Adaptive brain stimulation for movement disorders

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Abstract

Deep brain stimulation (DBS) has markedly changed how we treat movement disorders including Parkinson's disease (PD), dystonia and essential tremor (ET). However, despite its demonstrable clinical benefit, DBS is often limited by side effects and partial efficacy. These limitations may be due in part to the fact that DBS interferes with both pathological and physiological neural activity. DBS could therefore be potentially improved were it applied selectively and only at times of enhanced pathological activity. This form of stimulation is known as closed-loop or adaptive DBS (aDBS).

An aDBS approach has been shown to be superior to conventional DBS (cDBS) in PD in primates using cortical neuronal spike triggering and in humans employing local field potential biomarkers. Likewise, aDBS studies for essential and Parkinsonian tremor are advancing and show great promise, using both peripheral or central sensing and stimulation. aDBS has not yet been trialed in dystonia and yet exciting and promising biomarkers suggest it could be beneficial here too.

In this chapter we will review the existing literature on aDBS in movement disorders and explore potential biomarkers and stimulation algorithms for applying aDBS in PD, ET and dystonia.

Introduction

Movement disorders are diverse and disabling, encompassing syndromes of movement paucity (Parkinson's disease) through to conditions characterized by movement excess (essential tremor & dystonia). Remarkably though, despite significant divergence in their clinical presentations and underlying pathophysiology, they are unified by their beneficial response to electrical stimulation therapies.

Deep brain stimulation (DBS) was a major therapeutic and conceptual breakthrough in the treatment of advanced movement disorders. It is now an established treatment for Parkinson's disease (PD), essential tremor (ET) and dystonia in addition to being trialed in a range of other disorders including obsessive compulsive disorder, Tourette's and

Huntington's disease. However, much like early experiences using Levodopa, a growing understanding of DBS therapy has demonstrated that it also has limitations. As such, DBS treatment is currently restricted to a relatively small number of severely affected patients due to side-effects, incomplete clinical efficacy and costs.

It has now been established that DBS is effective for advanced movement disorders both in terms of clinical efficacy and quality of life (QOL). In PD, motor function improves by approximately 50%, with an associated 25% improvement in QOL, both of which are sustained with chronic stimulation [1]. In ET, DBS leads to a clinical improvement of 40-85% and in dystonia improvements are around 50-60% [2], [3]. Surgical complications of DBS implantation such as brain haemorrhage are now fortunately rare; however, a range of side-effects can occur secondary to the electrical stimulation itself, both acutely and chronically. Speech and balance deterioration with stimulation are a significant limitation of DBS therapy in subthalamic nucleus (STN) stimulation for PD and also in ventrolateral thalamic stimulation for tremor control [4], [5]. There is also evidence of neuropsychiatric complications related to stimulation including depression, cognitive decline, impulsive behaviour and increased rates of suicide.

Conventional DBS (cDBS) delivers brief electrical pulses of 2-3.5 volts at high frequency (130-150 Hz) for the duration of therapy with parameter changes only made intermittently and manually by a patient's physician. This regime does not take into account natural fluctuations in disease nor those resultant from concomitant pharmacotherapy. Therefore, inevitably, this form of stimulation interferes with physiological as well as pathological brain activity which could partly explain the emergence of side effects. It may also contribute to the diminishing efficacy seen in some patients with ET whereby continuous stimulation can lead to the development of tolerance over time.

If one could stimulate only when neural networks were in a pathological state and switch off or reduce stimulation when there was normal physiological activity – it should be possible to ameliorate side-effects, improve efficacy and reduce power consumption (with resultant cost

savings on costly battery replacements). This form of stimulation, where it is adapted according to the ongoing clinical state is known as closed – loop or adaptive DBS (aDBS).

