

## Toward adaptive deep brain stimulation for dystonia

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The presence of abnormal neural oscillations within the cortico-basal ganglia-thalamo-cortical (CBGTC) network has emerged as one of the current principal theories to explain the pathophysiology of movement disorders. In theory, these oscillations can be used as biomarkers and thereby serve as a feedback signal to control the delivery of deep brain stimulation (DBS). This new form of DBS, dependent on different characteristics of pathological oscillations, is called adaptive DBS (aDBS), and it has already been applied in patients with Parkinson's disease. In this review, the authors summarize the scientific research to date on pathological oscillations in dystonia and address potential biomarkers that might be used as a feedback signal for controlling aDBS in patients with dystonia.

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**A**CCORDING to the latest expert consensus, dystonia is clinically defined as "a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both."<sup>2</sup> Dystonia can be caused by numerous etiologies, including acquired and different biochemical, cellular, or genetic substrates. The similarity of the clinical dystonia phenotype, however, suggests a unifying common pathophysiological pathway at a functional or network level.<sup>4</sup> A currently leading hypothesis on its neurophysiological basis is that dystonia is the result of abnormal activity in cortico-basal ganglia-thalamo-cortical (CBGTC) and cerebellar networks.<sup>5</sup> The treatment for the majority of dystonia subtypes only provides symptomatic relief, without addressing the underlying cause of the disease. Options currently available include oral medication (e.g., anti-cholinergic and antidopaminergic drugs, benzodiazepines,

and baclofen), botulinum toxin (treatment of choice in focal dystonias), and deep brain stimulation (DBS).<sup>4</sup>

### DBS in Dystonia

Given the limited efficacy and high prevalence of adverse effects associated with oral medication in generalized dystonia, DBS of the internal globus pallidus (GPi) has become the preferred therapy in this patient group.<sup>4</sup> Several randomized controlled trials have demonstrated a sustained improvement in patients with (isolated) generalized dystonia following DBS, as shown by lower motor and functional scores on the Burke-Fahn-Marsden dystonia rating scale.<sup>29</sup> After 5 years of DBS, generalized dystonia is reported to show a reduction in the Burke-Fahn-Marsden dystonia rating scale score of 42%–61%.<sup>8</sup> Furthermore, the health-related quality of life after DBS for dystonia improves significantly, by about 24%–51%, among several

**ABBREVIATIONS** AA = agonist-antagonist; aDBS = adaptive deep brain stimulation; CBGTC = cortico-basal ganglia-thalamo-cortical; cDBS = continuous DBS; ECoG = electrocorticography; EEG = electroencephalography; EMG = electromyography; GPi = internal globus pallidus; LFP = local field potential; PD = Parkinson's disease.

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independent trials.<sup>27</sup> DBS therapy has also been utilized in other types of dystonia when an adequate response to botulinum toxin therapy could not be achieved.<sup>24</sup> A large, randomized clinical trial demonstrated that DBS is useful in medication-refractory cervical dystonia compared to sham stimulation, with a significant improvement of the Toronto Western Spasmodic Torticollis Rating Scale severity score (26% vs 6%, respectively), 3 months after implantation.<sup>73</sup>

Despite its good effect, the exact mechanism of DBS in dystonia remains unclear,<sup>10</sup> and clinical outcomes can differ from patient to patient, as well as among different subtypes of dystonia.<sup>8</sup> Patients at an early stage of the disease and with less disability usually respond better to DBS. This is especially the case in patients with *DYT1* mutations and tardive dystonia. In contrast, the response in other types of dystonia is less predictable, which makes the selection of appropriate candidates for DBS challenging.<sup>3</sup>

