REVIEW

# Adaptive Deep Brain Stimulation: From Experimental Evidence Toward Practical Implementation

Wolf-Julian Neumann, MD,[1] Roee Gilron, PhD,[2] Simon Little, MD, PhD,[3] and Gerd Tinkhauser, MD, PhD[4*]

[1]*Movement Disorder and Neuromodulation Unit, Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany*
[2]*Rune Labs, San Francisco, California, USA*
[3]*Movement Disorders and Neuromodulation Centre, University of California San Francisco, San Francisco, California, USA*
[4]*Department of Neurology, Bern University Hospital and University of Bern, Bern, Switzerland*

**ABSTRACT:** Closed-loop adaptive deep brain stimulation (aDBS) can deliver individualized therapy at an unprecedented temporal precision for neurological disorders. This has the potential to lead to a breakthrough in neurotechnology, but the translation to clinical practice remains a significant challenge. Via bidirectional implantable brain-computer-interfaces that have become commercially available, aDBS can now sense and selectively modulate pathophysiological brain circuit activity. Pilot studies investigating different aDBS control strategies showed promising results, but the short experimental study designs have not yet supported individualized analyses of patient-specific factors in biomarker and therapeutic response dynamics. Notwithstanding the clear theoretical advantages of a patient-tailored approach, these new stimulation possibilities open a vast and mostly unexplored parameter space, leading to practical hurdles in the implementation and development of clinical trials. Therefore, a thorough understanding of the neurophysiological and neurotechnological aspects related to aDBS is crucial to develop evidence-based treatment regimens for clinical practice. Therapeutic success of aDBS will depend on the integrated development of strategies for feedback signal identification, artifact mitigation, signal processing, and control policy adjustment, for precise stimulation delivery tailored to individual patients. The present review introduces the reader to the neurophysiological foundation of aDBS for Parkinson's disease (PD) and other network disorders, explains currently available aDBS control policies, and highlights practical pitfalls and difficulties to be addressed in the upcoming years. Finally, it highlights the importance of interdisciplinary clinical neurotechnological research within and across DBS centers, toward an individualized patient-centered approach to invasive brain stimulation. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

**Key Words:** closed loop DBS; adaptive DBS; local field potentials; basal ganglia; Parkinson's disease



*__Correspondence to:__ Dr. Gerd Tinkhauser, Department of Neurology, Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland; E-mail: gerd.tinkhauser@insel.ch

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## Toward Implantable Devices for Closed-Loop Adaptive Deep Brain Stimulation

Implantable deep brain stimulation (DBS) devices for fully embedded, invasive, closed-loop adaptive neuromodulation are now entering the clinical stage. These devices are capable of optimizing DBS in the temporal domain via physiologically informed delivery of stimulation according to subcortical or cortical electrophysiological feedback signals.[1] Until now, the required access to intracranial brain signals in DBS patients was generally limited to brief time windows within the operating theater (lead implantation/battery replacement surgery) or to the first days postoperatively when DBS lead extensions were temporarily externalized before being connected to the implantable pulse generator (IPG).[2] In these time windows electrophysiological biomarker research and closed-loop adaptive DBS (aDBS) trials could be performed under experimental laboratory conditions. These recording conditions however, came with several limitations, including time pressure, microlesion effects, limited flexibility (obstructive hardware, recording only in the lab), suboptimal clinical condition of the patient (perioperative period), and the inability to investigate biomarker stability over longer time periods. Next generation chronically implanted neurostimulators are capable of brain sensing and adaptive stimulation in addition to continuous stimulation. This represents an important innovation for the further development of the field. The first-generation of sensing-enabled devices (Medtronic PC + S) were distributed to selected research centers and facilitated the replication of key results from previous acute biomarker characterization and aDBS studies.[3-6] A technically improved and rechargeable version for chronic wireless sensing (Medtronic RC + S) that permits unlimited long-term recordings at home has been released, but was even further restricted to a limited number of United States (US)-based clinical research institutions.[1,7-10] The first commercially and widely available next generation neurostimulator (Medtronic Percept PC) was released in 2020. This represents a major development step,[11,12] but the fact that it is not rechargeable places a time limit on data streaming and experiments, as brain sensing and wireless data streaming contributes to battery depletion. Brain sensing-enabled devices are now being developed by a growing number of manufacturers (eg, AlphaDBS/Newronika, PINS Medical, and Picostim),[13-15] which will support neurophysiological biomarker characterization through chronic invasive brain signal recordings. This will facilitate the implementation of fully embedded aDBS in research and clinical practice. Beyond aDBS, brain sensing can serve as a tool to optimize open-loop DBS programming by identifying optimal stimulation contacts[16,17] and supporting refinement of stimulation amplitude according to biomarker levels.[12,18,19] However, as with any new development in DBS, sensing and aDBS adds a significant number of parameters and complexity to the therapy. This can be a notable burden and barrier to both patient and clinician if not handled carefully and in an informed way. There is a risk that without appropriate supportive tools and education, the DBS community could find the added complexity overwhelming and may not fully realize the practical and clinical utility of biomarker sensing or aDBS. This review aims to highlight key concepts related to aDBS and brain sensing, to raise awareness of the expanded DBS parameter space and call attention to the importance of a patient-tailored approach.