Adaptive stimulation techniques modulate therapy according to the ongoing clinical status of the patient. Therefore, critical to this approach is the identification and validation of biomarkers which can be used to control stimulation. The ideal biomarker should have perfect sensitivity, be robust over time and give a near instantaneous reflection of clinical state. Furthermore, the complexity of computation and time window over which it needs to be calculated should be minimised in order to minimize delays within the control loop. Biomarkers for adaptive stimulation could theoretically take many forms, from peripheral kinematic devices to central biochemical or neurophysiological signals [6]. However, as yet, rapid and robust neurochemical analysis equipment has not been validated for movement disorders nor miniaturised to allow human implantation. Therefore, at present, the most favourable biomarkers for aDBS in movement disorders are those directly related to neurophysiological signals such as local field potentials (LFPs) and electromyograms (EMGs) or inertial sensors such as accelerometers. These will be discussed along with their implementation in aDBS for Parkinson's disease, ET and dystonia.

Parkinson's disease

The pathophysiology of PD is now beginning to be understood at both the cellular and physiological / network levels. What is striking about PD is how loss of dopaminergic drive to the striatum leads to such marked changes in both neuronal firing rate and crucially in the firing pattern of a widely distributed network cortico-basal ganglia neurons [7]. This manifests as a change from stochastic to regularised firing and increased functional coupling of neurons and suggests that spike timing in PD may represent a biomarker of clinical state and a potential control signal for aDBS. This was first elegantly demonstrated in a non – human primate model of PD that underwent implantation of microelectrodes into the M1 cortical area as well as the Globus Pallidus Interna (GPi) [8]. Rosin et al. were then able to test whether delivering stimulation pulses to the GPi, triggered off neural spikes from either M1 or GPi, was effective in suppressing Parkinsonism motor symptoms and compare this to

cDBS. They found that the most effective aDBS paradigm was to trigger from M1 neurons and to deliver short trains of pulses to the GPi at a latency of 80 ms. Given that the dominant neuronal rhythm in this model of PD was 12.5 Hz, 80 ms corresponds to the start of the next oscillatory cycle. Importantly, improvements in akinesia were greater using this type of spike-triggered aDBS than with cDBS despite significantly less total stimulation time. This provided critical proof of principle that an adaptive stimulation approach could be beneficial for PD.

Neuronal firing pattern changes can also be detected at the population level through LFP recordings [9]. Basal ganglia LFPs in PD are characterised by rhythmic oscillations in the beta range (13 – 30 Hz) and these beta oscillations are suppressed by dopamine and DBS proportional to improvements in Parkinsonian motor deficits across subjects [10]. LFPs would make an attractive potential biomarker for aDBS in PD as they are stable over long periods, significantly more robust than single cell recordings and by aggregating population based firing may even be potentially richer in their information content. Additionally, they can be recorded from conventional clinical DBS electrodes, thereby precluding the need for further surgical exploration and risks. This approach has now been validated in PD patients following DBS electrode placement during the period of externalisation prior to stimulator implantation [11]. For this study, patient specific beta oscillations recorded from the STN were filtered and smoothed in real time to give an online measure of beta amplitude. The amplitude recording was then used to control the delivery of trigger signals to a DBS stimulator so that the stimulator switched on when beta amplitude exceeded a pre-determined threshold and switched off again when beta fell below the same threshold level (Fig 1a). aDBS stimulation parameters were the same as those used for cDBS, i.e. 2-3 volt stimulation pulses delivered at high frequency (130 Hz), except that delivery of stimulation was timed to be given only at periods that beta power exceeded the pre-defined threshold. Stimulation was also ramped at the onset and offset over 250 ms to limit paraesthesias induced by rapid switching. Motor performance was measured by the clinical rating of tremor, rigidity and bradykinesia and cross-validated with blinded video assessments. aDBS triggered by beta oscillations was compared to cDBS, no stimulation and finally to a random condition in