## Drawbacks of Current (Continuous) DBS

More than 15 years of experience with DBS in dystonia has demonstrated the efficacy of the current model of continuous DBS (cDBS) once the optimal stimulation parameters have been achieved.<sup>41</sup> Nevertheless, there are still limitations in terms of efficacy and side effects related to cDBS. Due to limited knowledge of CBGTC and cerebellar networks in dystonia, the modification of electrical stimulation parameters in DBS is essentially heuristic, and DBS programming is based on clinical records and examination. In this process, the clinician starts with the conventional initial settings of the DBS system, delivering a constant current or voltage through the selected electrode(s). The settings are then adjusted in a trial-and-error process, based on the clinical response and the absence of adverse effects.<sup>50</sup> However, an immediate response is often not possible to achieve, since it generally takes weeks to months to notice a perceptible change, especially in tonic dystonic components.<sup>53</sup> For this reason, it can take up to several weeks to modify the initial parameters.<sup>30</sup> In general, significant improvement can be expected approximately 3 months after the surgery, but it usually takes up to a year to achieve the maximum clinical effect.<sup>41</sup> Another technical problem is the voltage required for stimulation in dystonia. While a mean of 3.0 V is usually effective to obtain an adequate clinical response in Parkinson's disease (PD) patients, with electrodes implanted either in the GPi or the subthalamic nucleus,<sup>47</sup> the effective voltage in dystonia is more variable. It depends, among other things, on the type of dystonia, the area of the body affected, and the patient's tolerance of high voltages (due to the subsequent emergence of stimulation-related side effects), ranging from 2.2 up to 7.0 V.<sup>28</sup> Therefore, non-rechargeable batteries need to be replaced more often, with a mean longevity of 28.1 months for dystonia compared with 47.2 months for PD.<sup>53</sup> This not only increases the treatment costs, but it also exposes the patient to more surgical procedures, as well as their attendant risks.

Finally, there are significant side effects induced by cDBS in dystonia patients, such as dysarthria (in up to

12%)<sup>29</sup> and parkinsonism (13%).<sup>70</sup> Among patients with cranial-cervical dystonia treated with GPi DBS, 90% reported at least one motor symptom associated with parkinsonism, such as handwriting problems, difficulty with standing up from a chair, and gait disturbances.<sup>7</sup> In line with this, a correlation has been described between the increase in GPi stimulation frequency and the development of bradykinesia.<sup>26</sup>

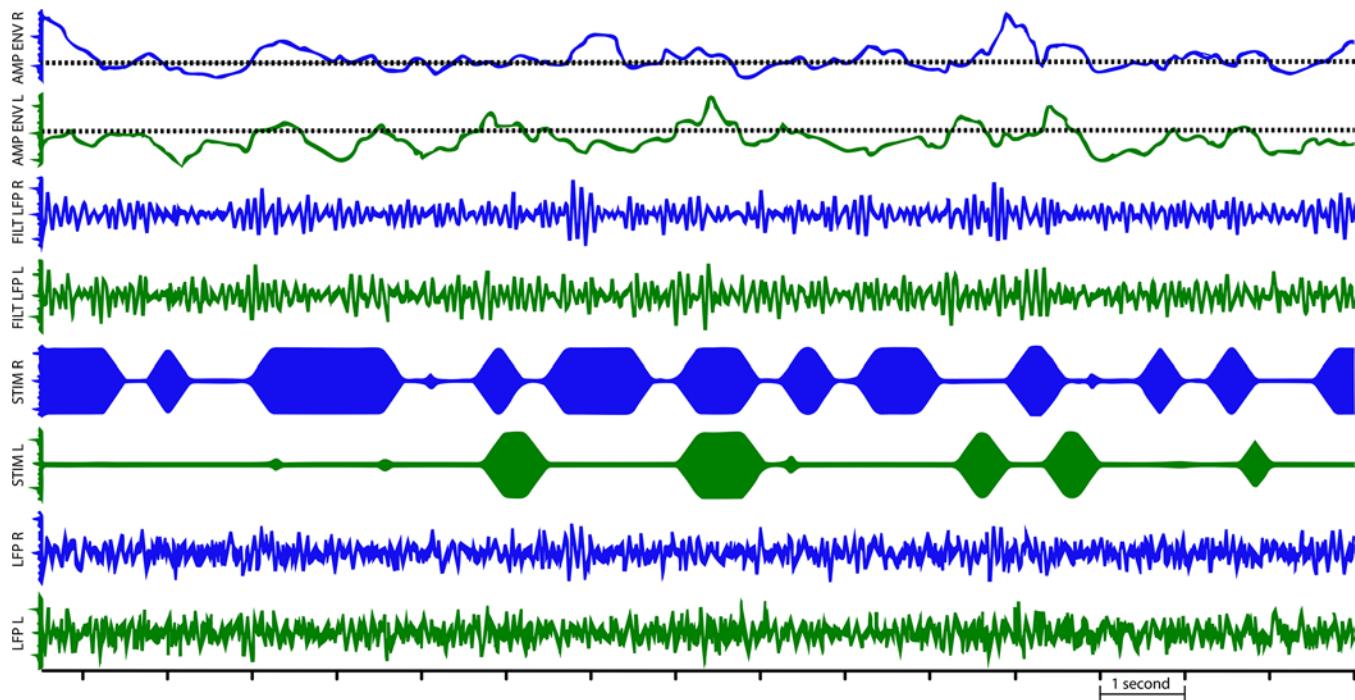
The appearance of these side effects after stimulation suggests that DBS interferes with both pathological activity in the CBGTC circuits<sup>39</sup> and physiological activity that helps to control voluntary movements.<sup>9,29</sup>

