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Deep brain stimulation: a review of the open neural engineering challenges

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Abstract

Objective. Deep brain stimulation (DBS) is an established and valid therapy for a variety of pathological conditions ranging from motor to cognitive disorders. Still, much of the DBS-related mechanism of action is far from being understood, and there are several side effects of DBS whose origin is unclear. In the last years DBS limitations have been tackled by a variety of approaches, including adaptive deep brain stimulation (aDBS), a technique that relies on using chronically implanted electrodes on 'sensing mode' to detect the neural markers of specific motor symptoms and to deliver on-demand or modulate the stimulation parameters accordingly. Here we will review the state of the art of the several approaches to improve DBS and summarize the main challenges toward the development of an effective aDBS therapy. *Approach.* We discuss models of basal ganglia disorders pathogenesis, hardware and software improvements for conventional DBS, and candidate neural and non-neural features and related control strategies for aDBS. *Main results.* We identify then the main operative challenges toward optimal DBS such as (i) accurate target localization, (ii) increased spatial resolution of stimulation, (iii) development of in silico tests for DBS, (iv) identification of specific motor symptoms biomarkers, in particular (v) assessing how LFP oscillations relate to behavioral disfunctions, and (vi) clarify how stimulation affects the cortico-basal-ganglia-thalamic network to (vii) design optimal stimulation patterns. *Significance.* This roadmap will lead neural engineers novel to the field toward the most relevant open issues of DBS, while the in-depth readers might find a careful comparison of advantages and drawbacks of the most recent attempts to improve DBS-related neuromodulatory strategies.

1. Introduction

Deep Brain Stimulation (DBS) is an effective treatment for a wide range of neurological disorders, such as Parkinson's disease [1–3] (PD), essential tremor (ET) [4, 5], dystonia [6–8] and Tourette syndrome (TS) [9, 10]. DBS is also becoming a valid alternative therapy for an expanding spectrum of non-motor diseases as pain, epilepsy and neuropsychiatric disorders [11]. Despite all the hype and the hope arising from the success of this technique, DBS is still associated with drawbacks, i.e. adverse effects [12] and limited efficacy [13], and the knowledge of its mechanisms of action is still in its prime: increasing consensus of its clinical utility was not paralleled by

comparable advancement in understanding its mechanism of action.

Critical aspects determining DBS efficacy are the patient selection, the choice of the appropriate anatomical targeting and the stimulation settings. Prior experience gained from surgical ablation studies allowed to extrapolate holistic clinical guidelines for DBS regarding the targeted brain region (e.g. the ventrolateral thalamus, the internal globus pallidus (GPi) or the subthalamic nucleus (STN)) [14, 15].

As a rule, the therapeutic effect currently achievable with DBS is affected by the surgical placement accuracy [16, 17].

Finding methods based on online analysis of neural activity [18] or on anatomical mapping and

Table 1. Summary of the open challenges discussed in the review.

Seven open challenges for neural engineering of DBS		
1	Online algorithms to assess optimal DBS electrode location and stimulation frequency during implant surgery	See Introduction and 3.1
2	Assess the relationship between BG LFP oscillations and i) specific symptoms, ii) residual physiological and/or compensatory activity	See 2.2
3	Increase the spatial resolution of DBS electrodes	See 3.1
4	Assess the biophysical mechanisms of clinical benefits associated to DBS	See 3.3
5	Develop in silico environment combining electrical field and spiking network models accounting for CBGT functional architecture to test DBS effects on pathological dynamics of the CBGT network	See 3.4
6	Identify symptom-specific (and task-related) biomarkers to use as control signals for aDBS	See 4.1 and 4.2
7	Online algorithms to assess optimal stimulation pattern based on patient condition in aDBS	See 4.3

Volume of Tissue Activated analysis [19–21] to support location and parameter selection by the neurologists is a key open challenge in DBS neural engineering (see table 1).

The stimulation settings ranges (e.g. 1–4 V for stimulation intensity, 50–100 μs for pulse width and 120–160 Hz for stimulation frequency) were defined in a series of clinical studies [22]. The optimal set of DBS parameters can significantly vary across patients, even within the same motor disorder and for the same targeted nucleus. These optimal stimulation settings cannot be entirely determined before electrode insertion, nor it is possible to test the whole parameter combinations during implants, so their selection relies on general best DBS practices to achieve clinical effectiveness in the absence of adverse effects [22, 23].

Most DBS systems in current use are open-loop devices meaning that, once parameters are manually configured, they provide a continuous stimulation regardless of the ongoing fluctuations of neural activity in the targeted nucleus. Studies on the effects of DBS over several years of stimulation showed the long-term efficacy of this approach in reducing motor symptoms in PD [24–27] with a low risk of adverse events [28, 29]. However, some adverse effects are present (e.g. in speech [30]) and the efficacy is reduced for some motor symptoms (e.g. freezing of gait [31]). To the aim of solving these issues adaptive deep brain stimulation (aDBS) systems stimulating only when necessary are currently under assessment. The basic idea is to use biomarkers carrying information about patient condition to trigger the stimulation, optimize its parameters (e.g. amplitude or frequency) or lock it (e.g. via phase-locking) to an acquired signal. Possible advantages of this approach are to decrease the likelihood of adverse effects and to cover a broader range of symptoms by means of specific stimulations. Starting from the pioneering work of Bergmann's group [32] in non-human primates and the groups of Simon Little and Peter Brown [33] and Alberto Priori [34] in humans, clinical

proof-of-concepts studies have already demonstrated the beneficial results of this approach for PD treatment [35, 36] with both neural and non-neural biomarkers as control signal for the stimulation.

In this review, we will briefly summarize the knowledge on DBS and move then to discuss current results on aDBS with an emphasis on the open issues in the neural engineering aspect of the therapy, as the selection of the optimal control and the optimal stimulation. We will first provide a neurophysiological description of the cortico-basal ganglia-thalamocortical (CBGT) network with a focus on the physiopathology of PD. We will then present DBS setup, clinical results and putative mechanisms, and describe the state of the art of aDBS discussing the rationale, the different approaches and the current perspectives. Finally, we will summarize open challenges for aDBS with a possible roadmap toward a sensible upgrade of this technology.

2. The cortico-basal ganglia-thalamocortical network

2.1. Anatomical pathways of the basal ganglia

The functional dynamics of the CBGT network (see figure 1(a)) involves inputs from different areas of the cortex to the BG, followed by the processing of this stimuli by the interplay of the different nuclei of the BG, resulting in a modulation of the activity of the GPi, and hence of the inhibition that this nucleus exerts on the thalamus [37]. Thalamic activity in turn provides a feedback to the motor cortex area from which the inputs came from. Other pathways, such as the one via Substantia Nigra pars reticulata (SNr) to mesenchephalic nuclei, which is relevant in the context of locomotion [38], will not be discussed here.

