that aDBS was significantly better than cDBS in terms of motor symptom improvement and speech intelligibility (more than 10 %). In the second [28], the authors studied the effects of bilateral aDBS and its interaction with levodopa in four patients in a more real-world environment to assess gait and PD-related axial symptoms. Their findings, obtained with bilateral STN aDBS, were consistent with their previous reports [40] describing only unilateral STN stimulation.

Aiming to estimate the clinical feasibility, tolerability, and side-effects of aDBS and its possible use in day-to-day life by patients, two studies assessed the effect of aDBS, controlled by the continuously "adaptive" mode, in an real-world setting and for longer periods of time [24,26]. Rosa et al. [24] studied the interaction between unilateral STN aDBS controlled by LFP beta oscillatory activity and levodopa treatment in ten freely moving PD patients for 2 h, while Arlotti et al. [26] studied eleven patients for 8 h. In the former study, adaptive and conventional DBS provided a similar therapeutic effect on motor scores, but aDBS better controlled levodopa-induced dyskinesia with a significantly lower (more than 70 % less) amount of energy delivered to the tissue. In the second

Table 1
aDBS studies in movement disorders.

Study	Sample size (N)	Adaptive strategy	Device	Type of sensing	Improvement in UPDRS – motor section	Other findings
Animal studies						
Rosin et al., 2011 [38]	2 monkeys (MPTP model of PD)	continuous adaptive strategy	IPG	action potential recorded either from the GPi or M1	aDBS induced significant improvement compared to no stimulation, but one third greater improvement compared to cDBS (although not significant)	.
Johnson et al., 2017 [39]	1 monkey (MPTP model of PD)	threshold ON-OFF system	IPG	STN LFPs - β band power	aDBS and cDBS had similar results in reducing rigidity; cDBS induced significant improvement in total movement time in reaching task compared to no stimulation	aDBS did not elicit serious side effects; average power saving was significantly less in aDBS than cDBS
Clinical studies						
Yamamoto et al., 2013 [15]	4 patients with bilateral ET	on-demand control system (threshold ON-OFF)	IPG	EMG – tremor frequency power (3 Hz)	.	aDBS significantly reduced ETRS items 5 and 6 to 0 (3.75 ± 0.46 in no stimulation) and ETRS items 11 and 14 to 1.5 ± 0.53 (11.75 ± 0.45 in no stimulation)
Little et al., 2013 [27]	8 PD patients with motor fluctuations/ dyskinesias	ON/OFF strategy	IPG	STN LFPs - β band power	aDBS induced a reduction of 66.2 % (unblinded assessment) and 49.7 % (blinded assessment); Improvement in aDBS condition compared to cDBS was 28.7 ± 10.6 % ($p = 0.03$) for unblinded assessment, 27 ± 7.8 % ($p = 0.005$) for blinded assessment	Mean total electrical energy delivered by aDBS was significantly less than cDBS
Rosa et al., 2015 [25]	1 PD patient	continuous adaptive strategy	IPG	STN LFPs - β band power	Assessment at 120 min showed that improvements in axial symptoms were similar in aDBS and cDBS conditions, but dyskinesias during gait were reduced more during aDBS than during cDBS; aDBS induced more improvement in bradykinesia than DBS ($p < 0.05$)	.
Malekmohammadi et al., 2016 [16]	5 PD patients	On-demand aDBS (ON/OFF strategy)	IPG	wearable watch - tremor frequency power (4–8 Hz)	.	Tremor in aDBS condition was lower than baseline (−36.6 %; $p = 0.014$). aDBS voltage was two-thirds lower than the one used in clinical cDBS and delivered by half the time.
Little, Tripoliti, et al., 2016 [40]	8 PD patient	threshold ON-OFF system	IPG	STN LFPs - β band power	Mean score in aDBS condition (19.7 ± 1.0) improved more compared to the one in cDBS condition (31.6 ± 4.3) ($p = 0.04$)	Stimulation in the aDBS condition was delivered almost half of the time. Speech intelligibility with aDBS was significantly higher (70.4 ± 6.4 %) than with cDBS (60.5 ± 8.2 %).
Little, Beudel, et al., 2016 [28]	4 PD patient	threshold ON-OFF system	IPG	STN LFPs - β band power	aDBS led to an average improvement of 43 % ($p = 0.04$); In aDBS condition, limb bradykinesia reduced by 37 ± 10 % and axial symptoms by 39 ± 5 %	Tremor, speech, facial expression and freezing items improved by 55 ± 12 % in aDBS condition. Mean total electrical energy delivered by aDBS (223 ± 31 mW) was less than cDBS would have delivered (491 ± 44 mW)
Rosa et al., 2017 [24]	10 PD patient	continuous adaptive strategy	external wearable prototype	STN LFPs - β band power	Levodopa + stimulation condition induced similar improvement regardless of the type of DBS (−46.1 ± 10.5 % with aDBS; −40.1 ± 17.5 % with cDBS)	Average power saving of 73.6 % ± 22.9 % in aDBS compared with cDBS; In levodopa + stimulation condition, aDBS (11.7 ± 67) was more effective on dyskinesias than cDBS (15 ± 8.7) ($p = 0.02$); No serious side effects were detected
Arlotti et al., 2018 [26]	11 PD patient	continuous adaptive strategy	Implanted electrodes	STN LFPs - β band power	aDBS/OFF levodopa condition led to significant improvement by almost 30 % (22.2 ± 3.3 vs 30.5 ± 3.4; $p = 0.003$). Cumulative effect of aDBS and levodopa provided a 45 % improvement, comparable to that elicited by levodopa alone (15.5 ± 2.3 vs 30.5 ± 3.4; $p = 0.4$).	No serious side effects were detected levodopa + aDBS condition did not elicit dyskinesias
Swann et al., 2018 [22]	2 PD patient	BCI-controlled aDBS (state machine strategy)	IPG	ECoG - cortical narrowband gamma (60–90 Hz) oscillation	.	video-recorded clinical ratings suggested no motor improvements
Velisar et al., 2019 [41]	13 PD patient	threshold ON-OFF system	IPG + external portable computing device.	STN LFPs - β band power	68 % mean improvement from NclDBS alone (off medication) after six months. NclDBS improved bradykinesia and tremor (Vrms: $p < 0.003$; average cycle frequency: $p < 0.001$);	Neural closed-loop DBS was safe and tolerated