To improve efficacy and limit side effects, much effort has been put into developing DBS systems that only stimulate when pathological activity and clinical symptoms are present.<sup>39</sup> Future DBS devices might be able to deliver electrical stimulation in response to pathological oscillations by increasing electrical current on demand—that is, only when, for example, the oscillatory power exceeds a threshold.<sup>46</sup> This adaptive form of DBS (aDBS) has already been successfully applied in nonhuman primate models of PD<sup>56</sup> by using the occurrence of cortical spikes as a biomarker. In patients with PD, there is also evidence of the effectiveness of aDBS.<sup>32,34,51,55</sup> In these studies, the power of subcortical beta (13–30 Hz) oscillations, which correlate with bradykinesia and rigidity in PD,<sup>54</sup> was used as a biomarker. The most important positive effects of human aDBS studies in PD were increased efficacy, energy-saving properties, and potentially fewer side effects. This line of evidence strongly suggests that pathological oscillations can successfully be used as a biomarker for controlling DBS.

## Preparing the Way for aDBS in Dystonia Neural Oscillations as Biomarker

Neural oscillations are part of the physiological components present in the regulatory pathways of voluntary movements and are potentially a means by which neuronal structures communicate among one another and with muscular units.<sup>61</sup> The relationship of oscillations between two different sources can be addressed by means of coherence analysis, which indicates the degree of mutual dependence.<sup>12</sup> Experiments carried out in healthy subjects have shown an increased coherence between cortical beta activity (13–30 Hz) and contralateral muscle discharges, respectively recorded with electroencephalography (EEG) and electromyography (EMG), suggesting that voluntary contractions are coupled with the physiological oscillatory activity of cortical neurons.<sup>12,60</sup>

In certain movement disorders, this physiological oscillatory activity is thought to be altered, since abnormal (pathological) oscillatory profiles have been detected.<sup>5,18,43</sup> The use of subcortical beta oscillations as a biomarker for aDBS in PD was motivated by recordings of synchronized activity of large populations of neurons in the basal ganglia, known as local field potentials (LFPs). These LFPs can be recorded from the same DBS electrode contacts that deliver electrical stimulation. During a recording, LFPs are rapidly processed, and changes in power on a selected frequency band (e.g., beta range) are detected



**FIG. 1.** Potential interface for aDBS using low-frequency oscillations. In this figure, the presence of low-frequency oscillations on an LFP is visualized and used for an adaptive stimulation algorithm. Raw signals (LFP L and R) are dynamically recorded and filtered around the low-frequency peak registered (FILT LFP L and R). Afterwards, the filtered signal would be rectified, and an amplitude threshold would be set, in order to trigger the stimulation (STIM L and R) every time that an increment in low-frequency activity is detected. A brief delay in the activation of the stimulation would ensure that the stimulation is triggered only by actual increments of low-frequency activity and not by short-lived artifacts. AMP ENV = amplitude envelope of the rectified filtered signal; FILT LFP = LFP filtered around the low-frequency peak detected in order to visualize low-frequency oscillations embedded in the signal; L = left; R = right; STIM = channels representing stimulation amplitude.

through spectral analysis. The increase in frequency power triggers DBS in PD, which is continued until the power drops below a selected threshold.<sup>25</sup>