## Targeting Brain Rhythms

In aDBS, electrical current is selectively delivered with the goal to modulate brain circuit activity. This can be translated using an aDBS control policy that describes the action to be taken based on the current state of a pre-defined brain rhythm as feedback signal.[20] A target brain rhythm could be certain features of brain signals and/or their specific spatio-temporal characteristics that index a symptom state to inform the delivery of stimulation. Conceptual frameworks on how single electrophysiological biomarkers could be embedded as feedback signals in aDBS control strategies have been maturing over the years with major discoveries in Parkinson's disease (PD), with potential for translation to other DBS indications as well.[21] The characterization of exaggerated beta activity (13–35 Hz) in local field potentials (LFP) from the basal ganglia in PD patients was crucial for the development of the field.[22-26] Indeed, most aDBS studies in PD used beta activity as a feedback signal for different control policies (Fig. 1). Beta activity is correlated with motor sign severity of bradykinesia/rigidity in PD. If high or low levels of beta activity are measured, this can inform a control policy that automatically adapts the stimulation parameters, such as stimulation intensity. The various control policies that have been tested so far include (1) a fast control with a single-threshold;[27-30] (2) a dual-threshold control;[6] and (3) a slower proportional control.[13,31,32] Fast control strategies can selectively modulate stimulation with millisecond precision.[6,28] This could lead to rapid suppression of particularly long duration beta bursts, which have been shown to be particularly related to PD motor signs.[33] Alternatively, "slower" control strategies can track and control slower average fluctuations of beta activity as well as clinical symptom fluctuations, particularly those related to medication cycles.[31,32] A different aDBS control policy that has

