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Bad oscillations in Parkinson's disease

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Summary. Recordings in humans as a result of functional neurosurgery have revealed a tendency for basal ganglia neurons to oscillate and synchronise their activity, giving rise to a rhythmic population activity, manifest as oscillatory local field potentials. The most important activity is synchronised oscillation in the beta band (13–30 Hz), which has been picked up at various sites within the basal ganglia-cortical loop in PD. Dopaminergic medication and movement suppress this activity, with the timing and degree of suppression closely correlating with behavioural performance. Accordingly synchronisation in the beta band has been hypothesised to be essentially antikinetic in nature and pathophysiologically relevant to bradykinesia.

The major model explaining the function of the basal ganglia (BG) in health and disease was that proposed by Albin and Delong at the end of the 1980s, which has been highly influential ever since. This model effectively synthesised neurochemical and anatomical data to explain how the BG might sway cerebral cortical activity. The influence of BG output over cortical motor areas was viewed as an increase or decrease in tonic excitation of the cortex by the thalamus, brought about by serial inhibition and excitation at earlier stages in the BG-cortical loop. Subsequently, however, it has become clear that neuronal discharge rate may not change in disease as predicted by the model, neither can it account for the major therapeutic benefits of functional neurosurgery in Parkinson's disease (PD). The implication is that it is not the degree of collective excitation or inhibition brought to bear at different stages of the BG-cortical loop, but rather the patterning of activities that lead to disease. Recent work has confirmed that synchronised oscillatory activity appears to be a fundamental feature of the BG, particularly in the diseased state.

Two possibilities exist for recordings of BG activity in humans as a result of functional neurosurgery: either single neuron recordings can be made intra-operatively through microelectrodes, or local field potentials (LFPs) can be recorded from the deep brain electrodes used for stimulation in the few days that follow implantation, while the electrode leads are externalized prior to connection to the subcutaneous stimulator. Both approaches have revealed a tendency for BG neurons to oscillate and synchronise their activity, giving rise to a rhythmic population activity, manifest as oscillatory LFPs (Kühn et al., 2005). The most consistent finding is synchronised oscillation in the beta band ($\sim$20 Hz), which has been picked up at various sites within the BG-cortical loop in PD.

Behaviourally related modulations of oscillatory activity

Synchronisation in the beta band has been hypothesised to be essentially antikinetic in

nature and pathophysiologically relevant to bradykinesia. This is supported by a number of observations relating changes in beta activity with behaviour and treatment. One of the earliest behavioural observations was that the beta LFP activity picked up in the subthalamic nucleus (STN) and globus pallidus interna (GPi) was reduced in PD patients prior to and during self and externally paced voluntary movements (Cassidy et al., 2002). Indeed, the mean timing of the drop in activity following a cue to move positively correlates with the mean reaction time across patients, which it precedes (Kühn et al., 2004). This relationship is so strong it may even be observed in individual subjects across single trials (Williams et al., 2005). If the reduction in beta activity is linked specifically to the facilitation of subsequent movement, an augmentation of power might also be predicted in this frequency band when a pre-prepared movement requires cancellation. This has been confirmed in subthalamic recordings during the 'Go-NoGo' paradigm (Kühn et al., 2004). In addition, a strong relationship between motor processing and beta suppression has been suggested by experiments that compare the suppression of beta activity following warning cues in reaction time tasks. These cues can be either fully informative or uninformative about the direction indicated by subsequent imperative cues eliciting movement with either the left or right hand. In the case of uninformative cues there is no prospective information about which hand will be called upon to move, so motor selection can only occur after the go cue, as confirmed by longer reaction times. Under these circumstances the suppression of the beta activity following the warning cue is far less than following an informative warning cue, indicating that the beta suppression related to the amount of motor preparation that was possible rather than to any non-specific alerting effect of the warning cue (Williams et al., 2003).

Treatment related modulations of oscillatory activity

The earliest observation relating to beta band oscillations in BG LFPs in patients with PD was that they were increased after the withdrawal of levodopa and suppressed following its return (Fig. 1). Thus background levels of beta activity were increased as motor performance deteriorated in the off medication state. More recently, it has also become apparent that the relative degree of beta suppression prior to and during movement is diminished after PD patients have been withdrawn from levodopa (Doyle et al., 2005). The increase in background levels of beta and the decrease in the reactivity of beta oscillations prior to and during movement might contribute to the paucity and slowness of voluntary movements, respectively.