Historically, the basic circuit model of BG network has been anatomically described as composed by the direct and indirect pathways [39], which are thought to control motor behavior in an opposite fashion: the former exerts a net facilitation effect on the motor cortex by two serial inhibitory connections
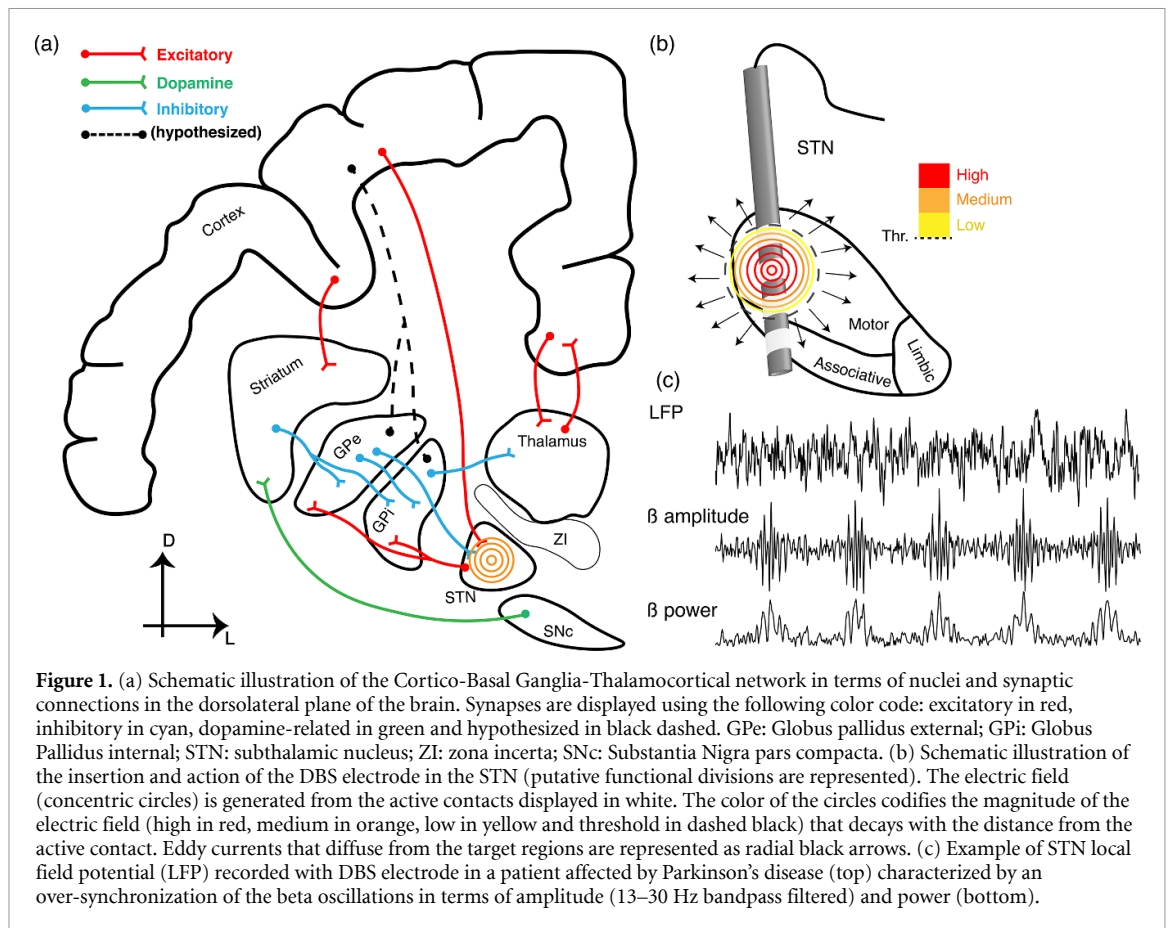
Figure 1. (a) Schematic illustration of the Cortico-Basal Ganglia-Thalamocortical network in terms of nuclei and synaptic connections in the dorsolateral plane of the brain. Synapses are displayed using the following color code: excitatory in red, inhibitory in cyan, dopamine-related in green and hypothesized in black dashed. GPe: Globus pallidus external; GPi: Globus Pallidus internal; STN: subthalamic nucleus; ZI: zona incerta; SNc: Substantia Nigra pars compacta. (b) Schematic illustration of the insertion and action of the DBS electrode in the STN (putative functional divisions are represented). The electric field (concentric circles) is generated from the active contacts displayed in white. The color of the circles codifies the magnitude of the electric field (high in red, medium in orange, low in yellow and threshold in dashed black) that decays with the distance from the active contact. Eddy currents that diffuse from the target regions are represented as radial black arrows. (c) Example of STN local field potential (LFP) recorded with DBS electrode in a patient affected by Parkinson's disease (top) characterized by an over-synchronization of the beta oscillations in terms of amplitude (13–30 Hz bandpass filtered) and power (bottom).

(e.g. striatum-GPi and GPi-thalamus) while the latter provokes an encumbrance effect by three serial inhibitory connections (e.g. striatum-Globus Pallidus external (GPe), GPe-GPi, and GPi-thalamus). Crucially, specific striatal neuron types participate to direct and indirect pathway, respectively D1- and D2-type. A third pathway, called hyperdirect pathway, was later integrated in this dyadic schema [40] thanks to the finding that the STN also receives excitatory afferents directly from the cortex. The net effect of this pathway is inhibition through the combination of one excitatory and one inhibitory connection (STN-GPi and GPi-thalamus).

The CBGT network is involved in a very broad range of functions within and beyond motor control, and discuss them goes beyond the scope of this work.

A classic view of the role of CBGT network based on the three pathways (see figure 1(a)) focuses on the role of the network in action selection [41]: to activate a desired motor pattern, the motor cortex wipes out competing and undesired motor outputs through hyperdirect pathway, funnels back the proper information to the thalamus and the cortex via the direct pathway, and suppresses excess and competing reinforcement through the indirect pathway.

Recent studies have called attention to the fact that BG integrate direct signals from an extensive cortico-subcortical network including the cerebellum [42]. Moreover, a recent tractography work showed

evidence of previously undetected projections from the cortex to pallidal and striatal neurons [43]. The dynamics of CBGT could then be even richer and complex than what currently thought.

2.2. Oversynchronization of basal ganglia and movement disorders

For several years, the most appealing theory underlying movement disorders phenomenology was the GPi rate theory [44]. This theory posited that an over-activation and under-activation of the GPi are a causal mechanism of hypokinetic disorders (e.g. PD) and hyperkinetic ones (e.g. ballism and Huntington disease), respectively. Despite the intuitiveness of this hypothesis, there are many contravening observations that make this theory no longer tenable [45].

Current theories on the BG genesis of movement disorders have been developed thanks to the paradigm shift of analyzing BG activity not through the rate of single neurons but through the local field potentials (LFPs) recorded with DBS electrodes (see section 3.1). LFP is a population level measure of the effects of synaptic input currents in the extracellular medium [46] (figure 1(c)). Most of the LFP studies in literature were performed through LFP recordings from externalized DBS electrodes few days after the DBS surgery. New devices such as the PC + S and Percept^TM (Medtronic Inc) or AlphaDBS (Newronika

Srl) allow LFP recordings also directly from chronically implanted impulse generator [47].

Pathophysiology of movement disorders is far from being completely clear, and a complete review goes beyond the scope of this work. Here we will focus on the relationship between motor disorders and basal ganglia oversynchronization in specific frequency bands. As detailed below, several movement disorders have been associated to abnormal synchronization of the CBGT network in specific frequency bands (beta band at 13–30 Hz for PD, lower frequencies for dystonia and TS), leading to the hypothesis that these disorders might indeed be 'oscillopathies'. According to this theory, an over-synchronization of the neural activity in a determined range may disrupt the physiological flow of a particular channel of neural information leading to behavioral deficits. This suggests that DBS might act through a modulation of such pathological oscillations (see section 3.3) and that these could be used as effective neural markers of motor symptoms (see section 4.1.1). In the next future, a more complete view on the pathophysiology of movement disorders could arise from recent studies highlighting in particular the role of synaptic plasticity [48–50] and of the interplay between the CBGT network and the cerebellum [51–53] where pathological oversynchronization has also been observed [54].

2.2.1. Parkinson's disease.
Subjects with PD display an abnormal LFP synchronization in the beta frequency range (13–30 Hz) [55, 56] both in the GP [57–59] and in the STN [57, 60–64]. In PD, levodopa intake and STN DBS therapy were found to suppress local beta oscillations to an extent correlated with the improvement of the parkinsonian symptoms [64–70]. Some studies also found beta power to be correlated with motor symptoms severity in absence of medication [61, 62] (but see [71]). Finally, STN DBS at beta frequencies induced a worsening of the PD symptoms supporting the idea that a beta resonance in the basal ganglia circuit is dysfunctional [72]. It is worth noticing that the physiological information carried by beta oscillations in coding movements (and movement phases) in humans is still largely unknown. Prior studies in healthy non-human primates demonstrated that movement execution requires beta synchronization to occur in a bursting manner and not as a tonic firing activity [73]. This suggested that the temporal organization of the LFP beta components might convey relevant information about the physiology of the underneath neural circuit. Indeed, in PD patients there is increasing evidence that more intense and longer beta oscillation bursts, i.e. prolongation of transient episodes of beta synchronization, are positively associated with motor impairments [74]. Moreover, levodopa was found to selectively suppress long-lasting pathological beta bursts and increase the probability of

short beta bursts, thus supporting the hypothesis that the latter may carry physiological information [73–77].