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size (N)	Adaptive strategy	Device	Type of sensing	Improvement in UPDRS – motor section	Other findings
Arlotti et al., 2019 [42]	1 PD patient	continuous adaptive strategy	IPG	STN LFPs - β band power	Tremor was below 0.15 rad/s (threshold visually observed) for 95.4 % of the trial stable improvement ranging between 30 % and 37 % throughout the study	No adverse events
Opri et al., 2020 [43]	3 ET patients	On-demand aDBS (ON/OFF strategy)	IPG	LFOs recorded from M1 hand motor region and VIM (contralateral to the most affected hand)	Total body TRS score improved by 33.8 % ± 17.8 % (cDBS vs DBS OFF) and 32.7 % ± 12.7 % (aDBS vs DBS OFF). No difference, but equivalence in clinical efficacy between cDBS and aDBS. Tremor amplitude percent decrease of 42.8 % ± 23.6 % (cDBS vs DBS OFF) and 44.4 % ± 16.3 % (aDBS vs DBS OFF). No difference in tremor amplitude between cDBS and aDBS.	aDBS energy expenditure was more than 50 % less than cDBS

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD = Parkinson's disease; IPG = implanted impulse generator; GPi = globus pallidus internus; M1 = primary motor cortex; STN = subthalamic nucleus; LFPs = local field potentials; cDBS = continuous deep brain stimulation; mUPDRS = Modified Unified Parkinson's Disease Rating Scale; ET = essential tremor; EMG = electromyography; ETRS = Essential Tremor Rating Scale; BCI = brain computer interface; aDBS = adaptive deep brain stimulation; ECoG = electrocorticography; Vrms = root-mean-square voltage; NclDBS = neural closed-loop deep brain stimulation; LFOs = low-frequency oscillations; VIM = ventralis intermediate nucleus; TRS = Fahn-Tolosa-Marin Tremor Rating Scale.

study, patients were studied for 8 h over two consecutive days, one with only LFP sensing and levodopa administration, and the other one with aDBS and routine levodopa administration, with the patients performing their daily activities in the hospital. Most striking was the direct evidence that throughout the 8-h experimental session, the beta band power significantly correlated with the clinical condition of the patient. Further, aDBS was safe and well-tolerated during normal daily activities and in conjunction with dopaminergic medication. These results represent Class IV evidence of safety, tolerability, and effectiveness of aDBS in controlling advanced PD motor symptoms, which paves the way for clinical-oriented aDBS devices.

In PD patients, the approach of aDBS controlled by EcoG was reported as well [22]. DBS amplitude was controlled using a “state” approach. The results aligned with many of the previous findings with STN LFP-based aDBS; they showed that aDBS used less total energy than cDBS, and aDBS and cDBS elicited similar motor improvements. Despite the important limitations arising from a single patient study and the need to implant an additional sensing electrode in the skull (with the related surgical risks), the work suggests the feasibility of an electrocorticographic-controlled aDBS algorithm.

Other two studies have examined the effects of chronic stimulation with LFP-based aDBS [41,42], with both the systems under continuous control in “adaptive mode”. In the first study [41], the authors tested the effect of bilateral STN aDBS in 13 freely moving PD patients after an average of 22 months of aDBS. Although the individual clinical data during aDBS are not clearly reported, the authors concluded that aDBS was more energy-efficient than cDBS, using only 55 % of energy, supporting the findings of previous studies. Similarly, the other experiment [42] reported STN-LFP recordings during aDBS in chronically implanted akinetic-rigid PD patients over two days with the patient free to perform activities of daily living. The feasibility of the approach as well as the possibility to detect specific LFP-based biomarkers for sleep was demonstrated. Lately, Opri et al. [43] demonstrates the feasibility of a fully embedded closed-loop system for 3 ET patients both in-clinic and at-home environments. cDBS and aDBS in on-demand mode (ON/OFF strategy), compared with OFF-DBS, resulted in an improvement of about one third in tremor suppression during movements, as suggested by clinical score (Fahn-Tolosa-Marin Tremor Rating Scale) and quantitative assessment (accelerometer). Moreover, aDBS energy expenditure was 57.98 % ± 14.12 % (during the clinic testing), and 50.15 % ± 11.47 % (while at home) less than cDBS. In this study, Vim contralateral to the most affected hand was stimulated, with electrodes driven by low-frequency oscillations (LFOs) of M1 hand motor region ipsilateral to Vim.

Taken together, these results suggest that aDBS could be effective in treating motor symptoms of ET and PD, with considerable saving of energy delivery compared to cDBS. Still, confirmations are needed, and technical issues might undermine a more general application.

3.3. Open issues and current limitations

Despite the encouraging results, aDBS for movement disorders is still not a reality. In fact, there are no commercial devices able to deliver chronic neurosignal-based aDBS. Apart from external devices (commercial or custom-based) only the Medtronic Activa PC + S allowed implementing an external or embedded closed loop DBS for research purposes. There are now available two IPGs that received CE-mark to deliver DBS with sensing capabilities (Medtronic Percept and Newronika AlphaDBSipg), but they cannot unlock aDBS modes, except for the use in clinical trials.