Of course another effective treatment for akinesia is high frequency deep brain stimulation (DBS). Here it has proven technically difficult to record beta activity during stimulation of the same site, but it has been possible to record beta activity from the GPi during stimulation of the subthalamic area in patients with PD. This has confirmed that

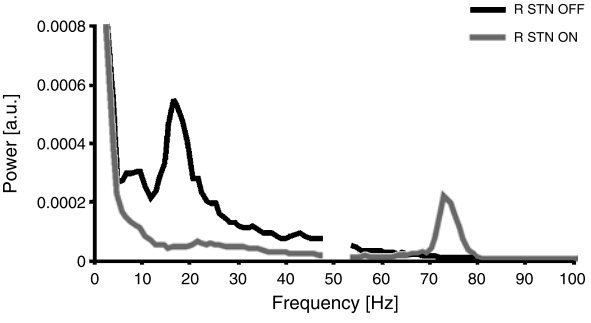

Fig. 1. Power spectra of LFP activity recorded from the contacts of a DBS electrode in the subthalamic nucleus of a patient with PD on and off their antiparkinsonian medication. Off medication, the LFP is dominated by oscillations with a frequency of around 20 Hz, in the so-called beta band. After treatment with levodopa there is suppression of the beta band activity and a new oscillation arises in the gamma band, – peaking at 75 Hz. Mains artefact at 50 Hz has been omitted

high frequency DBS also suppresses background levels of beta activity, in tandem with clinical improvement (Brown et al., 2004).

Earlier, it was stressed that increased synchronisation in the beta frequency band was a characteristic of activity throughout the BG-cortical loop. Accordingly, the same relationship between beta synchrony and motor impairment would be anticipated at the level of the cerebral cortex in patients with PD. A recent study in patients with chronically implanted DBS electrodes found that the degree of synchronisation in the beta band between cortical sites over central motor areas correlated with motor impairment, when patients were withdrawn from medication and therapeutic stimulation. In addition, both the reduction in beta synchronisation effected by high frequency stimulation of the STN, and that achieved with levodopa, correlated with treatment induced improvements in motor performance (Silberstein et al., 2005a).

Finally, if beta activity is essentially antikinetic in nature, could its excessive suppression following antiparkinsonian therapy or lesioning of the STN help explain hyperkinesias? Recent recordings in the GP of PD patients during levodopa-induced dyskinesias demonstrate that dyskinetic muscle activity may inversely correlate with pallidal beta activity, in keeping with the latter's posited antikinetic character (Silberstein et al., 2005b).

Why is beta activity inversely correlated with motor processing?

The above observations suggest that there is an inverse relationship between beta band synchronisation and motor processing. However, the relationship appears a generic one, inconsistent with an explicit role of synchronous population activity at these frequencies in motor processing. Thus BG LFP activity in the beta band is suppressed following behaviourally relevant stimuli, such as warning and go cues, and prior to and during self-paced movements. This inverse relationship between beta band synchronization and motor processing raises the possibility that the novel processing necessary for renewed movement may be actively antagonised by synchronisation in the beta band. Recordings in primates confirm an inverse relationship between oscillatory LFP activity in the beta band and local task-related rate coding, so that oscillations are preferentially suppressed in the local area of the striatum showing task-related increases in discharge rate (Courtemanche et al., 2003).

So one possibility is that synchronisation in the beta band impairs rate coding in the BG-cortical system. The finding of synchronisation at frequencies above 60 Hz in the STN LFP raises an additional possibility (Fig. 1). These gamma band oscillations are focal, increased by movement and appear after treatment with levodopa (Cassidy et al., 2002), suggesting that they might relate to specific coding of movement related parameters. Synchronisation at 60–90 Hz, in particular, is phase locked to similar activity in the motor areas of the cerebral cortex (Cassidy et al., 2002) and, at subcortical and cortical levels, may share a similar role to that posited for gamma band synchronization in the visual cortex. Given the apparent reciprocal relationship between beta activity and oscillations above 60 Hz in STN LFPs with respect to dopaminergic stimulation and movement, it is possible that extensive synchronisation under 30 Hz precludes the involvement of neuronal assemblies in a different pattern of synchronisation that is directly involved in information transfer. Consistent with this beta and gamma activities in the STN are inversely correlated at rest over time (Fogelson et al., 2005a).

There is, however, an alternative explanation for the beta activity and this is that it is a passive characteristic of basal ganglia-cortical networks when they are not engaged in active processing. In this formulation the oscillatory activity is viewed as a characteristic of the resting or idling state, rather than

a phenomenon that may actively impede novel processing. Several observations would argue against this possibility. First, there is the rebound synchronisation of beta activity following movement and the premature synchronization of this activity when movement is to be voluntarily suppressed (Cassidy et al., 2002; Kühn et al., 2004). Although there may be degrees of active suppression of dynamic movement related processing, it seems unlikely that the BG-cortical system would enter into a deeper idling state than at rest when movement has to be inhibited or terminated. Second, direct stimulation of the BG in the beta band may be antikinetic, although effects so far have been small (Fogelson et al., 2005b).

The above reviews the evidence that excessive synchronisation in the beta band in the BG-cortical system might antagonise motor processing, contributing to akinesia in PD. Much of this evidence, however, is correlative in nature, so that there remains a need for the direct demonstration of causality between synchronisation in the beta band and the suppression of novel movement related processing.

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