TOWARDS ADAPTIVE DEEP BRAIN STIMULATION FOR DYSTONIA

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» Abstract word count: 113

» Text word count : 3091

» Number of references: 75

» Number of tables and/or figures (total) :

1 table/ 2 figures

Abstract

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 has already been applied in patients with Parkinson's disease (PD). In this review, we 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 dystonia.

Introduction

According 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".[2] Dystonia can be caused by a long list of 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.[4] 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.[52] The treatment for the majority of dystonia subtypes is symptomatic. Options currently available include oral medication (e.g. anticholinergic and antidopaminergic drugs,

benzodiazepines, and baclofen), botulinum toxin (treatment of choice in focal dystonias), and deep brain stimulation (DBS).[4]

DBS in dystonia

Given the limited efficacy and high prevalence of adverse effects of oral medication in *generalized* dystonia, DBS of the internal Globus Pallidus (GPi) has become the preferred therapy in this patient group.[4] 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 (BFMDRS).[29] After five years of DBS surgery, generalized dystonia is reported to show a reduction in the BFMDRS score of 42-61%.[8] Furthermore, the health-related quality of life after DBS for dystonia improves significantly – by about 24-51% amongst several independent trials.[27] DBS therapy has also been utilized in other types of dystonia when an adequate response to botulinum toxin therapy could not be achieved.[24] 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 (TWSTRS) severity score (26% versus 6%, respectively), three months after implantation.[73]

Despite its good effect, the exact mechanism of DBS in dystonia remains unclear,[10] and clinical outcome can differ from patient to patient, and among different subtypes of dystonia.[8] 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.[3]

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.[41] 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 at the selected electrode(s). The settings are then adjusted in a trial-and-error process, based on the clinical response and absence of adverse effects.[50] 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.[53] For this reason, it can take up to several weeks to modify the initial parameters.[30] In general, significant improvement can be expected approximately three months after the surgery, but it usually takes up to a year to achieve the maximum clinical effect.[41] Another technical problem is that the voltage (V) required for stimulation in dystonia. While a mean of 3·0V 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 (STN),[47] the effective voltage in dystonia is more variable. It depends, among others, on the type of dystonia, the area of the body affected and the tolerance to high voltages (due to the subsequent emergence of stimulation-related side effects), ranging from 2.2 up to 7·0V.[28] Therefore, non-rechargeable batteries need to be replaced more often, with a mean longevity of 28·1 months for dystonia versus 47·2 months for PD.[53] This not only increases the treatment costs, but also exposes the patient to more surgical procedures, including their concomitant risks.

Finally, there are significant side-effects induced by cDBS in dystonia patients, such as dysarthria (up to 12%)[29] and parkinsonism (13%).[70] 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.[7] In line with this, a correlation has been described between the increase in GPi stimulation frequency and the development of bradykinesia.[26]

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

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.[39] Future DBS-devices might be able to deliver electrical stimulation in response to pathological oscillations by increasing electrical current on demand, i.e. only when, for example, the oscillatory power exceeds a threshold.[46] This adaptive form of DBS (aDBS) has already been successfully applied in non-human primate models of PD[56] by using the occurrence of cortical spikes as a biomarker. In patients with PD, there is also evidence for the effectiveness of aDBS.[33,34,51,55] In these studies, the power of subcortical beta (13-30 Hz) oscillations which correlate with bradykinesia and rigidity in PD[54] was used as a biomarker. The most important positive effects of human aDBS studies in PD were increased efficacy, energy-saving properties, and potentially less 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 adaptive DBS 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 mean by which neuronal structures communicate among each other and with muscular units.[61] The relationship of oscillations between two different sources can be addressed by means of coherence analysis, which indicates the degree of mutual dependence.[12] 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 electroencephalogram (EEG) and electromyogram (EMG), suggesting that voluntary contractions are coupled with the physiological oscillatory activity of cortical neurons.[12,60]

In certain movement disorders this physiological oscillatory activity is thought to be altered, since abnormal (pathological) oscillatory profiles have been detected.[5,18,43] 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 (BG), 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 through spectral analysis. The increase in frequency power triggers DBS in PD, which is continued until the power drops below a selected threshold.[25]

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),[32] and that the signal detected should be

powerful enough to be differentiated from artefacts, e.g. the noise caused by the stimulation itself (sensitivity).[57]

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 whether it is possible to transfer aDBS from PD to dystonia, it is necessary to identify biomarkers for the latter (Figure 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.[64] 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.[9] 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 from the subthalamic nucleus (STN) of dystonia patients[17,45] and between different EMG signals.[69] Directed transfer analyses suggest that this excessive oscillatory GPi activity is mostly driven from the GPi to the affected muscles.[62]

