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The functional role of beta oscillations in Parkinson's disease

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SUMMARY

Modulations of beta oscillations (13–30 Hz) during normal motor control suggest that they may act to promote current motor set at the expense of new movements. These oscillations are greatly enhanced in Parkinson's disease (PD) and there is strong correlative evidence linking beta activity at rest and beta changes in response to treatment with bradykinesia and rigidity. Some evidence that this link may be mechanistically important or causal comes from studies in which either cortical or subcortical sites have been stimulated in the beta frequency range causing modest but significant slowing of movements. However, recent trials in which high frequency deep brain stimulation (DBS) has only been delivered during periods of elevated beta activity have demonstrated major clinical effects that even exceed those of standard continuous high frequency DBS. These studies suggest that beta activity may be both causally and quantitatively important in the motor impairment of PD, and demonstrate how improvements in the understanding of the pathophysiology of PD can lead to enhanced therapeutic interventions in this condition.

1. Introduction

Oscillations in the beta frequency range, centered around 20 Hz, where discovered 75 years ago and are ubiquitous throughout the cortical–basal ganglia circuitry in Parkinson's disease (PD) [1]. A wealth of experimental data demonstrate selective beta modulation in response to movement and treatment with levodopa at multiple levels of the motor circuit and yet the function of beta activity remains elusive [2]. Indeed, the mapping of a single cohesive, conceptually simple, function to beta may be an over-simplification given the multi-frequency responses found in many circumstances and the complexities encountered in ascribing psychological concepts directly onto brain functions [3]. Despite this, exciting progress is being made in the understanding of motor control and the role of beta oscillations. Here, we review the empirical data in normal subjects and in patients with PD and discuss how current theories are attempting to integrate beta. We then look at how these ideas are informing and improving treatments through new closed loop deep brain stimulation (DBS) paradigms in animal models of PD and in patients with this disease.

2. Physiological role

EEGs and local field potentials (LFPs), at least those at frequencies under about 100 Hz, mainly represent the temporal–spatial summation of post synaptic potentials from the local neuronal population surrounding an electrode [4]. Beta oscillations therefore are the product of synchronisation across neurons and correspondingly, beta power indexes the strength of that synchronisation, the density and spatial extent of the involved neuronal pool and its constancy over time. Cortical beta power is robustly modulated by movements in healthy subjects and suppression is found to correlate with the degree to which warning cues are predictive of upcoming action [5]. Following movement, beta power rebounds to a higher than previous level and can also be augmented by tonic position holding and by stopping a pre-planned movement in a go/no-go task [6]. As such, it has been conceptualised as an idling rhythm or, alternatively, as a promoter of the status quo [7,8]. Periods of elevated beta are associated with slowing of spontaneous movement and increased corrective responses to postural perturbation suggesting that beta actively stabilises the current motor set [8].

3. Parkinson's disease

DBS treatment affords the opportunity to study subcortical beta activity in PD, either intra-operatively when single neuronal discharges can be picked up with microelectrodes, or post-operatively when beta oscillations in the LFP can be discerned in recordings made directly from the electrode used for chronic DBS. The former has confirmed that beta activity in the LFP is time locked

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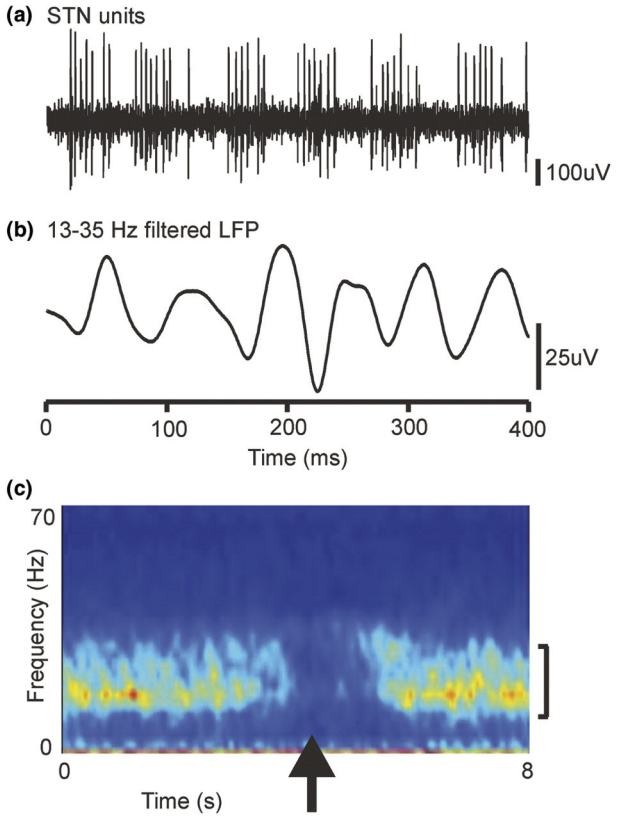

Fig. 1. Intraoperative recordings of neuronal and LFP activity in the STN of a patient with Parkinson's disease withdrawn from their medication. (a) Neuronal discharges. (b) Simultaneously recorded LFP. Note LFP oscillations at about 15 Hz coincide with bursts of neuronal discharges. (c) Plot of time-evolving Unit-LFP coherence averaged around 20 self-paced contralateral hand movements (movement onset is arrowed). Note suppression of beta activity (see vertical bar) before and during movement. Reproduced with permission [9].