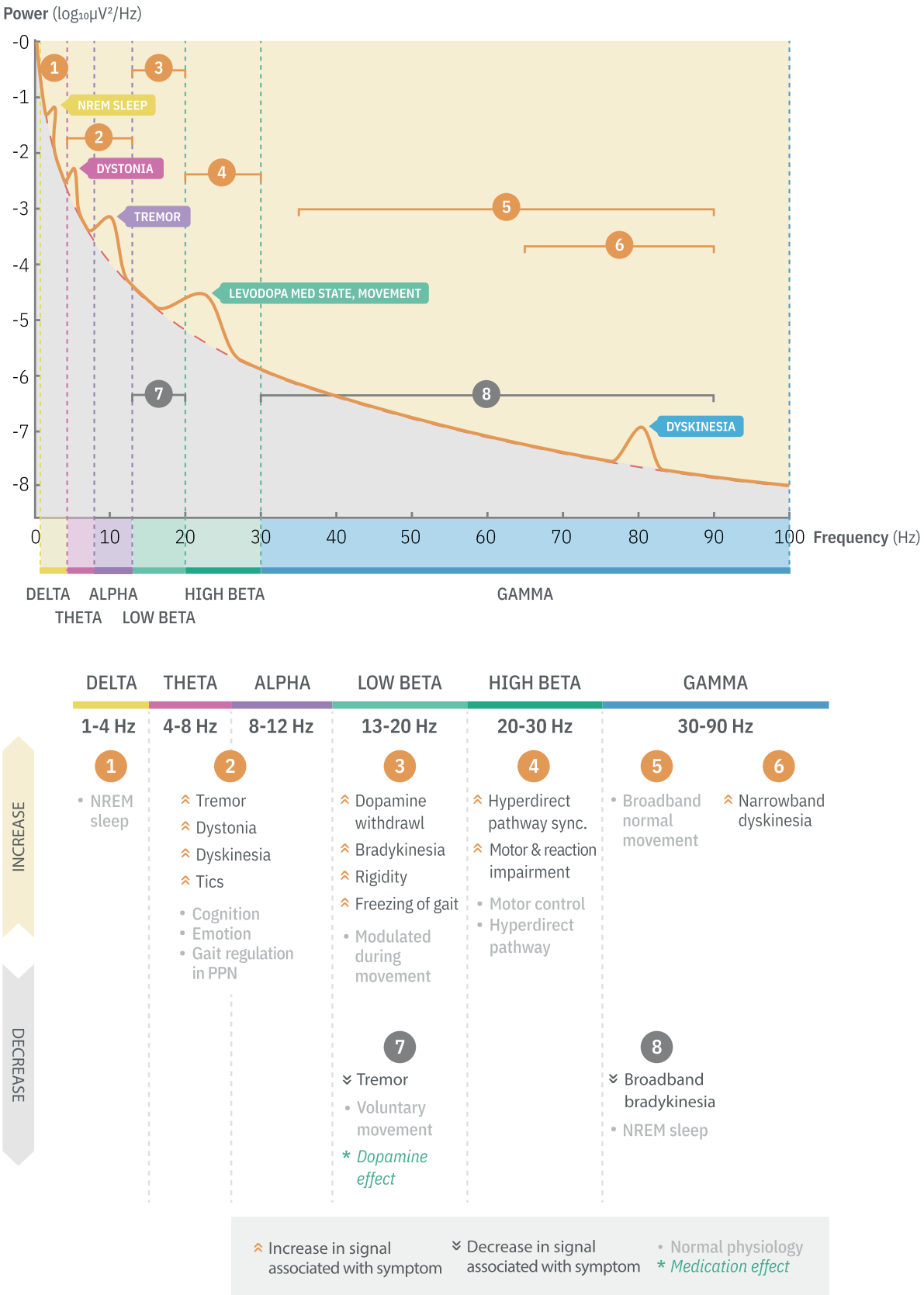


**FIG. 1.** Overview of oscillatory symptom biomarkers that can potentially be used as control signals for adaptive deep brain stimulation in patients with movement and neuropsychiatric disorders. [Color figure can be viewed at wileyonlinelibrary.com]

been piloted in PD involves recording of finely tuned gamma activity from the motor cortex electrocorticography (ECoG) as a feedback signal that can index dyskinesia.[34] Separating the sensing site from the stimulation site has the advantage that electrophysiological recordings in the stimulation target area leads to stimulation artifacts that may be difficult to manage. Moreover, using the same DBS electrode for sensing and stimulation can restrict the contact selection for therapy optimization (see "Technical Challenges For Brain Activity Recordings During Stimulation"). Cortical ECoG can provide a better signal-to-noise ratio and does not impact the degree of freedom in contact selection. Additionally, recording from a different site in the motor network has the potential to identify different biomarkers of clinical states, but this comes at the cost of additional neurosurgical invasiveness, which should be considered cautiously.[35] The first experimental aDBS trials with additional implanted cortical electrodes for brain signal sensing, demonstrated that reducing the delivery of stimulation during periods of high cortical narrow band gamma activity stabilizes dyskinesia driven symptom fluctuations.[1,36] It is important to note, that all clinical observations reported on both aDBS target biomarkers and different control policies remain experimental with requirement for further validation.

## Toward Electrophysiological Brain Biomarker Libraries

The now well-established acceptance of beta as a biomarker in PD has mainly been driven by group level inferences from short data recordings gathered across subjects.[23,37-39] Although first within subject assessments and longer-term follow ups corroborate these group studies,[12,14] it is not necessarily implied that subcortical beta will universally be the optimal biomarker for every individual patient. The best biomarker(s) to optimally represent the relevant and dynamic clinical profiles may vary from patient to patient, particularly in the presence of stimulation. For PD, different oscillatory signatures across the frequency ranges have been described not only for motor symptoms such as bradykinesia, tremor, freezing of gait, and dyskinesia,[12,34,37,40-44] but also for non-motor symptoms (eg, impulsivity, depression).[45,46] Even within defined frequency bands, multiple peaks or ranges may index different clinical and neurophysiological phenomena, for example, low beta activity (13–20 Hz) is more responsive to levodopa,[47] whereas high beta activity (20–35 Hz) couples stronger to motor cortex.[48,49] Potential motor symptom biomarkers also exist in the lower frequencies (3–14 Hz) that may index tremor and non-motor symptoms in PD. Furthermore, it has also been shown that combining several frequency ranges further improves tremor detection.[41,50] In contrast, for essential tremor decoding the oscillatory signature of voluntary movements onset could represent a future strategy to control aDBS.[51-54] In dystonia, theta to alpha (4–12 Hz) band activity has been shown to be increased and correlated to symptom severity[55-61] and was applied as a control signal in the context of an intraoperative aDBS pilot trial[57] and with an embedded device locked to cortical theta.[62] Similarly, the same frequency range recorded in globus pallidus internus and thalamic regions might be of value to index the severity of tics.[63-66] Overall, the current proliferation of brain sensing-enabled devices are helping to discover and refine frequency ranges relevant to symptom states and fluctuations (Fig. 1).[21,67] Here, a particular focus should be put on long-term monitoring of brain signals outside of the clinic.[68,69] Further refinement of biomarker characterization outside the clinic should use objective symptom tracking, ecological momentary assessments, medication-intake logging, and "snapshot" tools to collect spectral characteristics of defined clinical states.[1] Ultimately, open access biomarker libraries should be established in which symptom-specific feedback signals are collected and validated to facilitate informed aDBS programming. Generally, integrating multiple feedback biomarkers (linear, nonlinear, ratio etc.) into the control strategy is likely to provide better symptom prediction control in the future.[17,18,70]

## Increased Parameter Space for Tuning aDBS

Technological advances will bring an increasing number of tunable sensing and stimulation parameters into the clinic, which need to be optimized. Traditional DBS parameters to be defined by DBS clinicians are: (1) stimulation contact/location; (2) stimulation amplitude; (3) stimulation frequency; and (4) stimulation pulse width. Given that all parameters interact and can be set to a wide range of values, the parameter space of traditional DBS is already large and challenging to exploit. Notably, with aDBS, this parameter space gets further extended and becomes more complex. In the upcoming years, it is to be expected that clinicians and scientists will have to engage and explore this extended parameter space and learn how to tune aDBS.[71] In the long term, however, aDBS needs to evolve toward a user-friendly and efficient application, which will involve a yet to be defined balance between automatic- versus clinician-controlled parameters.