Apart from this technological drawback that will be likely solved in the near future, the aDBS concept is not yet robust enough. In fact, the traditional STN-LFP beta band used to drive the adaptive stimulation [44,45] presents some limitations [46,47]: it might be inconsistent among patients [47,48], especially considering different phenotypes [49], and may not represent sufficiently well the clinical scores [50,51]. In addition, when different symptoms occur, the interactions between different brain rhythms have to be considered [46,51]. Therefore, it has been suggested that LFP power alone might not provide a biomarker for aDBS [39]. More recently some other oscillations (e.g., low frequencies - 2–7 Hz, or high gamma band - 70–90 Hz) have been proposed as promising alternative feedback control biomarker [22,52–54]. Several findings also suggested that local oscillations might be too reductive in representing the highly complex scenario of cortical-subcortical circuits in PD, to the detriment of the patients' clinical situation [55–57]. The use of beta bursts, for instance, capturing their length and amplitude may better represent bradykinesia and rigidity [58]. Another approach, i.e., considering the network dynamics as feedback so that DBS could help normalizing the network activity or suppressing impaired circuit, have been proposed [59], but still no conclusive results have been reached.

In summary, despite the first clinical steps have been taken, there are some aspects to be faced to move to aDBS as established treatment for movement disorders. Future technological strategies need to focus on overcoming such technical issues (and better characterize clinical status).

4. Perspective on cognitive and psychiatric disorders

Cognitive and psychiatric disorders are increasingly addressed using neuromodulation and DBS. To date, trials have employed continuous stimulation in the same manner that DBS has been used for traditional indications (PD an ET) [60,61]. However, the use of continuous stimulation does not account for the episodic nature of some neuropsychiatric disorders, nor does it account for the complex physiological processes that underlie cognitive functions such as memory. The immediacy of aDBS strategy could fit well in these contexts, and several preliminary findings support, at least theoretically, its feasibility. The maturity of aDBS in movement disorders is consequent to the large adoption of cDBS that allowed both to study the neurophysiology underlying the disease and to hypothesize preliminary biomarkers. Indeed, although no human clinical data is currently available, neurophysiological studies suggest a great potentiality for aDBS in cognitive and psychiatric disorders.

4.1. Cognitive disorders

The advantages of DBS over lesioning and pharmacotherapy are that its effects are often instantaneous, titratable, and reversible. These advantages mean that DBS can be applied with temporal specificity. This is particularly pertinent as many cognitive processes, such as memory, are dynamic and multi-phasic. As a result, stimulation may have variable effects depending on when it is employed in the context of a cognitive process. Within the cognitive domain, the modulation of memory is of particular interest and clinical relevance. Mnestic function can be broadly divided into three sub-processes, which could present distinct targets for modulation: encoding, consolidation, and retrieval [62].

Hippocampal sharp-wave ripples (SPW-Rs) are neuro-oscillatory phenomena that are implicated in the consolidation stage of memory. Disruption of SPW-Rs has been shown to impair consolidation and memory performance [63], while the prolongation of SPW-Rs improved memory in rats during maze learning [64]. Crucially, SPW-Rs prolongation or disruption is contingent on where stimulation is applied in the ripple waveform (i.e., when stimulation is applied). Similarly, the need for precisely timed stimulation in order to enhance performance in encoding and retrieval preferentially was demonstrated [65]; stimulation in the mouse hippocampus at the peak of theta oscillations enhanced performance during encoding, while stimulation at the trough of theta oscillations enhanced retrieval performance [65]. The site of stimulation within the hippocampal theta waveform is also important in contributing to neuronal plasticity [65]. Moreover, stimulation in the CA1 region at the peak of theta oscillations preferentially induced long-term potentiation (LTP) – a persistent increase in synaptic strength – whereas stimulation at the trough of theta induced long-term depression (LTD, i.e., a persistent decrease in synaptic strength) [66].

In 2017, different brain states that were more (high encoding efficiency) or less (low encoding efficiency) amenable to memory encoding were identified [67]. Epilepsy patients who received stimulation in states of low encoding efficiency demonstrated relatively improved encoding, while encoding was impaired when stimulation was delivered during states of high encoding efficiency. These findings were further employed in the development of a closed-loop system, which stimulated the lateral temporal cortex when states of low encoding efficiency were detected [68]. Stimulation in this manner was associated with an increase in neural correlates of memory enhancement, along with improved performance in a free recall task. Taken together, these findings highlight the importance of well-timed stimulation in the modulation of cognitive processes.

4.2. Psychiatric disorders

For neuropsychiatric diseases in which symptoms occur as discrete episodes – such as tics in Tourette syndrome, ruminations or rituals in obsessive-compulsive disorder (OCD), and 'reliving' episodes in post-traumatic stress disorder (PTSD) – DBS could be employed sporadically as an abortive therapy, rather than chronically. In such diseases, DBS could be configured so that the system would only stimulate at, or immediately before the onset of symptomatic episodes/symptoms through the detection of a reliable and discernible biomarker. This model has been successfully applied in the setting of epilepsy, in which focal epileptiform discharges are sensed and terminated before the onset of a global seizure [69].

4.2.1. Tourette syndrome

In Tourette's, the analysis of tic-related local field potentials (LFPs) has yielded promising results for a tic biomarker. Indeed, spontaneous tics were found to be preceded by repetitive and coherent thalamocortical discharges in a study of three patients with Tourette's [70]. These results were later corroborated by the presence of a similar activity immediately before tic onset when recording simultaneously from the thalamic centromedian-parafascicular complex and precentral gyrus [71]. Additionally, tic-associated oscillatory patterns have been reported from recordings in the GPi. This activity was also observed during Parkinsonian tremor, but not at rest or during voluntary movement, suggesting that it may be more broadly associated with general involuntary movement [72]. Building on these studies, the first aDBS system in a patient with Tourette's was developed and implanted [21]. DBS leads in the thalamic centromedian-parafasicular complex were programmed to detect tic-associated neuronal activity and stimulate accordingly, which ultimately resulted in similar treatment efficacy and a 63.5 % improvement in battery life when compared to cDBS.

4.2.2. OCD

LFP recordings have also yielded potential neuronal correlates for obsessions and compulsions in OCD. Perioperative recordings in the caudate nucleus demonstrated a higher frequency of neuronal firing and increased inter-spike variability in OCD patients with high obsession scores than in patients with low obsession scores [73]. Looking at neuronal activity associated with compulsions rather than obsessions, recordings in the bed nucleus of the stria terminalis (BNST) were analyzed in a rat model of OCD [74]. During compulsions, the authors found an increase in delta oscillations and a decrease in gamma oscillations, whereas beta oscillations increased following the cessation of compulsions.