which stimulation was delivered with a temporal distribution matched to that of aDBS but uncoupled from beta amplitude. Although the study found that cDBS was effective in reducing the cardinal motor symptoms of PD it also showed that aDBS was significantly more effective than cDBS, by around 30%, despite stimulating for less than 50% of the time (Fig 1b). Random stimulation did not show a significant motor improvement. This result is notable for the fact that the stimulation in aDBS and cDBS conditions was identical apart from the fact that in the aDBS condition the stimulation was applied only at periods of high beta amplitude. Previous evidence has demonstrated that conventional stimulation can have deleterious effects on motor performance in subjects who are performing well prior to stimulation [12]. Therefore the paradoxical outcome of improved motor benefit through less stimulation could potentially be explained by considering that DBS may have suppressive effects on both pathological and physiological network activity. By targeting stimulation only to periods of excessive beta, physiological activity may be preserved - leading to an optimised overall network performance.

This proof of concept study is important for showing that it is possible to track an LFP biomarker in real time and use this to direct stimulation in a manner that improves motor function. However there were a number of limitations in that the total stimulation periods were short, clinical assessment was limited to three cardinal motor symptoms and the study did not assess side-effects or interactions with medications. Follow-up studies are currently ongoing and show encouraging results with regard to bilateral stimulation, axial symptoms, side-effect changes and interactions with levodopa medications (unpublished data).

aDBS in humans has thus far been triggered by the amplitude of STN beta oscillations. Beta is associated with bradykinesia and rigidity but does not have a strong relationship with tremor in PD. Therefore to target tremor directly in PD and also in ET - different biomarkers may well be more efficient for driving an adaptive approach.

Parkinsonian and Essential Tremor

Periodic neural firing at tremor frequency has been linked to resting tremor in PD and postural / kinetic tremor in patients with ET. Yet the relationship between corresponding low

frequency LFPs and tremor is significantly weaker than that found between beta amplitude and bradykinesia-rigidity in PD. Fortuitously however, using inertial sensors such as accelerometers or electromyography (EMG), tremor activity can be reliably evaluated peripherally, directly from the tremulous limb. These could then serve as a potential input signal for aDBS - either using tremor amplitude to detect tremor episodes or tremor phase to facilitate a more direct interaction with underlying pathophysiology.

Tremor amplitude

The onset of a tremor episode can be readily detected using either EMGs or limb accelerometers and this signal then used to trigger stimulation. Proof of concept of this approach has been demonstrated using conventional, chronically implanted DBS devices, combined with external sensing and triggering [13], [14]. Here, an increase in tremor amplitude above a predetermined threshold triggers a period of stimulation until tremor is again suppressed (Fig. 2). This was found to significantly reduce tremor in a small cohort of ET subjects but has not yet been directly compared to cDBS, precluding a formal comparative assessment of efficacy. It is notable however that tremor was suppressed despite using significantly reduced overall total stimulation. It is hopeful therefore that this method could, by stimulating intermittently at times of increased tremor, improve efficacy and reduce both side-effects and stimulation tolerance.

Tremor Phase

An alternative approach is to attempt to subvert the rhythmic oscillatory activity that drives tremor directly, by stimulating according to tremor phase. This was first investigated peripherally using temporally patterned stimulation applied to muscle groups driving tremor. Stimulating tremorgenic agonist-antagonist muscle groups out of phase with respect to each other significantly reduced tremor severity in patients with ET, PD and Multiple Sclerosis [15]. However, the therapeutic applicability of this form of peripheral electrical stimulation is limited by muscle fatigue induced by prolonged stimulation, suggesting the need for a more sophisticated approach that interacts with central tremor oscillators.