One of the lessons learned from aDBS in PD patients is that the feedback signal of a biomarker needs to be both sensitive and specific. This means that the biomarker should correlate well in time with the severity of clinical symptoms (specificity)<sup>33</sup> and that the signal detected should be powerful enough to be differentiated from artifacts—e.g., the noise caused by the stimulation itself (sensitivity).<sup>57</sup>

### Neural Oscillations in Isolated (Primary) Dystonia

As discussed above, increased beta oscillations have been found in patients with PD and used as a biomarker for aDBS. To answer the question of whether it is possible to transfer aDBS from PD to dystonia, it is necessary to identify biomarkers for the latter (Fig. 1, Table 1). Several studies have addressed the presence of (pathological) oscillations in patients with isolated dystonia. LFP recordings have shown increased power in low frequencies (4–12 Hz) in dystonia patients.<sup>64</sup> Chen et al. demonstrated a positive correlation between pallidal low-frequency oscillations and muscle (EMG) activity in dystonia patients that was consistent among all contact pairs of the tested DBS electrodes.<sup>9</sup> In the same experiment, an additional correlation was found in the beta range (13–30 Hz), but this was

not consistent among different contact pairs. Abnormal low-frequency oscillations have not only been found between GPi and EMG, but also in LFPs recorded in the subthalamic nucleus of dystonia patients<sup>17,45</sup> and between different EMG signals.<sup>69</sup> Directed transfer analyses suggest that this excessive oscillatory GPi activity is mostly driven from the GPi to the affected muscles.<sup>62</sup>

Furthermore, a sensorimotor modulation of GPi LFPs has been observed in response to active and passive movements, with a decreased LFP synchronization at 8–20 Hz and in dystonic involuntary muscle spasms with an increased activity in the range of 3–18 Hz.<sup>35</sup> This modulation of LFPs has also been observed in patients with an effective sensory trick (directing actions or movements to a specific part of their bodies where dystonia is present in order to alleviate their symptoms<sup>2</sup>).<sup>67</sup> In these patients, a suppression of the abnormally synchronized activity in the range of 6–8 Hz and beta bands was observed during the performance of the sensory trick, indicating a peripheral regulation of the CBGCT oscillations. In summary, information from peripheral stimuli also influences the behavior of neural oscillations, at least to a certain degree.

A major finding that directly supports the use of low-frequency (4- to 12-Hz) oscillations as a biomarker for dystonia was described by Barow et al.<sup>5</sup> In this study, increased low-frequency oscillations recorded from DBS electrodes of dystonia patients were significantly suppressed at the moment DBS was switched on, and they reemerged after

**TABLE 1. Potential biomarkers for aDBS in dystonia with their advantages, disadvantages, and challenges**

Biomarker	Advantages	Disadvantages	Further Questions
I. GPI LFPs of 4- to 12-Hz magnitude/spectral power	Most-studied oscillations. Correlated w/ phasic dystonia. Direct measurement of pathological network activity	Not correlated w/ tonic dystonia. Noise generated by stimulation might interfere	Evaluate the adequacy of the biomarker
II. Muscle activity (EMG) 4- to 12-Hz magnitude/spectral power	Coherent w/ LFPs. Direct measurement of dystonic activity	Additional device required for EMG	Investigate applicability of subcutaneous EMG in aDBS
III. Dystonic tremor (EMG) 4- to 12-Hz magnitude/spectral power	Potentially useful if tremor is the predominant symptom. Direct measurement of a clinical symptom	Nonspecific biomarker	Develop algorithms capable of increased specificity in detection of dystonic tremor
IV. ECoG 4- to 12-Hz spectral power	Potential alternative for aDBS use. High signal amplitude & less stimulation interference	Subdural electrodes needed to be placed. Still at an early phase	Elucidate which ECoG biomarkers could be used as a feedback for aDBS
V. Coherence between biomarkers (e.g., LFP-EMG)	Correlates two different sources of pathological oscillations	At least two different devices are required. Lower temporal resolution	Examine whether coherence estimation is sufficiently fast for adaptive stimulation
VI. EMG AA ratio/sum	Identifies when dystonic activity is present. Good time resolution	At least two different devices are required. Nonspecific. Not predictive (rather reactive)	Explore possibilities of using this statistic to increase the specificity & time resolution of aDBS biomarkers