Pathological hyperactivity of BG propagates in the CBGT network resulting in clinically identifiable cortical oscillations, which can be recorded through electrocorticography (ECoG) using invasive subdural grids on the motor cortex (M1). ECoG recordings in M1 have provided evidence of an excessive phase-amplitude coupling (PAC) between the beta phase and the gamma amplitude in PD patients [78–80]. Also, this M1-beta-gamma PAC is disrupted by both levodopa and high-frequency DBS [81]. In a recent work, authors suggested that DBS-induced PAC reduction is mediated by a shaping out of the asymmetry profile of the beta waveform [82]. Beta band excess synchronization and sustained beta bursts are now considered a relevant neural marker of PD conditions, but identifying a causal chain linking dopamine depletion to behavioral deficits through beta oscillations is still an open challenge (table 1).

2.2.2. Dystonia.
Pallidal and subthalamic LFP recordings in dystonia patients revealed an over-synchronization in the low-frequency range (4–12) Hz compared to LFP recordings in the same areas of PD patients [83, 84]. The power of this frequency range was found to correlate with symptoms' severity in a cohort of patients with cervical dystonia [85]. GPi DBS was found to suppress low frequencies oscillations in patients with phasic cervical dystonia [86], although this suppression was not evident in phasic patients where DBS benefits arise in a long timescale [87]. Finally, combined LFP-EEG studies found a correlation between the severity dystonic signs and pallido-cerebellar coupling on the same frequency band, suggesting a putative involvement of the cerebellum in the pathophysiology of dystonia [88–90].

2.2.3. Tourette syndrome.
Micro-recordings studies in anesthetized TS patients analyzing single neurons activity evidenced low firing rate and an increased oscillatory bursting activity in the theta range (4–8) Hz in GPi [91], thalamus [92] and STN [18]. Together these results support the idea that bursting is tightly linked to hyperkinetic disorders symptoms [93]. Furthermore, these bursting oscillations follow the rhythmic LFP activity in the same frequency band [92, 94]. Indeed, LFP recordings in awake patients have reported excessive theta activity in the centromedian-parafascicular nucleus and in the GPi [91, 92, 95]. Finally, a recent work demonstrated that higher preoperative motor tic severity scores in the Yale Global Tic Severity Scale (YTGSS) are correlated with higher theta power in the same regions in recordings without concomitant motor tics [96].

2.2.4. Essential tremor.
Neuroimaging [97] and clinical studies [98] suggest that the cerebellum is of mechanistic importance in ET and the tremor is likely the result of an abnormal activity in the cerebellar-thalamic-cortical loop. In older models of ET, the olivary nucleus was posited to be the prime generator of the tremor but this hypothesis is falling out of favor for several reasons, i.e. the normal appearance of the olivary nucleus on post-mortem comparisons of ET and control brains [99] and on most neuroimaging studies [100]. Thalamic LFP recordings revealed specific oscillatory activity in 8–27 Hz, and this band has been found to be correlated with both ipsilateral sensorimotor cortex and the contralateral muscles [101]. Moreover, in other LFP studies enhanced low frequencies (4–7) Hz, beta (around 20 Hz) and low gamma (around 40 Hz) oscillations were recorded [102, 103].

3. Deep brain stimulation

This section will first describe the state of the art and the open issues in the design of DBS hardware (3.1), then efficacy and possible drawbacks of DBS therapy (3.2) and some hypothesis on the underlying mechanisms (3.3). Finally, we will discuss computational modelling (3.4) and transcranial magnetic stimulation (TMS, 3.5) as useful tools for a better application and understanding of DBS.

3.1. DBS set-up
In brief, DBS consists in the insertion of a stimulating electrode (see 3.1.1 and figure 1(b)) into a specific brain area (see 3.1.2) to deliver electrical pulses (see 3.1.3) improving specific symptoms (see 3.2). A complete description of DBS hardware goes beyond the scope of this work and has been performed elsewhere (e.g. [104]). Here we will focus on the aspects of the hardware that are more relevant toward the development of an optimal aDBS.

3.1.1. DBS leads design.
Since the advent of DBS more than 25 yr ago, there has been little change to the classic DBS electrode which consists of a flexible 1.27 mm diameter cylinder with a series of four platinum/iridium cylindrical contacts at the distal end space either 1 or 0.5 mm (Medtronic Inc. Minneapolis, MN). The optimal functional area within DBS target structures is usually limited in size and is proximal to other surrounding neural structures. The ongoing challenge in DBS lead design is then to increase the spatial selectivity of the stimulation (see table 1). To address this issue with the current stimulation technology, segmented electrodes with higher spatial selectivity have already been designed. One novel electrode design (Boston Scientific Corporation, Marlborough, MA) can control independently the stimulation parameters for each of eight contacts of the electrode. This eight-contacts electrode was tested in a recent multi-center, non-randomized, bilateral STN DBS study of 40 PD patients giving positive clinical results [105]. Although this design allows a more tailored stimulation within the target, the current spreads radially from the active contact limiting the steering of the electrical field at the vertical axis of electrode. Two approaches have been proposed to address this need of an effective current steering and an effective electric field shaping around all three directional axes: (i) a novel electrode with 32 contacts distributed uniformly around the circumference of the lead which allows the electric field steering in four directions [106] and (ii) a lead with four rings where each ring is composed by three independent contacts [107]. Over a decade of computational studies have investigated a variety of possible electrode configurations [108] improving current steering [109], showing for instance the advantages of segmented [110] and directional electrodes [111] with decreased contact surface area, focusing the effect of stimulation on small, nearby axons. Recent works also showed the advantages of tuning the direction according to axonal fiber orientation [112]. Overall, technical advances are toward directional leads with increased numbers of smaller electrode contacts [113] with ad hoc stimulation programming [114].

3.1.2. Optimal DBS electrodes localization.
As previously mentioned (see Introduction and table 1), determining the right placement of DBS electrodes is a key challenge, as the clinical efficacy of the therapy strongly depends on the accuracy of the lead placement [16, 115, 116]. Indeed, sub-optimal positioning of DBS electrodes accounts for up to 40% of cases of inadequate efficacy of stimulation, and spreading of stimulation currents in surrounding regions can result in side effects [104]. Although the surgical procedure is center-specific, the localization procedure generally relies on preoperative stereotactic imaging and in intraoperative electrophysiological recordings via micro-recordings [117–119]. Multiple micro-recordings (up to five) are sequentially carried out at different depths (with 1 mm step or less) and the optimal track and depth are selected according to the firing pattern of the single unity activities and their responses to external sensorimotor stimuli [117, 120, 121]. As the time for the neurosurgeon to take this critical decision is limited during the implant procedure, the development of quantitative electrophysiological methods to define the optimal site of stimulation may help in this assessment and lead to better DBS clinical outcomes. In this direction, several works proposed different approaches either based on single cells or LFPs to define the sweet spot for DBS [122, 123]. For instance, in a recent work we proposed a method to select the optimal location of DBS electrode for TS according to a simple estimator of the burstiness of the local activity [18],

coherently with physiological and clinical findings [21]. Once the macro-electrode is implanted at the desired depth, the extent of the volume of tissue activated is configured to match with the target region to prevent the spreading of collateral currents outside (figure 1(b)). The volume of tissue activation around the electrode depends on the electrode shape (see previous section) but also on the stimulation parameters (e.g. amplitude and pulse width), modality of stimulation (e.g. monopolar or bipolar) and properties of the non-neural tissue surrounding the electrode (e.g. homogeneity and isotropy) [104]. Overall, the link between stimulation parameters and activated neurons is still far from being clear. Combining experimental analysis and simulations to determine this link would noticeably decrease the burden and the complexity of the task of parameter selection for the clinical team. Strategies that consider anatomical landmarks and electrode position with individualized diffusion tensor imaging could provide additional information to reduce the degree of arbitrariness and the consumed time related to DBS programming [124]. Finally, thanks to the great efforts of Horn and colleagues, and other groups (Reich et al [21]), identifying the electrode placement postoperatively has become relatively straightforward. Free open-source software (e.g. Lead-DBS [125, 126]) are now available to systematically determine postoperatively the location of the DBS electrode contacts, offering the possibility to define the spatial distribution of potential electrophysiological markers [85], DBS-induced network effects [127] and the location of optimal targets [19].

