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Adaptive deep brain stimulation in Parkinson's disease

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ABSTRACT

Although Deep Brain Stimulation (DBS) is an established treatment for Parkinson's disease (PD), there are still limitations in terms of effectivity, side-effects and battery consumption. One of the reasons for this may be that not only pathological but also physiological neural activity can be suppressed whilst stimulating. For this reason, adaptive DBS (aDBS), where stimulation is applied according to the level of pathological activity, might be advantageous. Initial studies of aDBS demonstrate effectiveness in PD, but there are still many questions to be answered before aDBS can be applied clinically. Here we discuss the feedback signals and stimulation algorithms involved in adaptive stimulation in PD and sketch a potential road-map towards clinical application.

1. Introduction

Deep Brain Stimulation (DBS) is one of the most effective treatments for advanced Parkinson's disease (PD). However, although it has been applied for over 25 years, there are still limitations in terms of efficacy, side-effects and efficiency. At present, conventional DBS targeted at the subthalamic nucleus (STN) or globus pallidus interna (GPi) provides, on average, only about 40% improvement in the motor items of the Unified Parkinson's Disease Rating Scale (UPDRS III) OFF dopaminergic medication. Furthermore, there is even evidence that DBS can, paradoxically, worsen motor functioning by not only influencing pathological but also physiological neural activity [1,2]. Next to this, the potential of conventional DBS is often limited due to stimulation induced side-effects. Finally, the capacity of non-rechargeable batteries is limited, and many patients are unsuitable for rechargeable devices. Thus in some patients battery replacement surgery may need to take place every few years.

Although there are many stimulation parameters that can be adjusted, the key attribute of conventional DBS is that stimulation is delivered continuously, and is thus non-adaptive. In theory, DBS could work more effectively with less side effects and be more efficient were it only to stimulate as and when necessary. This type of stimulation is called adaptive DBS (aDBS).

For aDBS to be achieved, it must be subject to feedback control and adjustments automatised. In PD, there are a variety of measurements that could form the basis for feedback, particularly the spontaneous electrophysiological activity recorded in the brain, termed the local field potential (LFP), and accelerometer measurements of tremor activity. The requirements of these feedback signals are partly dictated by the precise means of stimulation. High frequency DBS just requires feedback signals to be indicative of current clinical state, but not necessarily causally important. However, as we will discuss, some stimulation patterns under development require the sensed signal to be causally important, as stimulation is specifically tailored to suppress the sensed signal.

2. Potential feedback signals in aDBS according to impairment in Parkinson's disease

2.1. Bradykinesia and rigidity

At present there is substantial experimental evidence that elevated beta (13–35 Hz) frequency band power in the STN or pallidal LFP is associated with bradykinesia and rigidity, but not tremor, in PD [3]. This beta signal is also robust, remaining recordable over many years [4]. More recently, functional distinctions have been suggested between beta oscillations in the low (13–20 Hz) and high (21–35 Hz) beta frequency range. Although combined magnetoencephalography and STN LFP recordings show cortical-subcortical coherence in the high beta range [5], STN LFP

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recordings demonstrate particular modulation of low beta power after the application of dopaminergic medication [6] or in the correlation with Parkinsonian severity in the untreated state [7]. It remains unclear whether the power of low or high frequency beta might serve as the better feedback signal for aDBS.

Besides the power of beta oscillations, the volatility of beta power might potentially serve as a biomarker as well. The reason for this is that coefficient of variation (CV) of beta power in the OFF-state is significantly, inversely, correlated with UPDRS III scores and with the change in UPDRS III scores after the application of dopaminergic medication [8]. Another feature of activity in the beta frequency band that has recently come to the fore is the modulation of other frequencies of LFP activity by the phase of the beta signal. This has been noted in several forms. At the level of the motor cortex phase amplitude coupling (PAC) involves modulation of the amplitude of cortical broad gamma oscillations (from ~50 to 200 Hz) by the phase of beta oscillations in patients with PD. Such PAC decreases in relation to movements [9], and is decreased by DBS, with the degree of reduction correlating with motor improvement [10]. This cortical PAC has been suggested as another potential biomarker for aDBS [10].

Another form of PAC has been reported in the STN, and involves amplitude modulation of LFP activity in the range between 200 and 400 Hz, termed high frequency oscillations (HFO's), by the phase of STN beta activity [11]. The peak frequency of HFO's changes from around 250 Hz to about 340 Hz after treatment with dopaminergic medication, and the strength of HFO PAC correlates with the UPDRS III score OFF medication. However, it is not yet known which particular UPDRS III items best correlate and to what extent DBS influences HFO PAC, although electrodes that show greater HFO PAC turn out to be more likely the contacts that are clinically effective [11].