Tremor is driven by excessively synchronized neuronal activity, distributed across the motor nuclei [16]. Selective low frequency stimulation, delivered at precisely the right time during the oscillatory cycle, could therefore potentially disrupt central synchrony and consequently tremor. The impact of phase linked DBS was first explored in a group of ET patients based on the hypothesis that stimulation delivered at certain parts of a tremor cycle should selectively modulate the neural activity driving tremor [17]. These experiments did not track tremor phase in real time but retrospectively analysed the effect of low frequency DBS as the tremor and stimulation drifted in and out of phase with each other. Delivering one stimulation pulse per tremor cycle significantly amplified or suppressed essential tremor, depending on the timing of the stimulation with respect to the tremor cycle. Crucially, the degree of tremor suppression exponentially increased if stimulation was consistently delivered at those parts of the tremor cycle promoting suppression for a number of consecutive tremor cycles.

The modulatory effects of stimulation timing on tremor severity suggests that tremor phase could potentially be used to control stimulation. Brittain *et al.* demonstrated the potential of such a stimulation strategy in a group of Parkinson's disease patients using transcranial alternating current stimulation (TACS) that was controlled online by the ongoing phase of the tremor [18]. When TACS was applied over the motor cortex at a fixed, optimal phase relationship with respect to the tremor phase, tremor severity reduced by 50% (Fig. 3). Significantly, patients' tremor remained suppressed after stimulation was terminated, suggesting that temporally specific stimulation could be inducing plastic changes in the motor circuit. Such long-term effects are of great interest since they could be exploited for therapy to ensure that patients' symptoms continue to be controlled even in the absence of continuous stimulation.

These proof of principle studies are exciting and suggest that adaptive stimulation could be beneficial in patients with disabling tremor. However they will need to be further validated in a chronic real world setting and compared directly with conventional stimulation therapies before they can be widely implemented.

Dystonia

Currently, the most well-established neuromodulation strategy in dystonia is cDBS of the internal part of the globus pallidus (GPi) [19]. Although GPi DBS can induce dramatic improvements in primarily generalised and mobile dystonia, the effect of DBS on other dystonia types is still controversial with variable responder rates and Parkinsonian side-effects occurring in up to 10% of patients. Additionally, due to their high voltage requirements, battery replacement procedures are still required every few years. In theory therefore, given the dynamic and stimulus-sensitive character of some forms of dystonia, DBS may be able to stimulate more effectively and efficiently with less side-effects were it only to stimulate when necessary using an adaptive stimulation approach. However, contrary to ET and PD, biomarkers for dystonia are less well established and the response to neuromodulation is less immediate. Therefore aDBS has not been attempted for dystonia as yet. Here, we will discuss the possible benefits of adaptive stimulation in dystonia in conjunction with potential biomarkers and stimulation strategies. We will then discuss the most pertinent research questions that need to be answered in dystonia before adaptive stimulation could be applied.

Potential biomarkers of dystonia

In contrast to PD where basal ganglia structures are dominated by increased beta activity, in dystonia these same structures appear to show a predominance of low frequency oscillations (4 - 12 Hz) [20]. Furthermore, these low frequency oscillations show coherence with the muscles affected during involuntary dystonic movements, correlate with the strength of muscle spasms and decrease after the application of DBS [21]. Likewise, low-frequency oscillations are also present in the EMG of dystonic muscles in patients with focal dystonia where they have been considered to possibly encode the underlying ‘dystonic drive’ [22].

Potential adaptive stimulation strategies for dystonia

At present therefore, low frequency oscillatory power appears to be the most suitable potential biomarker for adaptive stimulation in dystonia. The first approach to testing aDBS then would be to selectively apply stimulation when the peak power of low frequency

oscillations in the LFP exceeded a pre-defined threshold. Particular consideration would need to be given to two aspects of this control algorithm. The first would be the absolute level of the threshold, which would determine the proportion of time that adaptive stimulation was triggered and second would be the windowing or smoothing of the amplitude trace which would determine the delay and temporal dynamics of stimulation. In PD, beta peak power can substantially increase and decrease on a sub-second scale. In dystonia the volatility of low frequency power is not yet well established. Therefore, in order to determine the optimal sampling frequency and delay durations (through moving average windows) further studies of low frequency LFPs in dystonia should be performed. Once the non-stationary nature of low frequency power is characterised, a stimulation delay can be determined and stimulation can be tested at different thresholds.