3.1.3. DBS stimulation patterns.

The pattern of stimulation is a key element of DBS devices. As described in the introduction, DBS is usually delivered with fixed stimulation settings. However, several works investigated the possible advantages of irregular DBS patterns, mainly through computational modeling (see section 3.4). In their seminal works, Feng and colleagues defined possible ways to look for optimal DBS patterns [128] and found that irregular patterns could be as effective as standard stimulation using lower amplitudes [129]. Grill and colleagues investigated the role of temporal irregularity in DBS efficacy for more than a decade [130, 131] and found that non-regular patterns could be more efficient in treating PD symptoms [132], in particular when optimized by means of genetic algorithms [133, 134]. Similar results hold for DBS for Obsessive Compulsive Disorders [135]. Another proposed optimization approach for DBS patterns tested in silico relies on the determination of the patient-specific phase response curve to stimulation [136].

3.1.4. Non-invasive neuromodulatory approaches.

As a final open issue in the improvement of the DBS hardware we would like to briefly mention interesting new attempts toward a non-electric and to some extent non-invasive neuromodulation modalities, even if they are still far from clinical utility. Albeit the surgical procedure for the implantation of DBS electrodes is well-established, surgical risks and complications are still possible during implants for DBS. Hence, the development of a non-invasive method to stimulate locally deep brain regions is potentially an interesting line of research. Ultrasound or laser thermal ablation and radiosurgery might provide a lesion-based alternative to DBS [137–139]. Critically, these therapies are based on lesioning procedures with exclusively symptomatic benefit and lack of the neuromodulatory effects of DBS [140]. Another approach for non-invasive stimulation was proposed by Grossman and colleagues [141]. They have tested in mice a technique called temporal interference stimulation that is able to excite deeper regions (e.g. hippocampal neurons) without affecting overlying cortical neurons by applying high-frequency oscillating fields in different locations outside the brain. The interference between two high-frequency oscillating fields filters the high frequency component and lets through a low frequency component that oscillates at the difference of the frequencies of two fields. Neurons in the deep regions are able to pick up and to follow these slow fluctuations. This temporal interference approach does not require neither chemical nor genetic manipulation of the brain and could be translated in human clinical trials in the next future.

3.2. Therapeutic efficacy of DBS for movement disorders

Over the last decades, DBS has established as mainstay treatment for several movement disorders. In PD the two most common targets for DBS are the STN and the GPi [142]. In a multicenter trial, 251 PD patients were randomized to receive either the best medical therapy or the STN DBS. After 2 yr, quality of life in the DBS group significantly increased and the levodopa dose was reduced on average of the 39% [143]. Many studies demonstrated that the suppression of PD upper limb motor symptoms was present after periods of as much as 5–10 yr after surgery, even with concomitant deterioration of gait and cognition due to the progression of the disease [144–146]. Drawbacks of DBS therapies for PD include the limited efficacy in ameliorating gait problems [147, 148] and the possibility of long-term adverse nonmotor effects [149, 150]. Recent studies found occurrence of dementia to be comparable with patients following medical treatment [28, 151]. Improvements in impulse control disorders have been observed [152] and mainly associated with medication reduction [153]. Observed adverse effects include instead increased apathy [152] and decreased verbal fluency [154].

DBS treatments for dystonia started about 10 yr after the development of DBS therapy for PD. GPi

DBS provides marked improvements for generalized, segmental and cervical dystonia with a low frequency for adverse effects [8, 155]. A recent meta-analysis of more than 300 dystonia pediatric patients treated with DBS showed that 66.1% exhibits a clinically significant improvement in dystonic scores. Additional targets that are under investigation for DBS in dystonia are the STN and the sensorimotor region of the thalamus [156–158].

In the case of ET, DBS of the thalamus (or, less often, of the STN) has become a routine treatment in the last 20 yr [159]. DBS has shown to lead to long-term tremor control in about 70% of more than 1000 patients since 1998, leading to a significant improvement of the overall quality of life [160]. Potential long-term side effects of chronic DBS in ET are habituation and gait ataxia [161].

Finally, for TS various DBS targets were proposed, including the GPi, the thalamus and the STN [10, 18, 162, 163]. The number of TS patients undergoing DBS is relatively low (around 300 worldwide). The efficacy of DBS in TS was demonstrated in several case reports with few patients [18, 164–167]. The complexity and the variety of TS symptoms (e.g. motor, psychologic, etc) makes it difficult to select the appropriate target for DBS, as sub-territories of basal ganglia are involved in motor and limbic pathways. DBS for TS patients is overall reputed a safe procedure but different side effects, probably stimulation-related, are reported, i.e. apathy, lethargy and also maniac ad sexual disorders [168, 169].

Overall, continuous DBS is a successful therapy for many motor disorders related symptoms but, as we will discuss in section 4, a number of side effects as those listed above could probably be avoided with a more selective stimulation. Other important weaknesses of the conventional open loop DBS are (i) subject-dependency, (ii) time-consuming programming, (iii) frequent visits to clinic for programming, (iv) involvement of programming experts, v) short battery life [22, 170–172].

3.3. Mechanisms of action of deep brain stimulation

At its most basic level, DBS generates electrical fields to stimulate neural elements, mostly axons around the stimulation site, resulting in ionic channels activity possibly leading to action potentials (APs) and/or the release of the neural transmitters [173]. Notwithstanding all the studies on DBS in the last decades, understanding how this basic mechanism translates into clinical benefits is still an open challenge (table 1). A possible limitation of older studies was that they focused mainly on the effects of DBS on local or immediately downstream structures starting from the assumption that the CBGT network worked as a feedforward network of local processor units. Subsequent studies showed instead a parallel and distributed functional organization [174] composed

of multiple distinct loops. The question is then whether and how local DBS perturbations percolate and reverberate through the whole CBGT network, rendering the therapeutic DBS mechanism a system effect. Many studies have confirmed a more systematic mechanism involving antidromic and orthodromic excitation of axon both afferent and efferent to the site of the stimulation [21, 175–179] with specific effects associated to the stimulation of the different pathways [127]. Effects of DBS of STN has been found to extend to antidromic activation of primary motor cortex [180] and modulation of cerebellar activity [181]. Recording from structures that receive the input from the DBS target are coherent with an increased activation of the stimulated regions: thalamic activity was found to decrease during GPi DBS [182] and GPi activity was found to increase during STN DBS [173]. Functional magnetic resonance imaging [183] and positron emission tomography [184] in humans confirmed a consistent activation of the efferent structures from the DBS target. However, recent results suggest an inhibitory effect of DBS on local activity [185–187]. A possible underlying mechanism might be that electrical stimulation induces a release of neurotransmitters from the presynaptic terminals of afferent projections, and this leads to (i) an overall hyperpolarization due to the high prevalence of GABAergic terminals over glutamatergic terminals, (ii) synaptic depletion, and (iii) differential potentiation of inhibitory synapses [187].

3.3.1. Information lesion hypothesis.

An interesting hypothesis focuses on the disruption of the pathological information transmission rather than on the disruption of the pathological activity. The underlying concept is that pathological information transmission could be disrupted by the new stimulation-induced activity [188]. DBS—especially at high frequencies—can influence the synaptic communication in two ways: (i) orthodromic DBS-induced APs outnumber the intrinsic ones and (ii) antidromic DBS-induced APs collide and block most of the intrinsic ones that travel orthodromically. This results in a shift of the repetitive pathological low-frequency bursting pattern with regularized and more tonic patterns at higher frequencies [189]. Since the stimulation frequency is constant, the information of the DBS input signal is null, generating what is known as the 'information lesion' effect [190]. Several studies focused on the role of synaptic filtering induced by DBS as the key mechanism of information lesion [191]. The synaptic filtering mechanism posits that synapses under DBS action act as high-pass filters, leading to a fast depletion of stored neurotransmitters. Though axons are able to fire until frequencies of approximately 100 Hz, synaptic transmission is not able to occur at the same consistency [192]. In the context of excessive beta oscillations as

in PD the insertion of 130 Hz stimulation can result in a selective suppression of the lower frequency pathological oscillations. This theory is supported by the fact that DBS can result in inhibition of cortically evoked responses and spontaneous discharges [193] but remains elusive in different aspects such as the neuronal mechanisms that would elicit pattern regularization, frequency-specific effects and systemic consequences in CBGT network of pattern regularization.