Here, we aim to provide an overview of the most important additions to traditional DBS parameters that clinicians, engineers and researchers will have to work

with in upcoming aDBS applications and clinical trials (Fig. 2).

## Sensing Contact and Montage

Adaptive control systems require a reliable and informative feedback signal to support appropriate therapeutic adaptations. For brain sensing, two brain signal recording contacts must be chosen to create a bipolar recording montage that measures the differential voltage change, similar to an electroencephalogram montage. During aDBS when recording and stimulation happens simultaneously in the same brain region, the sensing contacts adjacent to the stimulation contact are often chosen.[28,31] One advantage of this "sandwich" montage is that stimulation signals, which otherwise would cause stimulation artifacts in the brain signals, can be passively cancelled out through "common mode rejection." In this montage, the anode and cathode for sensing are situated symmetrically around the stimulation source. This however restricts the contact selection choices, because two stimulation contacts must be sacrificed for bipolar brain activity recordings. Nowadays, segmented or directional electrodes constitute the standard choice for many DBS centers. These electrodes typically have eight contacts, with the two central contacts being split into three equally sized segments in a circular arrangement. Segmented contacts provide more options to shape the stimulation field and perform neurophysiological recordings with greater spatial resolution.[16,72,73] However, previous studies on aDBS have not made use of directional stimulation and sensing and hardware solutions allowing such montages still need to be explored. The nature of stimulation artifacts as well as other sources of artifacts (eg, motion, electrocardiogram [ECG]) that may all critically limit the use of aDBS are further outlined below (see "Technical Challenges For Brain Activity Recordings During Stimulation").

## Frequency Band of Interest

Given the nature of biomarkers described above, most novel neurostimulator implants have focused on oscillatory LFP features that can be quantified in the frequency domain (Fig. 1). To derive these band power estimates, the IPG transforms the neural time-series data into a power spectrum using onboard Fourier transform based methods.[74] This is a frequency domain representation of the signal, indicating how much power there is at high versus low frequencies. A frequency-range of interest then needs to be selected by the clinician that encompasses the oscillatory feature to be used as an input biomarker (Fig. 1). For PD, a narrow band centering on the individual beta peak frequency in the recording contact-pair is usually chosen as the frequency range of interest. However, as mentioned above, the clinically relevant frequency range in any given patient might vary, hence requiring an individualized biomarker interrogation. For the future selection of the potential feedback signals it also needs to be considered how these are modulated in the context of various physiological states such as physical activity or sleep.[21,67]

## Control Policy

After identifying reliable biomarkers, the most impactful conceptual decision for the clinician will be the choice of the control policy (Fig. 2). The control policy that converts the biomarker/feedback signal into an adaptation of stimulation current delivery. There are multiple possible control strategies within and across aDBS devices that can automatically adjust DBS parameters in response to changes in oscillatory features. In current devices that are now available, stimulation changes are typically dependent on linear systems and threshold crossings of the feature or biomarker. Using a single-threshold policy, stimulation is ramped to a target amplitude depending on biomarker position in relation to a threshold (eg, beta activity crossing a threshold leads to stimulation increase, or increased gamma band activity leading to stimulation decreasing).[28,36] A common dual-threshold control policy uses a lower and an upper threshold.[6] If the biomarker is within the range of these thresholds, the stimulation is determined as effective and not altered. If the biomarker crosses either threshold, the stimulation amplitude is adjusted (eg, beta rises beyond the upper threshold leading to an increase in stimulation amplitude). Therefore, with a dual-threshold policy the biomarker magnitude can theoretically be kept within a predefined range, however, this is dependent on the temporal profile of the biomarker and the selected parameters. Another successfully tested control policy is proportional control, in which the stimulation amplitude changes proportionally to the biomarker amplitude[31] with predefined upper (highest effective stimulation amplitude without side-effects) and lower (lowest effective stimulation amplitude) boundaries. Generally, it is notable that these different policies can all interact with the same biomarker but at different temporal scales from sub second to min/h depending on the how the feedback signal is processed. Overall, this presents multiple different strategies on how to optimally interact with clinical and neurophysiological dynamics.[21] Currently, adjusting the stimulation amplitude is the standard adaptation mechanisms of aDBS, but potentially all available parameters (frequency, contact/field shape, pulse width/shape, etc.) could also be adjusted by control policies. In the future, automatized self-optimization techniques could greatly support the process of parameter