to the bursting of neurons (Fig. 1) [9]. The latter recordings have turned out to be remarkably robust even over periods of years [10], and reliably find an increase in beta power in patients withdrawn from dopaminergic medication [11]. Acutely, beta power is suppressed by levodopa and DBS in proportion to clinical improvement [11–13]. The relationship between absolute beta levels and concurrent clinical state is less clear but a number of normalised metrics of beta have shown strong correlations with rigidity and bradykinesia at rest [14,15]. The spatial extent of subcortical beta activity coupling has also been correlated with clinical state [16]. These functional correlates are broadly in keeping with the posited role of beta in the healthy state, as an exaggerated promoter of the motor status quo which might reasonably be expected to manifest as an increase in postural activity (rigidity) at the expense of new movements (bradykinesia).

The suppression of beta activity by levodopa has led to the proposal that beta might serve to index net dopamine levels at the sites of cortical input to the basal ganglia [17]. As such, beta would be intimately related to dopamine modulation by internal and external cues both before (and even in the absence of) movement and when movement is triggered. Those changes arising before (or in the absence of) movement have been considered as a marker of the likelihood that a new action will need to be performed [17].

In sum, beta activity is likely controlled by the level of dopaminergic activity in response to internal and external cues and serves to modulate the stability of the current motor state. However, it must be acknowledged that the work so far presented is essentially correlative and as such cannot definitively show that beta has a mechanistic role, and is not simply epiphenomenal [18]. In order to clarify this critical issue, we must consider attempts that have been made to directly manipulate beta activity and its behavioral consequences.

4. Manipulation of beta activity

Beta can be potentially enhanced by using a rhythmic electrical stimulus to entrain and boost the underlying physiological signal. At the cortical level this can be performed non-invasively using transcranial alternating current stimulation (TACS). Studies have demonstrated that beta frequency TACS slows movement and markedly reduces the force of errors of commission during no-go trials in healthy subjects [19,20]. These data are complemented by sub-cortical stimulation studies in PD patients in which DBS pulses are delivered at low frequency within the beta range. These have shown a small but significant deterioration in bradykinesia and rigidity in the low frequency stimulation condition [21]. Such studies support a mechanistic role for beta both in physiological motor processing and in the pathophysiology of PD. However, effect sizes have been small, bringing into question the quantitative importance of beta. More recently, studies that seek to selectively down-regulate beta oscillations through closed loop DBS are beginning to argue in favor of a major mechanistic role for beta activity, at least in mediating motor impairment in PD.

Current therapeutic DBS is delivered continuously at high frequency, typically at around 130 Hz. Although effective, it is partially limited by side effects, including speech and cognitive problems and even paradoxical motor deterioration in some subjects [22]. Some of these side effects may relate to the non-frequency selective attenuation of LFP activity by DBS, which may involve both suppression of exaggerated beta activity but also more physiological gamma activity (Fig. 2) [13,23]. Closed loop stimulation, where stimulation is automatically adjusted online according to the current state of the underlying network activity, could alleviate some of these difficulties. In using low frequency oscillations as a biomarker, these closed loop studies also provide powerful insight into the functional role of beta.

Rosin et al. have elegantly demonstrated effective closed loop stimulation in a non-human primate model of PD [24]. In this study they tested two monkeys rendered parkinsonian by the systemic application of the neurotoxin, methyl-phenyl-tetrahydropyridine (MPTP). The monkeys had surgical implantation of microelectrodes

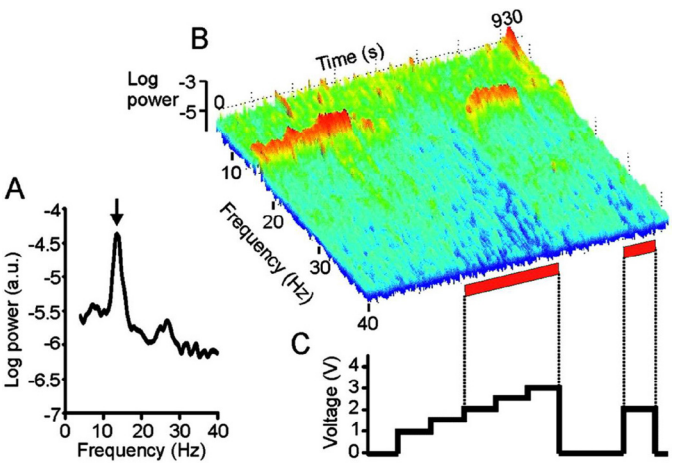

Fig. 2. Effect of DBS on the LFP recorded in the subthalamic nucleus in PD. (A) Power autospectrum of LFP recorded without stimulation. There is a large beta peak arrowed at 14 Hz. (B) Frequency–time log power spectrum of LFP. Bars along the time axis denote periods of clinically effective DBS intensities. Note suppression of not only beta peak at these stimulation intensities, but higher frequency activity too (see also ref. [13]). Adapted with permission [13].