Common to all biomarkers is the need to establish their robustness across time and their reliability during brain states like sleep.

stimulation was switched off. Additionally, increased coherence from EEG LFPs and EMG LFPs within the 4- to 12-Hz range was reduced after DBS stimulation. Another study showed that increased low-frequency activity in the cortex is normalized after applying DBS.<sup>40</sup> These findings indicate that the application of high-frequency GPi DBS modulates the abnormally increased low-frequency activity. For these reasons, a paradigm for aDBS in dystonia based on the level of low-frequency oscillations seems plausible (Fig. 2).

The studies mentioned so far in this section included a varying degree of patients with different types of local, segmental, and generalized forms of isolated dystonia (both sporadic and genetic/familial) in their cohorts. For that reason, the specific roles of low-frequency oscillations in each form of isolated dystonia are currently unclear. Recently, a study that only included patients with cervical dystonia showed that the power of low-frequency oscillations in the dystonic GPi positively correlates with Toronto Western Spasmodic Torticollis Rating Scale scores, and an increased coherence is present between dystonic GPi and EMG signals in the low-frequency band.<sup>44</sup> This gives a rationale for the employment of low-frequency oscillations as a biomarker for aDBS in this particular group.

Although several comparative studies have found increased subcortical low-frequency activity to be a characteristic of dystonia when compared to PD,<sup>17,64,75</sup> this has not always been replicated.<sup>65,68,74</sup> The co-occurrence of dystonia and PD might, at least partially, explain this phenomenon.<sup>71</sup> However, the exact role of (pathological) low-frequency oscillations in dystonia is yet to be clarified.

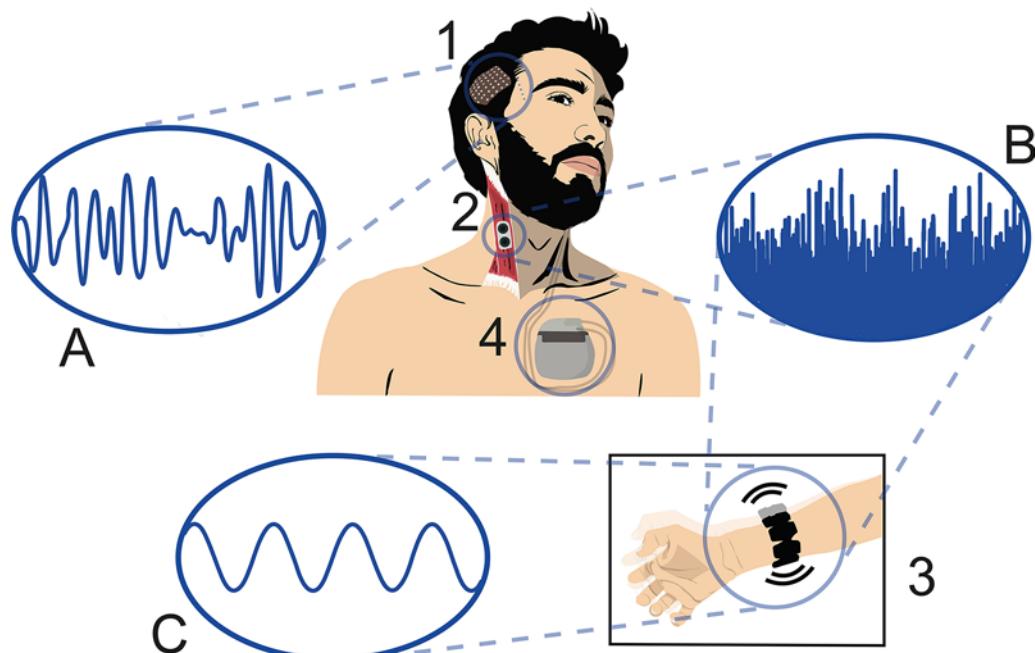
### Neural Oscillations in Other Types of Dystonia