**FIG. 2.** Traditional and additional adaptive deep brain stimulation (aDBS) parameters to be defined by deep brain stimulation (DBS) clinicians. (**A**) Traditional DBS parameters include stimulation contact, frequency, pulse width, and amplitude. (**B**) The additional minimal required parameters for aDBS are the sensing contacts, the frequency band of interest for oscillatory biomarkers and the control policy. Here, we show examples of three control policies that have been implemented in current aDBS devices and tested in humans: (1) single-threshold control requires the definition of a single biomarker threshold. Crossing of the baseline can trigger binary stimulation switches. In the case of parkinsonian beta band activity, biomarker crossing of the threshold would trigger ramping of stimulation to a predefined stimulation current until the biomarker falls below the threshold. (2) The second approach requires definition of a biomarker target range in between two thresholds. Stimulation targets are then defined for each of three possible states—the biomarker may be above the upper threshold, between thresholds or below the lower threshold. Stimulation is maintained when the biomarker remains in between thresholds. Crossing of these thresholds trigger continuous changes in stimulation until the biomarker returns to the defined target range, as shown here for a prototypical slow beta control policy. Both the single- and dual-threshold policy have been piloted as "fast" control strategies that track oscillatory patterns (eg, beta bursts). In addition, the standard threshold control stimulation could also be triggered "inversely." For example, when the biomarker power (eg, finely tuned gamma activity) falls above a given threshold, stimulation may be ramped down (to avoid stim induced dyskinesia in this case) and ramped up when biomarker power is below the lower threshold (ie, inverse biomarker stimulation correlation). (3) A third approach uses proportional control in which stimulation is modulated linearly to track biomarker levels between pre-set maximum and minimum stimulation amplitudes emulating the therapeutic window. This method has been piloted as a "slow" control strategy using a longer time constant. (**C**) Putative examples of the three control policies (single, dual, and proportional control) during medication induced fluctuations. Beta band activity is used as the target biomarker in this example. Single-threshold control policies display sparse triggering in the *levodopa on* state because of infrequent and low amplitude beta bursts; similarly in the dual-threshold control stimulation is trending downward. In both cases this may effectively avoid stimulation induced dyskinesia. In the *levodopa off* state both control strategies show a more frequent and higher level of stimulation to improve motor control, whereas a more balanced stimulation/biomarker interaction is evident in the optimal clinical state. The proportional control slowly adapts the delivery of stimulation to the slow levodopa *off*/*on* transitions. [Color figure can be viewed at wileyonlinelibrary.com]

selection, for example, by learning symptom changes from additional sensors or using machine learning based brain signal decoding.[18,41,70,75]

### Stimulation Amplitude Boundaries, Temporal Smoothing, and Stimulation Response Parameters

In addition to the more obvious choices that the clinicians face as described above, there are now multiple new hidden parameters inside the control policy themselves related to sensing and aDBS. Here we have summarized a non-exhaustive list of important new parameters that require informed decisions: "Stimulation amplitude boundaries" define the lower and upper bounds of the amplitude range within which aDBS can safely operate. These boundaries are defined clinically and should consider the minimally required stimulation amplitude during periods of relative *on* states (eg, after medication intake) and the maximal stimulation amplitude during relative *off* states, that is clinically effective without inducing side-effects, such as dyskinesia or pyramidical tract activation. In addition to the stimulation amplitude boundaries, the temporal characteristics of the biomarker and the stimulation response offer multiple important parameter decisions. The temporal resolution of the neurophysiological biomarker depends among others on the sampling frequency, the temporal settings of the signal analyses (ie, window size of the fast Fourier transform) and a "smoothing parameter." Although sampling frequency and analysis window size might be set by the manufacturer or user, the smoothing parameter is generally flexible and supports modification of the temporal stability of the feature signal and is closely linked to the behavior of the control policy. If no or very brief smoothing is set, variability is allowed to occur on short time-scales, which can be important for targeting pathological and/or transient synchrony states (eg, beta bursts or otherwise fast changing dynamics of the selected biomarker signal.)[28,33] Longer smoothing times instead support monitoring and interaction with slower state transitions (eg, *off* vs. *on* medication.)[31] Future aDBS control strategies could further be enriched by combining symptom biomarkers processed with different temporal parameters to simultaneously depict various neurophysiological states.[21] A partially similar control effect to that of the smoothing parameter can be achieved by adapting a "minimal threshold crossing time," which defines how long the biomarker needs to stay above/below threshold before stimulation is adapted. "Stimulation ramping," the maximal amplitude change over time can be important to ensure safe stimulation adaptation with minimal side effects. Here, an unwanted and unpleasant tingling sensation is sometimes reported, which might be the consequence of large or rapid stimulation amplitude changes. Finally, definition of a recording refractory period after each pulse, that is, detector blanking can be necessary to avoid contamination of the feedback signals with stimulation induced artifacts, particularly for fast control policies. These electrical artifacts can cause self-triggering of the stimulation, which is apparent from a highly stereotyped aDBS pattern (which does not respect the inherent stochastic variability of physiology). Importantly, for all parameters—safety mechanisms need to be built into the device to ensure that patient is not over (or under) stimulated. See Table 1 for a comparison of control policy-specific aDBS parameters.