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.[35] 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[2]).[67] 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 -12 Hz) oscillations as a biomarker for dystonia was described by Barow et al.[5] 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 re-emerged after stimulation was switched off. Next to this, increased coherence from EEG-LFP and EMG-LFP within the 4-12 Hz range was reduced after DBS stimulation. Another study showed that increased low-frequency activity in the cortex is normalized after applying DBS.[40] These findings indicate that 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 (Figure 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 role low-frequency oscillations in each form of isolated dystonia is 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 TWSTRS scores and is coherent to dystonic EMG activity.[44] 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,[17,64,75] this has not always been replicated.[65,68,74] The co-occurrence of dystonia and PD might, at least partially, explain this

phenomenon.[71] 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 withdiverse forms of isolated dystonia, some studies have shown similar results of increased low-frequency oscillations in other subtypes of dystonia, indicating at least a partially shared common pathophysiology for all of them. Prominent 5-18 Hz oscillations from the GPi and thalamus were recorded from a patient with acquired dystonia secondary to a cryptogenic stroke.[72] Furthermore, studies based on LFPs-EMG and EMG-EMG coherence analysis have found an increased abnormal coherence in the low-frequency range in patients with myoclonus-dystonia.[15,16] 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.[38,59]

Phasic and tonic components of dystonia

Whilst dystonia is usually composed of tonic (sustained) and phasic (rhythmic) abnormal movements,[2] increased low-frequency oscillations have only, thus far, been correlated with the phasic components of dystonia,[36,44] including the reduction of such abnormal oscillations after cDBS.[5] 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.[11] In contrast, when discontinuing stimulation, phasic components can recur rapidly, whilst tonic

components recur in a more gradual manner.[19] This temporal dissociation leads to the hypothesis that different pathophysiological mechanisms are involved.[1] 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.[22] It has been observed that the benefits of DBS may remain after stimulation is discontinued, even after 1-year follow-up period.[20,58,66] 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% amongst studies.[14] Lee et al. contrasted data of patients with task-specific primary bowing tremor (a task-specific tremor especially occurring in string musicians) matched with healthy controls, revealing coherence between the co-activation 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.[31] 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,[21] the ventral intermediate/ lateral thalamus is used as a primary target in dystonia patients.[42]

In a recent study, patients had an improvement of 77% in clinical tremor scales after DBS of the ventrolateral thalamus.[49] However, significant side-effects also occurred. This raises the question of whether aDBS based on tremor amplitude/ phase could be an alternative. However, at this moment, the assessment of tremor using current accelerometers is still non-specific, due 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,[37] so in theory similar devices to assess dystonic tremor might be applied in the future.[63]

Electrocorticography (ECoG)

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 disordersused this technique to measure cortical LFPs in patients with PD, essential tremor (ET), and (cranio-)cervical dystonia.[13] In the resting state, the authors found a peak in M1-LFP that occurred in the high-beta band for PD, and in the low-beta band for dystonia and ET. 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.[48] Some of the advantages of ECoG mentioned include higher amplitude signaling, less DBS noise interference and potentially 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-LFP's), and how fast they react to electrical stimulation, should be investigated in order to determine how aDBS 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 EMG agonist-antagonist (AA) ratio might provide a more informative biomarker than a single site recording. As mentioned before, increased coherence between LFPs-EMG and EMG-EMG has been correlated with the severity of dystonic contractions.[15,16] In relation to this, aDBS might be programmed based on the volatility in coherence. Nevertheless, in order 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 co-contraction and overflow of AA muscles have been found on EMG measurements of dystonic patients.[6] However, at present, AA sum or AA ratio are not yet specific enough to differentiate signals of pathological contractions from voluntary contractions.[23] In the future evaluation of the predictive value of combined signals through machine learning may lead to greater specificity.

Conclusion

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 (neuro)physiological parameters that can predict the individual clinical response of dystonia to DBS makes programming difficult. For these reasons, improvements in knowledge about the neuro-physiological 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, 4-12 Hz LFP oscillations appear to be the most promising candidate, but other neurophysiological signals (e.g. EMG, ECoG) and their interactions might also be suitable. However, many questions remain, such as what the influence of micro-lesion effects, sleep, and medication on DBS recordings is. Regardless of the source of the biomarker or biomarkers selected for aDBS, their volatility and robustness over time will have to be established. Critically 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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Acknowledgements

We would like to thank prof. Peter Brown for his advice.

Conflict of interest: All the authors declare no conflict of interest.

Funding: This review was carried out thanks to public funds received from the Dutch Brain Foundation ('Hersenstichting Nederland'), the National Mexican Council of Science and Technology (CONACYT) and the University of Groningen/University Medical Center Groningen (RuG/UMCG). S Little is personally supported by the Wellcome Trust (105804/Z/14/Z).

Tables and Figures

Table 1. Potential biomarkers

Potential biomarkers for aDBS in dystonia with their advantages, disadvantages and challenges. Common to all is the need to establish their robustness across time and their reliability during brain states like sleep.

Figure 1. (Potential) interface for aDBS using low-frequency oscillations.

LFP= raw local field potential, STIM= channels representing stimulation amplitude, FILT LFP= LFP filtered around the low-frequency peak detected, in order to visualize low-frequency oscillations embedded in the signal, AMP ENV= amplitude envelope of the rectified filtered signal, L= left, R= right. In this figure, the presence of low-frequency oscillations on a 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 prevent that short-lived artifacts could trigger the stimulation.

Figure 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 can be recorded either from subcutaneous electromyography (EMG) 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 Figure 1).