PAC provides an interesting potential feedback signal for aDBS, but also one that is challenging to record and analyse on-line, particularly given the very low amplitude of high frequency activities. Whether PAC it is more directly informative of clinical state than beta band power or its variation also remains to be seen. Nor is the causal relevance of any of these beta related phenomena established with respect to different Parkinsonian symptoms.

2.2. Tremor

Beta band LFP power does not correlate with tremor. Rather neural activity at tremor frequency (~5 Hz) and its first harmonic (~10 Hz) has been recorded in the cortico-basal ganglia-cortical loop in tremulous PD patients and its amplitude suggested as a possible feedback signal for aDBS [12]. It seems plausible that these central oscillations at tremor related frequencies might also be causally related to tremor, particularly as surgical lesioning or stimulation of key sites at which such oscillations have been recorded lead to tremor suppression. This opens up the possibility of aDBS based on phase-interference stimulation techniques (see below). Tremor is also easily recorded using peripheral accelerometers providing another potential source of feedback with which to modulate aDBS.

2.3. Dyskinesias

Although DBS generally affords dramatic amelioration of dyskinesias in PD, 2–4% of patients experience DBS induced dyskinesias. Spectral features in the LFP that have been associated with dyskinesias are a shift from elevated beta power to increased activity in the 4–10 Hz and/or 65–90 Hz ranges [13,14]. Interestingly, the low-frequency spectral peak is also seen in the LFP power spectrum of dystonia patients recorded in GPi [15] and stimulation of the STN at 5 Hz has induced involuntary choreiform movements in PD patients undergoing DBS surgery [16]. In theory such shifts in LFP frequency could serve to denote dyskinesias, but these might be more faithfully captured and fed back from peripheral inertial sensors. Alternatively, it might be that by tracking only beta power, stimulation can be reduced when such power falls low, thereby avoiding DBS induced dyskinesias.

2.4. Freezing & other axial features

After 10–15 years, it is often not limb bradykinesia-rigidity, but axial motor features that dominate the motor phenotype of PD. Contrary to 'appendicular' motor signs, axial symptoms respond less well to STN or pallidal DBS. Lately, the pendunculopontine nucleus (PPN) has been suggested as a more successful target for the treatment of gait and balance problems [17]. A recent report showed decreased 5–12 Hz activation in the PPN when patients were unable to step because of severe freezing of gait [18]. Conversely, when patients on dopaminergic medication were able to walk, 5–12 Hz activity increased [19]. Could PPN LFP power over 5–12 Hz form the basis for aDBS in this nucleus? So far, however, no data have been presented on the modulation of local oscillatory activity by PPN DBS, and the efficacy of stimulation of this target is still debated.

3. Stimulation parameters for aDBS

Many stimulation parameters can be used in aDBS. In the aDBS studies that have been published up to now [20–23], high frequency (~130 Hz) stimulation, with regular pulses with a fixed inter-pulse interval, were given. There are two different approaches to the application of high frequency aDBS: a binary approach, with effective stimulation either on or off, and a scalar approach with stimulation voltage being varied up to and including therapeutic values. Care has to be taken with both approaches that stimulation voltage is not rapidly increased with the induction of paresthesia. This issue is particularly important with binary on-off stimulation, where it is managed by the incorporation of a ramping of stimulation onset and offset. With regard to the scalar stimulation approach, the value of stimulating at sub-threshold voltages remains to be clarified.

Recent findings suggest an alternative approach to stimulation when oscillatory activity is believed to be causally important. This opens up the possibility of aDBS based on phase-interference stimulation techniques. When the thalamus is stimulated at low frequencies shocks delivered at certain phases of the peripheral tremor, and hence presumably of central tremor oscillations, reinforce peripheral tremor whereas those delivered at other phases attenuate tremor. By steering aDBS to the latter phases, a very selective form of aDBS treatment could potentially be performed [24,25]. Support for approaches in which oscillation phase is detected and then stimulation delivered to optimally disturb or cancel oscillations comes from two studies. The first will be described in the following section [26]. In the second study, a non-invasive technique, transcranial alternating current stimulation (TACS), was able to reduce PD tremor by delivering sinusoidal varying current at the correct frequency and phase offset to cancel central tremor oscillations [27].

4. Current experience of aDBS in non-human primates and patients with Parkinsonism

The first experimental evidence of the successful application of aDBS in Parkinsonism came from non-human primates [26]. In this landmark study two monkeys were implanted with electrodes in