## Technical Challenges For Brain Activity Recordings During Stimulation

Although first sensing-enabled aDBS devices are now on the market, recording and stimulating in the same target remains a significant challenge. Artifacts of

**TABLE 1** *Control policy-specific adaptive DBS parameters*

| | Adaptive DBS control policy | | |
|---|---|---|---|
| **Adaptive DBS parameter set** | **Single threshold** | **Dual threshold** | **Proportional** |
| Maximal and minimal stimulation boundaries (amplitude) | x | x | x |
| Temporal biomarker smoothing (time) | ms | ms–min | sec–min |
| Minimal threshold crossing time required before stimulation is adapted (time) | x | x | |
| Stimulation ramping/minimal maximal stimulation amplitude change (amplitude/time) | x | x | x |
| Recording refractory period (time) | x | x | |

Abbreviation: DBS, deep brain stimulation.

various kinds can impact signal fidelity and in the worst case, even prevent the use of aDBS for one or both hemispheres in some patients.[76-78] Best described today are electrocardiographic artifacts that result from electric coupling of the stimulation electrode and the implantable pulse generator. A recent study found that implanting the IPG in the right chest at a relative distance from the electric dipole of the heart can mitigate ECG contamination and lower the probability and amplitude of ECG artifacts in available sensing contacts.[76] In addition to ECG artifacts, DBS electrode cable movement can be observed as causing large transients in brain signals.[69] Both of these artifacts contaminate broad bands of the frequency spectrum and therefore, potentially prevent threshold-based control policies from effectively and selectively reacting to the target biomarker and leading to uncontrolled increase (eg, beta-driven aDBS) or decrease (eg, finely driven aDBS) of stimulation. For hyperkinetic movement disorders like dystonia, tremor, and Tourette's syndrome an even lower frequency band (3–12 Hz) has been demonstrated to signal symptom severity.[79] This low frequency band is particularly prone to both ECG and movement artifact contamination, which combined with the hyperkinetic nature of these disorders, will remain a significant technological challenge. Additionally, higher frequency broadband gamma activity may again suffer from over-shadowing through artifacts or limited sensitivity in current systems, because of the notoriously low signal-to-noise ratio in these frequencies. Ultimately, these factors should remind both clinicians and engineers that the current device generation is really optimized for beta activity, and therefore, stepping outside the beta range will require careful attention from neurophysiologists and clinicians. However, even in the beta frequency range, presence of artifacts will require optimizing the choice of sensing contacts and sensing parameters (eg, very short artifacts may be partially counteracted through the refractory period parameter described above.) The relative impact of an imperfect control system may be tolerable given that we are transitioning from a chronic continuous DBS paradigm and that the upper threshold can be chosen cautiously, to avoid "artifact-driven" overstimulation with dyskinesia. A signal check needs to be performed to rule out contamination by movement and ECG related artifacts that can be present in brain signal recordings and users should be aware of these potential neurophysiological confounds. Beyond ECG and movement artifacts, the direct effect of high-frequency stimulation (eg, through subharmonic signal induction or aliasing related artifacts) is often more difficult to handle and potentially obviates safe use of aDBS control policies.[78,80] Here, high amplitude artifacts contaminate the signal leading to multiple harmonic frequency bands correlating directly with the DBS amplitude. One key problem here, is that these artifacts can sometimes only appear at higher stimulation amplitudes. Therefore, if a dual-threshold is chosen and the biomarker crosses the upper threshold, stimulation amplitude may increase causing stimulation artifacts to appear, leading to falsely high feature amplitudes and a continuously increasing and constantly high stimulation amplitude (ie, self-triggering).[78] Aliasing and DBS high-frequency artifacts could be more likely to occur in segmented leads, because of physical properties of the sensing contacts and a lack of symmetry in the recording montage that influences artifact mitigation through common mode rejection. However, recently released leads have also been designed for sensing and improvements in design of electromechanical insulation and tissue-electrode interfaces may partially offset the challenges of smaller electrode contacts. Nevertheless, a full integration of directional contacts for sensing or stimulation in aDBS may require additional strategies for artifact rejection because of the differences in biophysical properties that will be dependent on shape and size of the contact surface. In the future, optimization of DBS lead technology for sensing as well as head mounted pulse generators, will enable key improvements to increase the technical feasibility of aDBS as a new standard of care. Moreover, future discussions on the optimal aDBS set-up design need to include the spatial separation of the sensing and stimulation site. As such, ECoG based cortical sensing of the feedback signal would enable an unrestricted choice of subcortical stimulation contacts conferring advantages regarding signal quality and stimulation flexibility.[36]