4.2.3. PTSD

While there is undoubted promise in LFP biomarkers, less invasive avenues should also be pursued. To this end, a method of detecting emotion-related brain states by non-invasively measuring skin conductance was developed [75]. This technique may be of particular value in neuropsychiatric diseases such as PTSD, in which flashbacks and nightmares of previous trauma induce states of heightened arousal.

4.2.4. Treatment-resistant depression

Autonomic effects have also been assessed as biomarkers of post-operative response and efficacy of DBS for treatment-resistant depression (TRD). Since depressive symptoms generally do not occur in discrete episodes, reliable biomarkers of clinical efficacy are important to program aDBS systems. Two studies [76,77] found that tachycardia and increases in skin conductance observed intraoperatively correlate with accurate lead placement (as measured via tractography) and an improvement in symptoms. Upon examining neural-oscillatory changes with electroencephalography (EEG), it was found that frontal theta activity at 1-month post-DBS predicted clinical responses at 6-months post-DBS [78]. Similarly, LFP recordings from the subgenual cingulate cortex (SCC) in patients with major depression suggest that alpha activity in the limbic system may be a signature of symptom severity [79]. These quantifiable physiological changes could be employed in aDBS for TRD.

Ultimately, continuous stimulation may fail to employ DBS to its full potential. With a more considered and physiological approach to neuromodulation, including precise temporal and spatial delivery, there is significant scope to improve the efficacy and efficiency of DBS in the management of cognitive and psychiatric disorders.

5. Possible future development

With further development, aDBS technology, characterized by simultaneous recording and stimulation of brain structures, has the potential to improve clinical practice. Programming, which is one of the most challenging processes in a patient's management, could benefit from aDBS' ability to adjust DBS parameters according to a patient's state automatically, thereby enabling either fully automatic or partially supported programming procedures. In PD, knowledge of the localization capability of endogenous STN rhythms is extensive [80–83]. Appropriate algorithms or machine learning programs could be designed to scan the STN region through LFPs recorded from different electrode contacts, and then to select the most appropriate according to known LFP patterns. Additionally, LFP responses to different stimulation parameters could be automatically scanned and used to suggest the best configurations to the programming clinician, thus decreasing the burden associated with programming. These possibilities are particularly pertinent in the context of directional leads, which further increase the complexity of programming as they add more degrees of freedom to optimize settings. In addition, such a programming support system could be applied remotely using a patient's remote control and telemonitoring. This would reduce the need for frequent patient visits, increase the DBS center's catchment area, and provide full support in emergencies and situations that require social distancing.

Technological progress could also concern the driving biomarkers and the characteristics of stimulation. For example, since current biomarkers used for PD patients seems to be too simplistic to explain cortical-subcortical dynamics [59], future efforts should be focused on the ability to re-establish the physiological oscillatory pattern within the network [58,84]. Nonetheless, possible feedback variables currently under investigation include neurochemical signals [14,85] and external variables such as surface electromyography [15] or wearable accelerometers [16]. As for the neurochemicals, despite this field is still in its infancy and the evidence is quite weak, some promising results suggest the correlation with PD symptoms [86,87]; as for external sensors, despite being accurate in capturing symptoms such as tremor [11], dyskinesias [88], and freezing of gait [89], they are limited by their feasibility, since they require additional sensing equipment and they might induce social burden.

Since any stimulation parameter and pattern could be adapted in aDBS systems (at least theoretically), novel stimulation patterns (e.g., square biphasic pulse, phasic burst stimulation) could be studied to expand the therapeutic window and minimize stimulation-induced adverse effects [90–93]. For example, varying the pulse widths (<60 μs) has shown to improve clinical effects and reduce stimulation-induced adverse effects such as dysarthria and gait ataxia in essential tremor [94,95], or stimulation at different frequencies has improved levodopa unresponsive freezing of gait in PD patients [96].

In conclusion, a growing body of evidence suggests that aDBS may be incorporated in clinical practice in the near future, with the potential of bringing even more advances to the field of DBS. These evidences need to be further confirmed in large-scale clinical studies, that would allow to better understand clinical efficacy and limitations of aDBS.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author statement

Matteo Guidetti: Writing - Original Draft, Writing - Review & Editing, Visualization. **Sara Marceglia**: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Visualization. **Aaron Loh:** Writing - Original Draft, Writing - Review & Editing. **Irene E. Harmsen:** Writing - Original Draft, Writing - Review & Editing. **Sara Meoni:** Writing - Original Draft, Writing - Review & Editing. **Guglielmo Foffani:** Writing - Review & Editing. **Andres M. Lozano:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing. **Elena Moro:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing. **Jens Volkmann:** Conceptualization, Methodology. **Alberto Priori:** Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision.

Declaration of interest

M.G., I.H., A. L., 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.

Acknowledgement

Matteo Guidetti is a PhD student at Politecnico of Milano and is supported by the University of Milan, "Aldo Ravelli" research center.

References

[1] Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron 2013;77:406–24. https://doi.org/10.1016/j.neuron.2013.01.020.
[2] Roy HA, Green AL, Aziz TZ. State of the art: novel applications for deep brain stimulation. Neuromodulation 2018;21:126–34. https://doi.org/10.1111/ner.12604.
[3] Harmsen IE, Elias GJB, Beyn ME, Boutet A, Pancholi A, Germann J, et al. Clinical trials for deep brain stimulation: current state of affairs. Brain Stimul 2020;13:378–85. https://doi.org/10.1016/j.brs.2019.11.008.