Although virtually all neurophysiological studies described above have been carried out in patients with diverse forms of isolated dystonia, some studies have shown similar results for increased low-frequency oscillations in

other subtypes of dystonia, indicating at least a partially shared common pathophysiology for all of them. Prominent 5- to 18-Hz oscillations from the GPi and thalamus were recorded in a patient with acquired dystonia secondary to a cryptogenic stroke.<sup>72</sup> Furthermore, studies based on LFP EMG and EMG-EMG coherence analysis have found an increased abnormal coherence in the low-frequency range in patients with myoclonus-dystonia.<sup>15,16</sup> These findings suggest that another potential biomarker to modulate the intensity of aDBS could include the low-frequency common drive to motor units detected through EMG; detection of this could be technically possible thanks to the development of subcutaneous EMG registers that can transmit the information wirelessly to the DBS generator.<sup>38,59</sup>

### Phasic and Tonic Components of Dystonia

While dystonia is usually composed of tonic (sustained) and phasic (rhythmic) abnormal movements,<sup>2</sup> increased low-frequency oscillations have only, thus far, been correlated with the phasic components of dystonia,<sup>36,44</sup> including the reduction of such abnormal oscillations after cDBS.<sup>5</sup> With conventional cDBS, the clinical improvement of phasic and tonic components differs in time; phasic components improve faster (sometimes even immediately) following the application of DBS, whereas improvement in tonic components can take weeks to months.<sup>11</sup> In contrast, when discontinuing stimulation, phasic components can recur rapidly, while tonic components recur in a more gradual manner.<sup>19</sup> This temporal dissociation leads to the hypothesis that different pathophysiological mechanisms are involved.<sup>1</sup> The rapid improvement seen in the phasic components is thought to be due to a direct DBS effect, whereas changes in tonic components are attributed to stimulation effects on neuronal plasticity.<sup>22</sup> It has been observed that the benefits of DBS may remain after stimulation is discontinued, even after the 1-year follow-



**FIG. 2.** Potential biomarkers and recording sites. Dystonic brain activity (A) (e.g., increased low-frequency oscillations) can be recorded either in the form of local field potentials—from the electrodes used for stimulation or from electrodes placed on the cortical surface of the brain (electrocorticography) (1). Dystonic muscle activity (B) can be recorded either from subcutaneous EMG (2) or through wearable devices (3), which could also detect dystonic tremor (C), thanks to integrated accelerometers. Signals can be instantaneously processed in the battery (4), to modulate stimulation according to the biomarker selected (to visualize a stimulation algorithm [see Fig. 1]). Copyright Dan Piña-Fuentes. Published with permission.

up period.<sup>20,58,66</sup> This could imply that DBS produces a series of readjustments in CBGTC and cerebellar networks that persist after stimulation has ceased. It remains to be elucidated how aDBS might influence the tonic components of dystonia.

### Dystonic Tremor

A specific component of phasic dystonia in which aDBS might be considered is the presence of dystonic tremor. The prevalence of tremor in patients with dystonia varies from 11% to 87% among studies.<sup>14</sup> Lee et al. contrasted data of patients with task-specific primary bowing tremor (a task-specific tremor especially occurring in string musicians) with data obtained in matched healthy controls, revealing coherence between the coactivation of wrist antagonist muscles (measured with EMG) and tremor fluctuation (measured with accelerometers on the metacarpal-phalangeal joint of the index finger) in the low-frequency range only in the patient group.<sup>31</sup> Whereas this might indicate an influence of the dystonic oscillatory activity in dystonic tremor, more studies are required to elucidate this relationship. At present, when the tremor is the most disabling symptom,<sup>21</sup> the ventral intermediate/lateral thalamus is used as a primary target in dystonia patients.<sup>42</sup>

In a recent study, patients had an improvement of 77% on clinical tremor scales after DBS of the ventrolateral thalamus.<sup>49</sup> However, significant side effects also occurred, which raises the question of whether aDBS based on tremor amplitude/phase could be an alternative. How-

ever, at this moment, the assessment of tremor using current accelerometers is still nonspecific, owing to the difficulties in distinguishing accelerometer signals resultant from voluntary movements. Advanced tremor-specific accelerometer computation paradigms to treat patients with PD are currently being explored,<sup>37</sup> so in theory similar devices to assess dystonic tremor might be applied in the future.<sup>63</sup>