3.4. Computational models of DBS

Computational modelling is a fundamental tool in the challenge to improve targeting and stimulation parameters in DBS. The construction of models that successfully may reproduce activity in healthy and unhealthy conditions and characterize the effects of DBS applied to a specific target is nowadays an open-challenge (table 1) for many reasons: (i) CBGT neural circuits are distributed and complex, (ii) DBS directly modulates whole network's dynamics, and (iii) experimental data of an entire circuit in different conditions (e.g. healthy, unhealthy with and without DBS) are currently impossible to collect. Overall, then, the challenge is to build a model describing the complex dynamics of the CBGT network to the extent to be able to predict the functional consequences of DBS, starting from the limited information that can be extracted from data collected asynchronously in different nodes of the network. Current models of neural networks and DBS are predominantly biophysical, and they account for several factors that affect the electrophysiological behavior of neurons, such as the dendritic integration of synaptic inputs, the electrical excitability and the processing of external stimuli like DBS pulses [188, 194–197]. A general biophysical DBS model for electrode placement is composed by two fundamental components: an electric field model and a neural activation model [198, 199]. The former is an abstraction of the voltage distribution generated by the stimulating electrode while the latter resembles the reaction of the neuron to the stimulation. The voltage field generated by an implanted DBS electrode is a 3D complex phenomenon that can be simulated using finite element methods at different orders of detail (e.g. point source electrodes in an infinite homogeneous medium [200], to clinical electrodes in a human brain [188], to detailed representations of the electrode–tissue interface [197]), knowing the geometry of the electrode, the spatiotemporal properties of the stimulus and the electrical properties of the surrounding tissue. A lot of effort was spent on developing patient-specific DBS models due to their impact on analysis of the anatomical and electrical target of the stimulation. The electric field predictions from modern DBS models have been compared to experimental activation of internal capsule defined from electromyography (EMG) recordings from different muscle groups in the contralateral side

of the patient, making a connection between DBS model and experimental activation [197]. The neural response can be simulated with multicompartment cable models where each compartment is an electrical resistor-capacitance (RC) circuit and they are connected in series by resistors representing the intracellular resistance [201, 202]. As a result, each neuron can be hyperpolarized or depolarized in different ways according to the relative electrical source-cell distance and the stimulation settings. Computational models can be useful to test hypothesis about network dynamics and potential DBS therapeutic mechanisms that cannot be simply tested experimentally as they would require synchronous multi-site recordings. A model of STN DBS has been used to reconcile the experimental paradox of soma inhibition and outflow excitation during DBS stimulation [203]. This model predicted that soma and axon of the same cell may exhibit unrelated firing patterns, i.e. the somatic firing was suppressed while the axon fired at approximately the stimulation frequency. Also, many studies showed numerically that antidromic activation of axon terminals can lead to widespread activation or inhibition of targets remote from the site of stimulation and that antidromic mechanisms should be carefully integrated in the interpretation of DBS mechanisms using evoked potential studies or functional imaging [204–206]. Santaniello and colleagues showed that high-frequency DBS may achieve a global pattern regularization through the emergency of resonance effects in the CBGT loop (reinforcement-loop mechanism) [196]. Interestingly, this hypothesis overcomes the limitations of information lesion hypothesis as it suggests that pattern regularization is a systemic effect and a by-product of simultaneous occurrence of several conditions: (i) CBGT is a network of parallel, polysynaptic and re-entrant loops, (ii) DBS produces time-locked stimuli and (iii) they travel along different polysynaptic pathways and eventually they are gathered in the same structure (i.e. striatum). Neuron models have been used also in DBS design problems such as closed-loop regulation of DBS and offline optimization of low-frequency and irregular DBS patterns. Several works focused on single-site linear [207, 208], multi-site linear [209], or non-linear delayed feedback stimulation techniques [210]. They inherently operate in a system with an input signal where the delayed activity of the pathological population is fed back into the system in such a way to shift the activity to desynchronized state (figure 2(a), bottom right). Popovych and colleagues proposed a method combining high-frequency DBS stimulation and pulsatile linear or non-linear delayed feedback to suppress over-synchronization in a parkinsonian STN-GPe model [211]. In this work, the amplitude of the DBS pulses was modulated by a delayed and filtered version of the LFP. In this experimental design, the time between the cathodic and anodic phases of the biphasic charge-balanced pulse
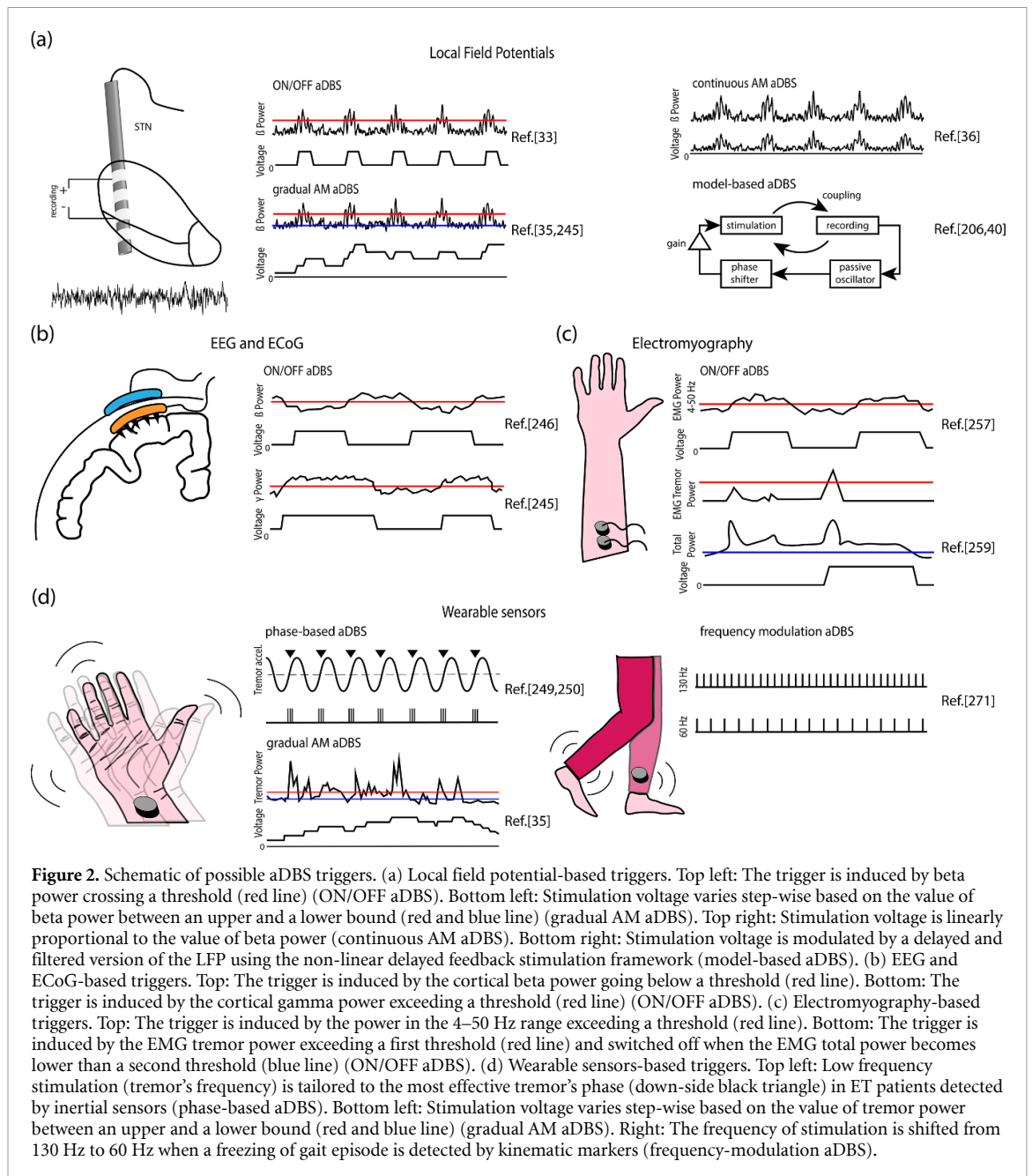
Figure 2. Schematic of possible aDBS triggers. (a) Local field potential-based triggers. Top left: The trigger is induced by beta power crossing a threshold (red line) (ON/OFF aDBS). Bottom left: Stimulation voltage varies step-wise based on the value of beta power between an upper and a lower bound (red and blue line) (gradual AM aDBS). Top right: Stimulation voltage is linearly proportional to the value of beta power (continuous AM aDBS). Bottom right: Stimulation voltage is modulated by a delayed and filtered version of the LFP using the non-linear delayed feedback stimulation framework (model-based aDBS). (b) EEG and ECoG-based triggers. Top: The trigger is induced by the cortical beta power going below a threshold (red line). Bottom: The trigger is induced by the cortical gamma power exceeding a threshold (red line) (ON/OFF aDBS). (c) Electromyography-based triggers. Top: The trigger is induced by the power in the 4–50 Hz range exceeding a threshold (red line). Bottom: The trigger is induced by the EMG tremor power exceeding a first threshold (red line) and switched off when the EMG total power becomes lower than a second threshold (blue line) (ON/OFF aDBS). (d) Wearable sensors-based triggers. Top left: Low frequency stimulation (tremor's frequency) is tailored to the most effective tremor's phase (down-side black triangle) in ET patients detected by inertial sensors (phase-based aDBS). Bottom left: Stimulation voltage varies step-wise based on the value of tremor power between an upper and a lower bound (red and blue line) (gradual AM aDBS). Right: The frequency of stimulation is shifted from 130 Hz to 60 Hz when a freezing of gait episode is detected by kinematic markers (frequency-modulation aDBS).