## Practical Management of Adaptive DBS: From Individualized Optimization to an Automatized Clinical Tool

Adaptive DBS may become a powerful, but complex precision medicine tool to control the heterogeneously weighted symptom profile of a given patient. For the upcoming years, it is expected that, in contrast to conventional DBS, more time and effort will be required to probe and understand the nuances and clinical effects of aDBS. Iterative clinical algorithms for setting-up aDBS need to evolve and clinicians, scientists, and industry partners have to work in conjunction to establish a sustainable and comprehensive user-interface. Figure 3 suggests procedural steps that may be considered for future aDBS programming algorithms. Notably, this is a starting point and further protocol adjustments are expected with improving knowledge and technical advancement of adaptive therapies. The clinical-electrophysiological interrogation of the patient will be the backbone for configuring aDBS, and this

needs to be simplified for non-specialist users. In previous aDBS trials, the selection of the aDBS feedback signal was mainly based on the patient's resting state spectral profile (eg, selection of the individual beta peak). However, future aDBS set-up pipelines should be more refined and may take advantage of spectral characteristics obtained during various states (eg, movement, *on–off* medication, ON–OFF continuous stimulation) (Fig. 3). Moreover, it is often neglected that biomarkers can also be affected by changes attributable to circadian and potentially other biorhythms in individual patients. The combination of signals obtained during a clinical session combined with home monitoring may, therefore, help to determine the relevant circadian biomarker profile and its temporal dynamics during day and night.[1,21,67,81] We expect configuration to likely initially be limited to the selection of single biomarkers, but with the extension of software and hardware capabilities, a combination of multiple biomarkers combined with machine learning may significantly extend the clinical utility of aDBS.[75] Beyond the selection of feedback biomarkers, the parametrization of the aDBS control policy as well as potential technical limitations (eg, ECG, stimulation artifacts) need to be considered.[76] In the future, we will face patient-specific situations, in which aDBS cannot be performed (unilaterally or bilaterally), because of artifacts or the lack of reliable feedback signals to optimally control DBS better than is achievable with continuous DBS. Both clinicians and patients should be informed about this possibility for the sake of expectation management.