[4] Moreau C, Defebvre L, Destée A, Bleuse S, Clement F, Blatt JL, et al. STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. Neurology 2008;71:80–4. https://doi.org/10.1212/01.wnl.0000303972.16279.46.
[5] Xie T, Padmanaban M, Bloom L, MacCracken E, Bertacchi B, Dachman A, et al. Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: a mini-review. Transl Neurodegener 2017;6:13. https://doi.org/10.1186/s40035-017-0083-7.
[6] Schrader C, Capelle HH, Kinfe TM, Blahak C, Bäzner H, Lütjens G, et al. GPi-DBS may induce a hypokinetic gait disorder with freezing of gait in patients with dystonia. Neurology 2011;77:483–8. https://doi.org/10.1212/WNL.0b013e318227b19e.
[7] Priori A, Foffani G, Rossi L, Marceglia S. Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. Exp Neurol 2013;245:77–86. https://doi.org/10.1016/j.expneurol.2012.09.013.
[8] Priori A, Foffani G, Rossi L. APPARATUS FOR TREATING NEUROLOGICAL DISORDERS BY MEANS OF CHRONIC ADAPTIVE BRAIN STIMULATION AS A FUNCTION OF LOCAL BIOPOTENTIALS. n.d.
[9] Rossi L, Foffani G, Marceglia S, Bracchi F, Barbieri S, Priori A. An electronic device for artefact suppression in human local field potential recordings during deep brain stimulation. J Neural Eng 2007;4:96–106. https://doi.org/10.1088/1741-2560/4/2/010.
[10] Stanslaski S, Herron J, Chouinard T, Bourget D, Isaacson B, Kremen V, et al. A chronically implantable neural coprocessor for investigating the treatment of neurological disorders. IEEE Trans Biomed Circuits Syst 2018;12:1230–45. https://doi.org/10.1109/TBCAS.2018.2880148.
[11] Basu I, Graupe D, Tuninetti D, Shukla P, Slavin KV, Metman LV, et al. Pathological tremor prediction using surface electromyogram and acceleration: potential use in "ON-OFF" demand driven deep brain stimulator design. J Neural Eng 2013;10. https://doi.org/10.1088/1741-2560/10/3/036019.
[12] Wang DD, Chen W, Starr PA, de Hemptinne C. Local field potentials and ECoG. Stereotact. Funct. Neurosurg. Cham: Springer International Publishing; 2020. p. 107–17. https://doi.org/10.1007/978-3-030-34906-6_9.
[13] Mitchell KT, Starr PA. Smart neuromodulation in movement disorders. Handb Clin Neurol 2020;168:153–61. https://doi.org/10.1016/B978-0-444-63934-9.00012-3. Elsevier B.V.
[14] Arlotti M, Rosa M, Marceglia S, Barbieri S, Priori A. The adaptive deep brain stimulation challenge. Park Relat Disord 2016;28:12–7. https://doi.org/10.1016/j.parkreldis.2016.03.020.
[15] Yamamoto T, Katayama Y, Ushiba J, Yoshino H, Obuchi T, Kobayashi K, et al. On-demand control system for deep brain stimulation for treatment of intention tremor. Neuromodulation 2013;16:230–5. https://doi.org/10.1111/j.1525-1403.2012.00521.x.
[16] Malekmohammadi M, Herron J, Velisar A, Blumenfeld Z, Trager MH, Chizeck HJ, et al. Kinematic adaptive deep brain stimulation for resting tremor in Parkinson's disease. Mov Disord 2016;31:426–8. https://doi.org/10.1002/mds.26482.
[17] Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295–304. https://doi.org/10.1212/WNL.0b013e3182302056.
[18] Heck CN, King Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia 2014;55:432–41. https://doi.org/10.1111/epi.12534.
[19] Rossi PJ, Opri E, Shute JB, Molina R, Bowers D, Ward H, et al. Scheduled, intermittent stimulation of the thalamus reduces tics in Tourette syndrome. Park Relat Disord 2016;29:35–41. https://doi.org/10.1016/j.parkreldis.2016.05.033.
[20] Okun MS, Foote KD, Wu SS, Ward HE, Bowers D, Rodriguez RL, et al. A trial of scheduled deep brain stimulation for tourette syndrome: moving away from continuous deep brain stimulation paradigms. Arch Neurol 2013;70:85–94. https://doi.org/10.1001/jamaneurol.2013.580.
[21] Molina R, Okun MS, Shute JB, Opri E, Rossi PJ, Martinez-Ramirez D, et al. Report of a patient undergoing chronic responsive deep brain stimulation for Tourette syndrome: proof of concept. J Neurosurg 2018;129:308–14. https://doi.org/10.3171/2017.6.JNS17626.
[22] Swann NC, de Hemptinne C, Thompson MC, Miocinovic S, Miller AM, Gilron ee, et al. Adaptive deep brain stimulation for Parkinson's disease using motor cortex sensing HHS Public Access. J Neural Eng 2018;15:46006. https://doi.org/10.1088/1741-2552/aabc9b.
[23] Arlotti M, Rossi L, Rosa M, Marceglia S, Priori A. An external portable device for adaptive deep brain stimulation (aDBS) clinical research in advanced Parkinson's Disease. Med Eng Phys 2016;38:498–505. https://doi.org/10.1016/j.medengphy.2016.02.007.
[24] Rosa M, Arlotti M, Marceglia S, Cogiamanian F, Ardolino G, Fonzo A Di, et al. Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. Mov Disord 2017;32:628–9. https://doi.org/10.1002/mds.26953.
[25] Rosa M, Arlotti M, Ardolino G, Cogiamanian F, Marceglia S, Di Fonzo A, et al. Adaptive deep brain stimulation in a freely moving parkinsonian patient. Mov Disord 2015;30:1003–5. https://doi.org/10.1002/mds.26241.