A second approach to adaptive stimulation would be to use the low-frequency power from EMG signals of the most affected agonistic and antagonistic muscles for triggering DBS. One of the advantages of using a peripheral signal is the absence of stimulation-induced artefacts. Furthermore, by using a biomarker local to the site of dystonia, adaptive stimulation based on EMG spectral power might be more efficient than central biomarkers in more focal and task specific dystonia's. The characteristic finding in dystonia is of abnormal co-contraction of antagonistic muscles, and therefore a comparison of two EMG electrode recordings is foreseen as being necessary for detecting dystonia. However, completely differentiating dystonic activity from voluntary movements and particularly normal postural positioning (necessitating co-contraction) will require further investigation. It may be possible that aDBS could be programmed in such a way that stimulation would only be applied when a patient is having a focal dystonic episode such as writer's cramp for example. With the recent developments of EMG electrodes that can be implanted subcutaneously and then communicate wirelessly, these adaptive strategies could theoretically soon be applied.

One of the remaining issues is the treatment of non-phasic, tonic, contractions in dystonia and the question arises whether aDBS could be effective against this component also. Contrary to

the phasic symptoms that can be alleviated rapidly, tonic contractions typically take weeks or even months to disappear after the start of DBS and don't show a simple relationship to low frequency oscillatory activity. An exciting current theory regarding these tonic contractions in dystonia is that they may be caused by cortical compensatory mechanisms acting to inhibit the excessive movements induced by low frequency oscillations [21]. Therefore, if adaptive stimulation techniques turned out to be successful in dystonia, longer term aDBS studies could address whether these tonic contractions were also decreased by adaptive stimulation, thereby lending support to the proposal that tonic contractions are secondary to low frequency oscillations and phasic movements. Indeed, with the dawn of new implantable DBS devices that are able to simultaneously record and stimulate, plasticity induced changes could also theoretically be monitored over longer periods. Although, current ideas relating to adaptive DBS for dystonia remain speculative there is hope that the advances found in PD and tremor disorders could soon be extended to dystonia.

Conclusions

The emergence of adaptive DBS techniques is an exciting development in the treatment of movement disorders and demonstrates the potential to improve therapy but also to advance our understanding of the pathophysiology underlying these conditions. aDBS for PD has been demonstrated to be more efficacious than cDBS in both non – human primate models and patients with PD in a laboratory setting. Critically this was achieved with significantly less overall stimulation and thus raises the exciting prospect of a reduction in associated side-effects although this remains to be demonstrated experimentally. aDBS for tremor conditions are also advancing, thus far being successfully triggered off peripheral sensors including EMGs and accelerometers. Two approaches have been employed for tremor aDBS – to use a simple amplitude trigger, similar to that employed for beta oscillations in PD, or alternatively to attempt to directly and selectively interfere with the underlying pathological oscillatory networks through stimulation in a phase controlled manner. Direct comparison studies between aDBS and cDBS for tremor are eagerly anticipated. aDBS has not yet be trialed for dystonia and yet the intermittent phasic component of dystonia, with its associated low

frequency LFP biomarker, presents an exciting possibility for testing. Furthermore, selectively targeting the phasic component of dystonia will allow for the testing of the hypothesis that longer term tonic and plastic changes are a secondary response to abnormal low frequency oscillations and phasic drive.

At present the main challenge for aDBS is to extrapolate these initial findings to the bedside. This will require the use of emerging devices which can sense and stimulate simultaneously and therefore enable testing in chronically implanted patients [23]. Further studies are needed evaluating longer periods of stimulation with concomitant medication usage, side-effect assessments and optimal biomarker and stimulation algorithm selection. However, it is hoped that this emerging field will result in improved efficacy of DBS whilst reducing side-effects and thereby extend therapeutic benefit to a wider cohort of patients.

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