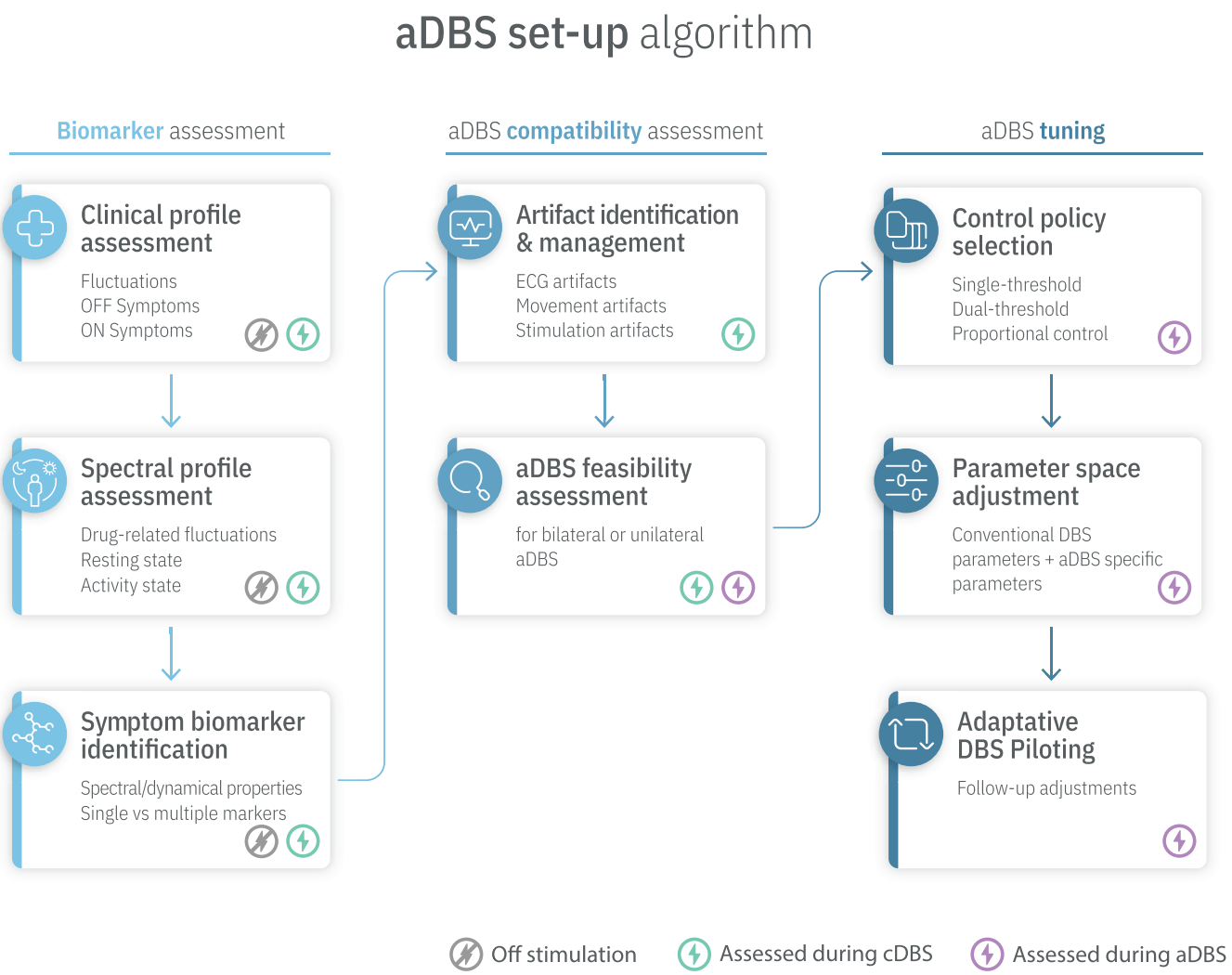


**FIG. 3.** Practical approach to set up adaptive deep brain stimulation (DBS). The implementation of adaptive deep brain stimulation (aDBS) for a given patient requires a step-wise procedure. This involves the assessment of the individual clinical and spectral characteristics for the identification of symptom-specific biomarkers. In principle and depending on the target biomarker, this assessment can be informative if conducted during different clinical conditions as well as OFF and ON continuous stimulation. Special consideration should be given to signal artifacts that could potentially interfere with a control system. Overall, the question should be answered, whether aDBS is feasible to be applied unilaterally and/or bilaterally. There are different control policies that can be selected (also see Figs. 1 and 2) and the clinical and electrophysiological response during continuous DBS may inform the fine tuning of aDBS-specific stimulation parameter boundaries. As with conventional DBS, aDBS parameters need to be reassessed and tuned over time. [Color figure can be viewed at wileyonlinelibrary.com]

Therefore, an aDBS feasibility assessment should be part of the clinical pipeline. Additionally, there will be more than one control-policy available, which may be selected according to the patients' main symptom and biomarker profiles. Each control-policy comes with a set of different stimulation parameters that need to be tuned according to the neurophysiological target biomarker dynamics. Hence, the parameter space of a fast control policy (eg, to truncate beta bursts) may differ from policies to control neurophysiological manifestations at slower time scales. In principle, the commercially available sensing-enabled neurostimulators should have capabilities that span the parameter space to allow for different interaction with neurophysiological brain biomarkers at different time scales. The configuration of the optimal aDBS parameters for an individual patient may include the assessment of clinical and spectral characteristics without stimulation, as well as different levels of continuous stimulation to determine parameter boundaries. Moreover, the selection of the control policy and parameters must be evaluated and selected in the light of potentially limiting artifacts.[78] Finally, chronic recordings and electrophysiological readouts as part of regular follow-ups together with objective clinical assessments should help to optimally tune aDBS control policies over time.[21,30,82]

## How to Evaluate the Clinical Effect

Adaptive DBS may become a clinical precision medicine tool for targeting individual neurophysiological manifestations and symptoms.[21] To achieve this aim, know-how and technological improvements will require knowledge sharing within the community, derived from iterative adjustment procedures on individual patients and case series in addition to sparser group level studies. This needs to be considered in the context of appropriate trial designs, especially if clinical differences are subtle, patient-specific, and difficult to observe in the clinic setting. In essence, conducting multiple n-of-1 studies and results-oriented frameworks to evaluate patients' clinical response in this context might be key.[83,84] In addition, objective symptom assessment using wearable technologies, monitoring in controlled study environments as well as long-term home recordings are potentially valuable to evaluate and tune these next generation therapies.[1,85-87]

## Closed-Loop DBS: Starting Simple and Thoughtful

Given the remarkable knowledge gain on electrophysiological symptom biomarkers, it seems intuitive that adaptive bidirectional neuromodulation could address individual symptom fluctuations more accurately than continuous DBS. In brief, the current translational state of aDBS entails (1) a number of small sized, but promising clinical pilot studies; (2) first commercial release of closed-loop DBS capable neurostimulators; and (3) first ongoing feasibility and safety trials for aDBS in PD. Looking further ahead, the development of clinically sustainable aDBS systems will bring new challenges, with many of them being technical in nature, including artifact free interaction with brain activity. In the future, some of these challenges could be addressed by pairing additional external devices wirelessly with the DBS implants to support physiological and behavioral tracking and increase the precision of the patient-tailored control strategies.[1,88] In the long term for chronic treatment, an all-in-one implanted system is preferable over putting additional hardware burden to the patient. With this article we hope to inspire the discussion in the community to address strategies for handling the growing degrees of freedom of the parameter space required to calibrate adaptive stimulation according to heterogeneous symptom profiles. The now widely available access to brain signals in chronically implanted patients through the new neurostimulators will push and change the architecture of this research field. We hope to encourage the involved researchers to emphasize open-science practices, to make code, and data available and empower new multicenter research consortia to work together with patients in the clinics to systematically investigate the various facets of aDBS and to establish robust control strategies that can be adopted into clinical practice. Exciting, but also challenging times are ahead of us and a previously mentioned statement in this context[89] can only be reemphasized: "first walking, then running."

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Not applicable.

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## Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

W.J.N.: 1A, 3A, 3B
R.G.: 3A, 3B
S.L.: 3A, 3B
G.T.: 1A, 3A, 3B