[26] Arlotti M, Marceglia S, Foffani G, Volkmann J, Lozano AM, Moro E, et al. Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. Neurology 2018;90:e971–6. https://doi.org/10.1212/WNL.0000000000005121.
[27] Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol 2013;74:449–57. https://doi.org/10.1002/ana.23951.
[28] Little S, Beudel M, Zrinzo L, Foltynie T, Limousin P, Hariz M, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. J Neurol Neurosurg Psychiatry 2016;87:717–21. https://doi.org/10.1136/jnnp-2015-310972.
[29] Popovych OV, Tass PA. Adaptive delivery of continuous and delayed feedback deep brain stimulation - a computational study. Sci Rep 2019;9:1–17. https://doi.org/10.1038/s41598-019-47036-4.
[30] Tass PA. Desynchronizing double-pulse phase resetting and application to deep brain stimulation. Biol Cybern 2001;85:343–54. https://doi.org/10.1007/s004220100268.
[31] Tass PA. A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. Biol Cybern 2003;89:81–8. https://doi.org/10.1007/s00422-003-0425-7.
[32] Adamchic I, Hauptmann C, Barnikol UB, Pawelczyk N, Popovych O, Barnikol TT, et al. Coordinated reset neuromodulation for Parkinson's disease: proof-of-concept study. Mov Disord 2014;29:1679–84. https://doi.org/10.1002/mds.25923.
[33] Ho AL, Feng AY, Barbosa DAN, Wu H, Smith ML, Malenka RC, et al. Accumbens coordinated reset stimulation in mice exhibits ameliorating aftereffects on binge alcohol drinking. Brain Stimul 2021;14:330–4. https://doi.org/10.1016/j.brs.2021.01.015.
[34] Tass PA, Qin L, Hauptmann C, Dovero S, Bezard E, Boraud T, et al. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. Ann Neurol 2012;72:816–20. https://doi.org/10.1002/ana.23663.
[35] Wang J, Nebeck S, Muralidharan A, Johnson MD, Vitek JL, Baker KB. Coordinated reset deep brain stimulation of subthalamic nucleus produces long-lasting, dose-dependent motor improvements in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine non-human primate model of parkinsonism. Brain Stimul 2016;9:609–17. https://doi.org/10.1016/j.brs.2016.03.014.
[36] Popovych OV, Lysyansky B, Rosenblum M, Pikovsky A, Tass PA. Pulsatile desynchronizing delayed feedback for closed-loop deep brain stimulation. PloS One 2017;12. https://doi.org/10.1371/journal.pone.0173363.
[37] Popovych OV, Lysyansky B, Tass PA. Closed-loop deep brain stimulation by pulsatile delayed feedback with increased gap between pulse phases. Sci Rep 2017;7:1–14. https://doi.org/10.1038/s41598-017-01067-x.
[38] Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, et al. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. Neuron 2011;72:370–84. https://doi.org/10.1016/j.neuron.2011.08.023.
[39] Johnson Luke A, Nebeck Shane D, Muralidharan Abirami, Johnson Matthew D, Baker Kenneth B, Jlv. Closed-loop deep brain stimulation effects on parkinsonian motor symptoms in a non-human primate – is beta enough? Physiol Behav 2017;176:139–48. https://doi.org/10.1016/j.physbeh.2017.03.040.
[40] Little S, Tripoliti E, Beudel M, Pogosyan A, Cagnan H, Herz D, et al. Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. J Neurol Neurosurg Psychiatry 2016;87:1388–9. https://doi.org/10.1136/jnnp-2016-313518.
[41] Velisar A, Syrkin-Nikolau J, Blumenfeld Z, Trager MH, Afzal MF, Prabhakar V, et al. Dual threshold neural closed loop deep brain stimulation in Parkinson disease patients. Brain Stimul 2019;12:868–76. https://doi.org/10.1016/j.brs.2019.02.020.
[42] Arlotti M, Palmisano C, Minafra B, Todisco M, Pacchetti C, Canessa A, et al. Monitoring subthalamic oscillations for 24 hours in a freely moving Parkinson's disease patient. Mov Disord 2019;34:757–9. https://doi.org/10.1002/mds.27657.
[43] Opri E, Cernera S, Molina R, Eisinger RS, Cagle JN, Almeida L, et al. Chronic embedded cortico-thalamic closed-loop deep brain stimulation for the treatment of essential tremor. Sci Transl Med 2020;12:7680. https://doi.org/10.1126/SCITRANSLMED.AAY7680.
[44] Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp Neurol 2004;189:369–79. https://doi.org/10.1016/j.expneurol.2004.06.001.
[45] Giannicola G, Marceglia S, Rossi L, Mrakic-Sposta S, Rampini P, Tamma F, et al. The effects of levodopa and ongoing deep brain stimulation on subthalamic beta oscillations in Parkinson's disease. Exp Neurol 2010;226:120–7. https://doi.org/10.1016/j.expneurol.2010.08.011.
[46] Beudel M, Brown P. Adaptive deep brain stimulation in Parkinson's disease. Park Relat Disord 2016;22:S123–6. https://doi.org/10.1016/j.parkreldis.2015.09.028.
[47] Kühn AA, Volkmann J. Innovations in deep brain stimulation methodology. Mov Disord 2017;32:11–9. https://doi.org/10.1002/mds.26703.
[48] Kühn AA, Kempf F, Brücke C, Doyle LG, Martinez-Torres I, Pogosyan A, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory β activity in patients with Parkinson's disease in parallel with improvement in