was found to play an important role in the stimulation efficacy.

Coordinated reset (CR) stimulation is an experimental neuromodulation protocol engineering by Tass and colleagues to desynchronize pathological neural activities through the use of intermittent, pseudo-randomized, low intense and spatially distributed pulse trains employing multiple DBS electrode contacts [212]. The possible advantage of CR relative to the conventional DBS is the reduction of the spread of the electrical current outside the target and, hence the probability to generate side-effects. Furthermore, a CR DBS approach may provide comparable motor benefits and less disturbances in cognitive processing, reducing the power consumption. Until now, the potential of CR DBS to desynchronize

oscillatory activity is well-supported by computational models [213] and initially corroborated by MPTP non-human primate studies and in a proof-of-concept study of a small group of PD patients [212, 214] but lacks clinical tests in humans. CR stimulation could be potentially applied both in open-loop and adaptive scenario.

Recently, computational models are beginning to enter in clinical tests, and they may serve as virtual testing environments for the assessment of future innovations in DBS: stimulation modalities, DBS pulse waveforms and electrode geometries [130, 215–217]. A step forward in this direction is represented by the work of Brocker and colleagues [133]. The authors determined through genetic algorithms an optimal stimulation pattern with a frequency far

outside the usual stimulation range (45 Hz) and, crucially, experimental tests in PD patients proved that this frequency performed as good as established frequencies. Of note, an interesting model developed by Frankemolle and colleagues [218] was used to define parameter settings that minimized current spread to non-motor regions of STN and clinical outcomes were compared in a randomized and blinded fashion with those obtained during standard clinical practice. Results showed that model-defined settings exhibited the same improving in motor symptoms, a significative reduction of the power consume (67%) and better cognitive performance during cognitive tasks.

3.5. DBS and transcranial magnetic stimulation

A comparison with other neuromodulation techniques can provide a complementary viewpoint to understand better DBS network level effects and suggest novel approaches. For instance, TMS is a useful tool to measure cortical excitability through a non-stationary magnetic field that provokes an electric flow through electromagnetic induction in a specific cortical area [219]. Pairing of STN DBS and TMS at different interstimulus intervals can be used to test effects of single pulse DBS on primary motor cortex excitability and the connection between it and the basal ganglia [220]. Single pulse DBS followed by single-pulse TMS at the early phase (2–5 ms) or later phase (~20 ms) showed an amplification of the motor-evoked potentials amplitude, indicating increased motor excitability at those latencies. These intervals likely represent transmission in the hyperdirect cortico-subthalamic pathway (2–5 ms) and in the indirect basal-ganglia-thalamo-cortical pathway (~20 ms). In the same work, STN DBS increased the motor-evoked potentials amplitude by means of its action on motor cortex rather than basal ganglia structures. Furthermore, repetitive pairing of STN DBS and TMS pulse was found to elicit long-term potentiation-like effects at the same latencies.

4. Adaptive deep brain stimulation

One key idea of aDBS is to tailor the stimulation according to a biomarker signal providing information about clinical state and underlying neurophysiopathology. The main incentive behind aDBS is the minimization of the stimulation-induced side effects (see section 3.3) and the possibility to give a stimulation accurately tuned to the needs of the single patient. For instance, a study in a short-trial of 10 patients suggested that aDBS may potentially control levodopa-induced dyskinesias in implanted patients with additional dopaminergic medication [221]. However, further studies in a more chronic setup are necessary to generalize this result due to potential confounding effects induced by microlesional effects and edemas. A collateral advantage of

aDBS is the possibility of reducing battery consumption relatively to DBS, although energy demands of the sensing device must be considered. The crucial steps to develop a valid aDBS system are (i) to identify reliable biomarkers indicating the optimal stimulation delivery time (table 1) and (ii) the availability of IPGs capable to record and monitor such biomarkers and to adapt one or more stimulation parameters online [36] of note, such biomarkers do not need to necessarily be causal to the mechanisms of the disease, but can be an epiphenomenon correlating with the symptoms' severity [64, 79, 81] and evolving during the course of the disease [61, 85]. Furthermore, the biomarker should display a high signal to noise ratio, and be robust to external artifacts such as movements and cognitive processes [222] or the stimulation itself. aDBS acts typically as a closed loop device as stimulation is switched on and off based on external neural or motor marker (see sections 4.1 and 4.2) but in several cases the parameters of the stimulation are fixed over the whole interval (e.g. [33]). In section 4.3 we will present more complex control strategies in which a continuous closed loop strategy is implemented, as the stimulation parameters are adjusted online according to the biomarker evolution (e.g. [221]).

4.1. Neural triggers for aDBS

A broad range of neural recordings were tested as biomarkers for aDBS systems: LFPs [33, 223, 224], APs [32, 225], ECoG [226] and electroencephalogram (EEG) [227]. In the following we will discuss how differences as information content, spatial and temporal resolution, and invasiveness affect the clinical performance of these signals.

4.1.1. Local field potentials recordings.
LFPs are the most studied signals for aDBS systems [224, 228] (figure 2(a)). By experimental design, LFPs are the result of a low-pass filtering of extracellular recordings at 500 Hz and reflect the neural processes occurring around the electrode in the extracellular space with a spatial resolution of some hundreds of μm [46]. Two key advantages of using LFPs as control variable in aDBS systems are that (i) they can be recorded using the same DBS macro-electrodes used for stimulation avoiding further surgical procedures and (ii) they display long-term stability at the electrode-tissue interface. On the other hand, LFP recordings can be affected by post-operative lesion effects, i.e. stun effects [229], and simultaneous sensing and stimulation can be hampered by stimulation artifacts, since the presence of a strong stimulation artifact can saturate the amplifiers of the sensing module of the device. To overcome this problem, Rossi and colleagues designed an artifact-free recording system for STN DBS called 'FilterDBS' that removes the noisy harmonics using a bandpass filter (2–40 Hz) with an overall gain of 100 dB and 130 dB of common mode rejection ratio [230]. A

combination of hardware-based strategies was also developed by Kent and Grill [231] to allow an artifact-free recording of DBS evoked potentials [232, 233]. Other approaches use instead a template of the stimulation signal that is subtracted from the recorded signal generating an artifact-free track. However, this template method is not suitable for aDBS where the stimulation rate is not constant. Several DBS control strategies can be developed starting from LFP recordings and will be discussed in detail in section 4.3. For instance, Priori and colleagues were among the first to test LFP control for aDBS systems in PD proposing the beta-band power as a biomarker of the clinical state of the disease [224]. In a series of studies, the beta amplitude of the LFP signal was used to trigger the stimulation with fixed DBS parameters (figure 2(a) top left), obtaining akin or even better clinical outcomes than the conventional stimulation with a concomitant reduction of both the battery consumption (~40%) and the stimulation-induced side effects in both unilateral and bilateral therapies [33, 34, 221, 234, 235]. These studies were conducted using lead externalized electrodes in a short time window after the surgery for electrodes implants in a laboratory environment. Recently, a study with a portable aDBS device tested for the first time the feasibility of this system in 13 PD patients during 8 h of daily activities [36]. A very promising alternative approach does not rely on the detection of an increase in beta oscillations power, but on the detection of long bursts of beta LFP [74] that are tightly related to behavioral dysfunctions (see section 2.2.1).