### Electrocorticography

Electrocorticography (ECoG) recording is another neurophysiological tool that might be considered for aDBS. It uses electrodes implanted in the subdural space, giving a powerful spatial resolution of local cortical activity. One of the first ECoG studies on movement disorders used this technique to measure cortical LFPs in patients with PD, essential tremor, and (cranio-)cervical dystonia.<sup>13</sup> In the resting state, the authors found a peak in motor cortex LFPs that occurred in the high-beta band for PD and in the low-beta band for dystonia and essential tremor. They also found an impaired cortical beta desynchronization related to movement, present in both motor and somatosensory areas. Low-frequency oscillations (4–12 Hz) were not analyzed in this study due to roll-off interference of the high-pass filter in the recordings. Recently, the utility of ECoG to measure neural oscillations in the CBGCT network was addressed in a series of 189 patients (200 recordings) with movement disorders undergoing DBS surgery.<sup>48</sup> Some of the advantages of ECoG mentioned included higher-amplitude signaling, less DBS noise interference, and poten-

tially a safe clinical profile (no significant adverse events added to the DBS procedure were reported in this study). These findings give rise to the potential use of ECoG to further investigate oscillations within the CBGTC network and, ultimately, find a potential biomarker for aDBS.

### Temporal Dynamics of Prospective Biomarkers

One of the main questions that need to be answered before implementing aDBS in dystonia is what the temporal characteristics of the selected biomarker are. The latency and duration of the biomarkers mentioned (e.g., GPi-LFPs), and how fast they react to electrical stimulation, should be investigated to determine how the aDBS system must be programmed and how well it can anticipate rather than react to the appearance of symptoms.

### Combining Neurophysiological Techniques

In addition to single signals, the relation between oscillatory activity at two different sources, by means of coherence and/or other statistics might be used for aDBS. For example, LFP-EMG coherence or the EMG agonist-antagonist (AA) ratio might provide a more informative biomarker than a single-site recording. As mentioned before, increased coherence between LFP-EMG and EMG-EMG has been correlated with the severity of dystonic contractions.<sup>15,16</sup> In relation to this, aDBS might be programmed based on the volatility in coherence. Nevertheless, to perform a “real-time” coherence analysis, the original signal has to be estimated over a finite period of time, limiting temporal resolution.

Besides coherence, other indicators of dystonic muscle activity can be obtained from EMG. This is based on the evidence that the co-contraction and overflow of AA muscles have been found on EMG measurements of dystonic patients.<sup>6</sup> However, at present, an AA sum or AA ratio is not yet specific enough to differentiate signals of pathological contractions from voluntary contractions.<sup>23</sup> In the future, evaluation of the predictive value of combined signals through machine learning may lead to greater specificity.

### Conclusions

After years of successful application in dystonia, the potential of cDBS is still limited in terms of efficacy, side effects, and efficiency. Next to this, the current lack of neurophysiological parameters that can predict the individual clinical response of dystonia to DBS makes programming difficult. For these reasons, improvements in knowledge about the neurophysiological alterations underpinning dystonia and the emergence of DBS devices capable of simultaneously recording neural activity and providing stimulation should allow aDBS to be developed for the treatment of dystonia in the future. At present, 4- to 12-Hz LFP oscillations appear to be the most promising candidate, but other neurophysiological signals (e.g., those from EMG and ECoG) and their interactions might also be suitable. However, many questions remain, such as the effects of microlesion effects, sleep, and medication on DBS recordings. Regardless of the source of the biomarker or biomarkers selected for aDBS, their volatility and robustness over time will have to be established. Critical too, most of

the potential biomarkers described here relate to phasic aspects of dystonia, and therefore the more delayed response of more tonic dystonic elements to aDBS remains to be established.

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## Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

## Author Contributions

Conception and design: Piña-Fuentes, Beudel. Drafting the article: Piña-Fuentes, Beudel. Critically revising the article: Piña-Fuentes, Beudel, Little, van Dijk, Tijssen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Piña-Fuentes. Administrative/technical/material support: Piña-Fuentes. Study supervision: Beudel.

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