motor performance. J Neurosci 2008;28:6165–73. https://doi.org/10.1523/JNEUROSCI.0282-08.2008.
[49] Quinn EJ, Blumenfeld Z, Velisar A, Koop MM, Shreve LA, Trager MH, et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. Mov Disord 2015;30:1750–8. https://doi.org/10.1002/mds.26376.
[50] Leblois A, Meissner W, Bioulac B, Gross CE, Hansel D, Boraud T. Late emergence of synchronized oscillatory activity in the pallidum during progressive parkinsonism. Eur J Neurosci 2007;26:1701–13. https://doi.org/10.1111/j.1460-9568.2007.05777.x.
[51] Özkurt TE, Butz M, Homburger M, Elben S, Vesper J, Wojtecki L, et al. High frequency oscillations in the subthalamic nucleus: a neurophysiological marker of the motor state in Parkinson's disease. Exp Neurol 2011;229:324–31. https://doi.org/10.1016/j.expneurol.2011.02.015.
[52] Marceglia S, Fumagalli M, Priori A. What neurophysiological recordings tell us about cognitive and behavioral functions of the human subthalamic nucleus. Expert Rev Neurother 2011;11:139–49. https://doi.org/10.1586/ern.10.184.
[53] Alegre M, López-Azcárate J, Alonso-Frech F, Rodríguez-Oroz MC, Valencia M, Guridi J, et al. Subthalamic activity during diphasic dyskinesias in Parkinson's disease. Mov Disord 2012;27:1178–81. https://doi.org/10.1002/mds.25090.
[54] Lofredi R, Neumann WJ, Bock A, Horn A, Huebl J, Siegert S, et al. Dopamine-dependent scaling of subthalamic gamma bursts with movement velocity in patients with Parkinson's disease. Elife 2018;7. https://doi.org/10.7554/eLife.31895.
[55] Marceglia S, Bianchi AM, Baselli G, Foffani G, Cogiamanian F, Modugno N, et al. Interaction between rhythms in the human basal ganglia: application of bispectral analysis to local field potentials. IEEE Trans Neural Syst Rehabil Eng 2007;15:483–92. https://doi.org/10.1109/TNSRE.2007.907893.
[56] Marceglia S, Foffani G, Bianchi AM, Baselli G, Tamma F, Egidi M, et al. Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. J Physiol 2006;571:579–91. https://doi.org/10.1113/jphysiol.2005.100271.
[57] Foffani G, Bianchi AM, Baselli G, Priori A. Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. J Physiol 2005;568:699–711. https://doi.org/10.1113/jphysiol.2005.089722.
[58] Cagnan H, Mallet N, Moll CKE, Gulberti A, Holt AB, Westphal M, et al. Temporal evolution of beta bursts in the parkinsonian cortical and basal ganglia network. Proc Natl Acad Sci U S A 2019;116:16095–104. https://doi.org/10.1073/pnas.1819975116.
[59] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol 2019;15:148–60. https://doi.org/10.1038/s41582-018-0128-2.
[60] Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase i trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010;68:521–34. https://doi.org/10.1002/ana.22089.
[61] Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatr 2008;64:461–7. https://doi.org/10.1016/j.biopsych.2008.05.034.
[62] Melton AW. Implications of short-term memory for a general theory of memory. J Verb Learn Verb Behav 1963;2:1–21. https://doi.org/10.1016/S0022-5371(63)80063-8.
[63] Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB. Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 2009;12:1222–3. https://doi.org/10.1038/nn.2384.
[64] Fernández-Ruiz A, Oliva A, de Oliveira EF, Rocha-Almeida F, Tingley D, Buzsáki G. Long-duration hippocampal sharp wave ripples improve memory. Science 2019;364(80-):1082–6. https://doi.org/10.1126/science.aax0758.
[65] Siegle JH, Wilson MA. Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. Elife 2014;2014. https://doi.org/10.7554/eLife.03061.001.
[66] Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J Neurosci 2003;23:11725–31. https://doi.org/10.1523/jneurosci.23-37-11725.2003.
[67] Ezzyat Y, Kragel JE, Burke JF, Gorniak R, Rizzuto DS, Kahana Correspondence MJ, et al. Direct brain stimulation modulates encoding states and memory performance in humans article direct brain stimulation modulates encoding states and memory performance in humans. Curr Biol 2017;27:1251–8. https://doi.org/10.1016/j.cub.2017.03.028.
[68] Ezzyat Y, Wanda PA, Levy DF, Kadel A, Aka A, Pedisich I, et al. Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. Nat Commun 2018;9:1–8. https://doi.org/10.1038/s41467-017-02753-0.
[69] Ma BB, Fields MC, Knowlton RC, Chang EF, Szaflarski JP, Marcuse LV, et al. Responsive neurostimulation for regional neocortical epilepsy. Epilepsia 2020;61:96–106. https://doi.org/10.1111/epi.16409.
[70] Bour LJ, Ackermans L, Foncke EMJ, Cath D, van der Linden C, Visser Vandewalle V, et al. Tic related local field potentials in the thalamus and the effect of deep brain stimulation in Tourette syndrome: report of three cases. Clin Neurophysiol 2015;126:1578–88. https://doi.org/10.1016/j.clinph.2014.10.217.
[71] Shute JB, Okun MS, Opri E, Molina R, Rossi PJ, Martinez-Ramirez D, et al. Thalamocortical network activity enables chronic tic detection in humans with Tourette syndrome. NeuroImage Clin 2016;12:165–72. https://doi.org/10.1016/j.nicl.2016.06.015.
[72] Jimenez-Shahed J, Telkes I, Viswanathan A, Ince NF. GPi oscillatory activity differentiates tics from the resting state, voluntary movements, and the unmedicated parkinsonian state. Front Neurosci 2016;10:436. https://doi.org/10.3389/fnins.2016.00436.
[73] Guehl D, Benazzouz A, Aouizerate B, Cuny E, Rotgé JY, Rougier A, et al. Neuronal correlates of obsessions in the caudate nucleus. Biol Psychiatr 2008;63:557–62. https://doi.org/10.1016/j.biopsych.2007.06.023.
[74] Wu H, Tambuyzer T, Nica I, Deprez M, Van Kuyck K, Aerts JM, et al. Field potential oscillations in the bed nucleus of the Stria terminalis correlate with compulsion in a rat model of obsessive-compulsive disorder. J Neurosci 2016;36:10050–9. https://doi.org/10.1523/JNEUROSCI.1872-15.2016.
[75] Wickramasuriya DS, Rafiul Amin M, Faghih RT. Skin conductance as a viable alternative for closing the deep brain stimulation loop in neuropsychiatric disorders. Front Genet 2019;10. https://doi.org/10.3389/fnins.2019.00780.
[76] Riva-Posse P, Choi KS, Holtzheimer PE, McIntyre CC, Gross RE, Chaturvedi A, et al. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol Psychiatr 2014;76:963–9. https://doi.org/10.1016/j.biopsych.2014.03.029.
[77] Crowell AL, Garlow SJ, Riva-Posse P, Mayberg HS. Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective. Front Integr Neurosci 2015;9:41. https://doi.org/10.3389/fnint.2015.00041.
[78] Broadway JM, Holtzheimer PE, Hilimire MR, Parks NA, Devylder JE, Mayberg HS, et al. Frontal theta cordance predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. Neuropsychopharmacology 2012;37:1764–72. https://doi.org/10.1038/npp.2012.23.
[79] Neumann WJ, Huebl J, Brücke C, Gabriëls L, Bajbouj M, Merkl A, et al. Different patterns of local field potentials from limbic DBS targets in patients with major depressive and obsessive compulsive disorder. Mol Psychiatr 2014;19:1186–92. https://doi.org/10.1038/mp.2014.2.
[80] Chen CC, Pogosyan A, Zrinzo LU, Tisch S, Limousin P, Ashkan K, et al. Intra-operative recordings of local field potentials can help localize the subthalamic nucleus in Parkinson's disease surgery. Exp Neurol 2006;198:214–21. https://doi.org/10.1016/j.expneurol.2005.11.019.
[81] Yoshida F, Martinez-Torres I, Pogosyan A, Holl E, Petersen E, Chen CC, et al. Value of subthalamic nucleus local field potentials recordings in predicting stimulation parameters for deep brain stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry 2010;81:885–9. https://doi.org/10.1136/jnnp.2009.190918.
[82] van Wijk BCM, Pogosyan A, Hariz MI, Akram H, Foltynie T, Limousin P, et al. Localization of beta and high-frequency oscillations within the subthalamic nucleus region. NeuroImage Clin 2017;16:175–83. https://doi.org/10.1016/j.nicl.2017.07.018.
[83] Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z. Subthalamic span of b oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. J Neurol 2010. https://doi.org/10.1093/brain/awq144.
[84] Sinclair NC, McDermott HJ, Fallon JB, Perera T, Brown P, Bulluss KJ, et al. Deep brain stimulation for Parkinson's disease modulates high-frequency evoked and spontaneous neural activity. Neurobiol Dis 2019;130. https://doi.org/10.1016/j.nbd.2019.104522.
[85] Habets JGV, Heijmans M, Kuijf ML, Janssen MLF, Temel Y, Kubben PL. An update on adaptive deep brain stimulation in Parkinson's disease. Mov Disord 2018;33:1834–43. https://doi.org/10.1002/mds.115.
[86] Grahn PJ, Mallory GW, Khurram OU, Berry BM, Hachmann JT, Bieber AJ, et al. A neurochemical closed-loop controller for deep brain stimulation: toward individualized smart neuromodulation therapies. Front Neurosci 2014;8. https://doi.org/10.3389/fnins.2014.00169.
[87] Trevathan JK, Yousefi A, Park HO, Bartoletta JJ, Ludwig KA, Lee KH, et al. Computational modeling of neurotransmitter release evoked by electrical stimulation: nonlinear approaches to predicting stimulation-evoked dopamine release. ACS Chem Neurosci 2017;8:394–410. https://doi.org/10.1021/acschemneuro.6b00319.
[88] Delrobaei M, Baktash N, Gilmore G, McIsaac K, Jog M. Using wearable technology to generate objective Parkinson's disease dyskinesia severity score: possibilities for home monitoring. IEEE Trans Neural Syst Rehabil Eng 2017;25:1853–63. https://doi.org/10.1109/TNSRE.2017.2690578.
[89] Pardoel S, Kofman J, Nantel J, Lemaire ED. Wearable-sensor-based detection and prediction of freezing of gait in Parkinson's disease: a review. Sensors 2019;19. https://doi.org/10.3390/s19235141.
[90] Akbar U, Raike RS, Hack N, Hess CW, Skinner J, Martinez-Ramirez D, et al. Randomized, blinded pilot testing of nonconventional stimulation patterns and shapes in Parkinson's disease and essential tremor: evidence for further evaluating narrow and biphasic pulses. Neuromodulation 2016;19:343–56. https://doi.org/10.1111/ner.12397.