aDBS approaches using LFPs were mainly tested on PD patients, for which conventional DBS practice is more consolidated. However, an aDBS-like approach was used to develop proof-of-concepts for other disorders such as TS and dystonia using LFP as control signal, based on the centromedian-parafascicular 5–15 Hz oscillations and pallidal theta oscillations as biomarker input, respectively [236, 237]. Overall, the use of LFP as aDBS control signal is driven by the findings of spectral markers of motor symptoms discussed in section 2.2., but this is not necessarily be the optimal approach. We recently advanced the hypothesis that the most informative frequency coding a specific movement or movement phases in the context of a pathological state (e.g. PD) might not lie within the most prominent spectral peak.

4.1.2. Action potentials.

The high information content and fine temporal and spatial resolution make APs virtually a good candidate as biomarker for aDBS [238]. A study in an MTMP primate model of PD indeed demonstrated the possibility to use APs as trigger for the stimulation [32]. However, several issues prevent APs from being suitable for aDBS applications: (i) chronic intracellular recordings are difficult to achieve and require

additional surgery and (ii) the APs signal is not stable over long intervals of time and needs a continuous recalibration process [239].

4.1.3. Electrocorticography.

ECoG signals have an amplitude up to 50–400 μV with a frequency range up to 500 Hz. ECoG has been extensively studied in patients with epilepsy implanting subdural electrodes in the brain epidural or subdural spaces and is currently used as a biomarker in a brain-responsive neurostimulator (RNS system, Neuropace) to treat drug-refractory mesial temporal lobe epilepsy [240, 241]. The use of ECoG as biomarker, requires the implantation of additional electrodes in the brain in a region far from the stimulation site. A recent single-center analysis suggests that ECoG implant procedure adds minimal intraoperative risks to surgery if it is performed by experienced hands [242]. Nevertheless, adding ECoG to DBS extends the surgery time slightly, which is always a risk factor per se for all surgery procedures. Moreover, the analysis of 695 extraoperative (i.e. post-surgery) epilepsy ECoG cases showed that main complications are the cerebrospinal fluid leakage, blood transfusions and hemorrhages [243]. In few preliminary studies in PD patients with dyskinesia, STN DBS was combined with unilateral ECoG electrodes [244, 245]. In one study in particular the subthalamic stimulation voltage was triggered by cortical gamma-band (60–90 Hz) oscillations, which are thought to be related to dyskinesia [245] (figure 2(b), low). Interestingly, this approach was able to maintain the clinical benefit with an energy saving of ~40% relative to continuous stimulation. These findings provide preliminary evidence that signal detectable in ECoG recordings might be a viable biomarker for aDBS to treat PD-related dyskinesias. A different approach to aDBS than what previously described has been used for ET. In these patients, DBS is required to suppress hand tremor during intentional movements. The stimulation was therefore triggered by biomarkers identifying the movement onset (rather than the onset of the tremor). In a recent study, the hand movement was detected using movement-related beta-band desynchronization recorded by ECoG placed over the hand sensorimotor area [246]. Once the movement was decoded, the stimulation was triggered for the duration of the movement (figure 2(b), high). In this case, the therapeutic stimulation was delivered only when the patient was actively using their arms, thus reducing the total energy delivered and potential side-effects. Of note, in ET the tremor suppressive effects of DBS are almost immediately evident. The accuracy of the decoder was perfect as the stimulation was on in 100% of movement tasks such as spiral drawing or water pouring. Nowadays, more complex algorithms are trying to avoid the use of a simple 'on-off' logic, that turns the system abruptly from a fully 'off' to a therapeutic stimulation level, limiting the slew rate of

the voltage potential. The limitation of the slew rate could reduce paresthesia episodes, accepting the cost to not suppress the initial tremor in the first instants of movement.

4.1.4. Electroencephalography.

As discussed in section 2, abnormal network synchronization in BG propagates in the CBGT network, and might be observed in cortical recordings [227]. For instance, a high thalamocortical theta coherence was found in PD patients [247]. These findings suggested the use of EEG as a potentially relevant biomarker for PD symptoms, with the crucial asset of non-invasiveness. However, no proof-of-concept study of EEG-based aDBS systems has been disclosed so far. This can be due to different reasons: (i) EEG signals are low in amplitude (~10 μV) and are prone to artifacts and high noise, (ii) EEG spatial resolution is low (~5 cm) and (iii) the attachment of the electrodes on the head can cause discomfort to the patient [248].

4.2. Non-neural triggers for aDBS

Neurophysiological-recordings-based biomarkers have not been the only type of feedback inputs tested for aDBS. Other kind of signals were proposed for this scope: kinematic [249, 250], EMG [251], biochemical potential [252] and eHealth and mHealth monitoring [253, 254].

4.2.1. Electromyography recordings.

Surface EMG from symptomatic extremities has been successful in tremor detection and prediction [255, 256]. Hence, EMG has been considered as a potential control signal for aDBS [257] (figure 2(c), high). EMG recordings were used to trigger aDBS in a tremor-dependent fashion in ET and tremor-dominant PD patients and in a movement-dependent fashion in ET patients (see 4.1.3). In the former case, one study used the EMG power in a 3 Hz tremor band to trigger stimulation [258] (figure 2(c), low) while another study employed the wavelet entropy in the 8–16 Hz, obtaining ~85% of accuracy in ET and ~80% in PD [256]. In the latter case, the stimulation was delivered whenever a movement was detected by the EMG signal [259]. Results showed a ~90% control of the tremor with the 50% usage of the power storage compared to continuous stimulation. The main drawback of EMG signals are the artifacts originated by small movements of the electrodes, leading to difficulties in achieving a reliable trigger in a real-word scenario. Other limitations in using EMG sensors are: (i) patients will have to wear chronically the sensors with a possible discomfort and (ii) signal processing and wireless data transmission may affect the power storage of EMG sensors and impulse generator. Finally, reliable EMG-based biomarkers for other symptoms (e.g. bradykinesia) have not been yet developed.

4.2.2. Kinematic recordings.

Wearable sensors embedded with accelerometers and gyroscopes have gained considerable interest in monitoring PD symptoms. In several studies, these sensors successfully detected or even predicted tremor onset and might be useful also at assessing dyskinesia, bradykinesia and freezing of gait episodes [255, 260–262]. Several studies have supported the feasibility and the efficacy of aDBS systems based on tremor detection, in particular for ET and tremor-dominant PD patients [35, 249]. A tremor-modulated stimulation was used in PD patients in a study in which the stimulation amplitude was modulated using the tremor power (4–8 Hz) detected by the triaxial gyroscope (figure 2(d), left), obtaining a substantial decrease of the tremor amplitude (~40%) and of the mean delivered stimulation voltage (~75%) [35]. An alternative approach was tested in patients with ET and dystonic tremor using the dominant phase of tremor [249]: the most effective phase offset from the tremor's onset was assessed and triggered the delivery in each tremor's cycle of a packet of pulses (e.g. a burst of 4–6 pulses in 35 ms) during a tremor-provoking posture holding. The intra-burst DBS frequency was the same as that used during conventional high frequency DBS, while the inter burst frequency was determined according to patient's tremor frequency (~4 Hz). This approach achieved promising but still unsatisfactory results with tremor suppression on average of 35% in ET and 20% in dystonic patients. Of note, wearable sensors share the same drawbacks of EMG sensors regarding comfort and battery life. Moreover, algorithms to monitor other motor symptoms than tremor need further development to allow the use of this approach in PD patients.

4.2.3. Biochemical potentials.

As dopamine depletion plays a crucial role in the pathophysiology of PD (see section 2.1), short term fluctuations of this neurotransmitter have been proposed as biomarker for aDBS. The development of technologies (e.g. fast-scan cyclic voltammetry) able to monitor real-time the dynamic of the dopamine during neural changes might lead to the possibility to use the dopamine to act as real-time trigger for aDBS [263, 264]. Dopamine fluctuations were found in rodent models of PD during DBS [252] and an increase of striatal dopamine release was found in pig with STN DBS [265]. In one study ET patients exhibited a voltage-dependent release of adenosine during thalamic DBS [266]. However, so far, no correlations were found between the release of neurotransmitters and the clinical state of the patients, hence its use as aDBS trigger is still debated.

4.2.4. eHealth and mHealth monitoring.

The biomarkers described in the previous sections provide a quantitative description (usually with one single variable) of the clinical state of the patient

according to neural state or a specific motor symptom. However, adding a subjective experience of the motor symptoms could improve the interpretability of the features extracted by the signals. Moreover, non-motor symptoms are strictly related with the quality of life and they could be a strong predictor of the DBS clinical outcome [267]. Electronic health (eHealth) and mobile health (mHealth) applications have the capability to fill this gap combining a subjective assessment of the own feeling of the disease with objective input signals [268]. Different clinical trials tested the possibility to monitor in a multimodal way the condition of the PD patients in their home environment using the experience sampling method (ESM) and mobile applications. ESM, also referred to as a daily diary method, involves asking patients to note their feelings, thoughts, behaviors on multiple occasions over time [253]. For instance, DBS settings could be adjusted by telemonitoring and smartphone applications can track symptoms fluctuations during the day [269, 270]. Notwithstanding this proof-of-principle the feasibility and efficacy of these approaches needs to be investigated further.

4.3. aDBS control strategies

Identifying and processing online symptoms-related biomarkers is the first important step toward the development of an aDBS system and it is the aspect most research currently focuses on. The second major challenge is the design of an efficient online control mechanism of the stimulation pattern (see table 1). There are several factors to consider, such as data computation, battery consumption, data transfer, and the modality and frequency of stimulation parameter adjustments. Furthermore, the possible improvements of the current clinical DBS systems range from the electrode configurations to the variation of amplitude, frequency and pulse-width of the stimulation train. *A priori*, all these parameters may be modified online in an aDBS approach.

4.3.1. Amplitude-based aDBS.

Most of aDBS systems rely on control architectures that operate only on one of the pulse parameters, usually the amplitude [33, 35, 234, 246, 259]. The simplest paradigm is to deliver the stimulation a predefined set of amplitude, frequency and pulse width, but only when it is necessary in an ON/OFF fashion (figure 2(a), top left). To avoid paraesthetic effects, the onset of the stimulation should be a smooth linear ramp from zero toward the desired value of amplitude. ON/OFF AM systems were implemented (i) in akinetic-PD patients using the beta-LFP amplitude and (ii) in tremor-dominant PD and ET patients using machine learning algorithm on wearable sensor and EMG data [33, 255, 256]. Other approaches implement instead an amplitude modulation (AM) through different designs: gradual AM

and continuous AM. The former is a closed-loop regulation that relies on a quantized policy to maintain the voltage amplitude between two desired values, i.e. upper and lower thresholds (figure 2(a), bottom left). In this paradigm, the upper and lower thresholds and the quantization policy are crucial but a common consensus on these values has not been achieved yet [35, 245]. The latter is a closed-loop regulation where the control policy is a continuous feedback signal proportional to the instantaneous vale of the biomarker (figure 2(a), top right). Thus, the output amplitude reflects the envelope of the input signal. Rosa and colleagues presented this approach in akinetic-PD patients using the beta amplitude of the STN LFP as input to control the level of stimulation [34, 36, 221].

4.3.2. Phase-based aDBS.

Cagnan and colleagues showed that continuous stimulation at patients' tremor frequency (3–8 Hz) entrains tremor-related neural oscillation revealing stimulation induced transitory amplification and suppression of neural synchrony reflected peripherally as transient tremor AM. From this observation, they tailored the low frequency stimulation timing to the most effective tremor's phase in ET patients detected by inertial sensors, reducing the likelihood to elicit side-effects due to a lower total stimulation delivered without compromising the clinical efficacy [249, 250] (figure 2(d)). Of note, in contrast to amplitude-based approaches, these model-based approaches may not interfere with other rhythmic activities not phase-locked to the stimulation.

4.3.3. Adaptive modulation of stimulation frequency and pulse width.

Recent studies in PD patients [271] have suggested the possibility to use low frequency DBS (50–80 Hz) to treat axial symptoms (e.g. freezing of gait, speech and swallowing) that did not respond, or were evoked, by conventional high-frequency DBS (figure 2(d), right). However, these beneficial effects were not consistently present or exhausted over time and low-frequency DBS led sometimes to a worsening of appendicular symptoms, in particular tremor [272, 273]. Modulation of frequency may become even more interesting when integrated in a feedback approach that includes the ability to decode behavioral states from an implanted DBS electrode. Preliminary results suggest that, if proper features are extracted from all four contacts STN LFP signals, is possible to build a hierarchical decoder of a variety of behaviors, including speech, mouth movements, arm movements (reach), and random movements [274]. With the random movement class, they refer to those parts of the recorded signal where the subject is in the rest position and no specific activity is done. The reason behind using the random segments is to train the classifier to recognize other tasks rather than the defined

ones. The synergy between the possibility to decode the behavioral patient's state using LFP features and the modulation of the frequency parameter could be an alternative aDBS approach to AM. Finally, pulse-width modulation might provide clinical benefits targeting more selectively axons belonging to the direct cortico-subthalamic pathway. Shorter pulse-widths may increase the therapeutic window while reducing battery consumption [275].

5. Perspectives and challenges for aDBS

DBS greatly evolved in the last years. Advances in DBS systems (e.g. sensing devices), combined with electrodes with higher spatial selectivity could provide more efficient and virtually side-effect free therapies for patients affected by movement disorders. However, there are still many open issues that will challenge researchers in the next years (see table 1).

One of the major challenges is the identification of a set of reliable biomarkers that can track the clinical state considering the different demands per phenotype of the disease. For example, besides bradykinesia PD patients experience many other motor (e.g. rigidity, tremor, gait freezing) and non-motor symptoms (e.g. cognitive dysfunction, apathy and depression, sleep disorders, etc) [276]. These symptoms are linked to different pathophysiological neural circuitry and hence may require different biomarkers to be detected. In particular, pathological beta oscillations are thought to be correlated with PD-related akinetic-rigid symptoms while tremor severity does not seem to correlate with beta power. Moreover, pathological pathways are probably interweaved with residual physiological or compensatory ones, so non-specific stimulation might interfere with them.

It is likely that in future aDBS therapies each patient will undergo an initial calibration period where the value of the parameters of the control strategy will be tuned to the individual characteristics, but even in this case the robustness of the biomarkers over time will be of paramount relevance. Biomarkers should be able to cope over the long timescale with confounding factors as (changes in) concomitant medication, aging, progression of the disease. Once the optimal biomarkers set is selected, the control policy should tailor the stimulation pattern not only according to pathology and its circuits manifestations, but also according to everyday actions and behaviors of patients. Indeed, consideration of patient behavior such as grasping, walking, talking, sleeping etc could also further improve the determination of the optimal stimulation paradigm. For example, tremor-dominant PD patients should require low levels of stimulation during the sleep because of a lower disease burden. Wearable sensors, electromyographic signals and LFP signals could be used in combination to detect the state of the patient using machine learning algorithms, implementing

an individual patient-state disease-specific control policy of the stimulation in the aDBS system. In the next future, technology such as Internet of Things and Cloud Computing will help the automation and information processing to allow the implementation of complex algorithms in a real-time scenario without the insertion of further electronic in the patient. The use of rechargeable systems and telemetry could allow a continuous wireless flow of data with marginal impact on device battery and the possibility to assess continuously the patient in a more complex scenario.

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