[91] De Jesus S, Almeida L, Shahgholi L, Martinez-Ramirez D, Roper J, Hass CJ, et al. Square biphasic pulse deep brain stimulation for essential tremor: the BiP tremor study. Park Relat Disord 2018;46:41–6. https://doi.org/10.1016/j.parkreldis.2017.10.015.

[92] Almeida L, Martinez-Ramirez D, Ahmed B, Deeb W, Jesus S De, Skinner J, et al. A pilot trial of square biphasic pulse deep brain stimulation for dystonia: the BIP dystonia study. Mov Disord 2017;32:615–8. https://doi.org/10.1002/mds.26906.

[93] Kirsch AD, Hassin-Baer S, Matthies C, Volkmann J, Steigerwald F. Anodic versus cathodic neurostimulation of the subthalamic nucleus: a randomized-controlled study of acute clinical effects. Park Relat Disord 2018;55:61–7. https://doi.org/10.1016/j.parkreldis.2018.05.015.

[94] Choe CU, Hidding U, Schaper M, Gulberti A, Köppen J, Buhmann C, et al. Thalamic short pulse stimulation diminishes adverse effects in essential tremor patients. Neurology 2018;91:e704–13. https://doi.org/10.1212/WNL.0000000000006033.

[95] Kroneberg D, Ewert S, Meyer AC, Kühn AA. Shorter pulse width reduces gait disturbances following deep brain stimulation for essential tremor. J Neurol Neurosurg Psychiatry 2019;90:1046–50. https://doi.org/10.1136/jnnp-2018-319427.

[96] Valldeoriola F, Muñoz E, Rumià J, Roldán P, Cámara A, Compta Y, et al. Simultaneous low-frequency deep brain stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the subthalamic nucleus to treat levodopa unresponsive freezing of gait in Parkinson's disease: a pilot study. Park Relat Disord 2019;60:153–7. https://doi.org/10.1016/j.parkreldis.2018.09.008.