



Editorial

Cueing brain rhythms in Parkinson's disease

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In a seminal observation on “awakened” parkinsonian patients, Oliver Sacks reported that akinesia remarkably improved when the patients danced (Sacks, 1973). One of the reasons why music may improve motor execution in Parkinson's disease (PD) is that, particularly when rhythmic and stereotyped (e.g., tango), it provides externally timed cues (Hackney and Earhart, 2009). External input may cause networks of neurons to interact, often resulting in rhythmic activity within defined frequency ranges that can engage in temporal synchronization and de-synchronization. Classic PD tremor is a visible epiphenomenon of oscillating cerebello-thalamo-cortical networks that are likely synchronized by an abnormal beta rhythm in the basal ganglia (Hallett, 2014). Particularly in PD, brain rhythms, their synchronization and desynchronization, form an important part of the organization of perception, motor action and conscious experience. The disruption of oscillation or temporal synchronization is a relevant variable associated to PD motor phenomenology.

In healthy subjects, cortical beta power is robustly modulated by movements and it is suppressed in correlation with the degree to which warning cues are predictive of upcoming action (Doyle et al., 2005). Beta power desynchronization is more strongly cued by externally stimuli with no internal timing demands, as in the case of dance or of an externally triggered arm movement. Beta power is considered an idling rhythm or a promoter of inaction (Gilbertson et al., 2005). Periods of elevated beta are associated with slowing of spontaneous movement and increased corrective responses to postural perturbation, suggesting that beta actively stabilizes the current motor set. PD patients have elevated beta band oscillations (13–35 Hz) in the basal ganglia, which correlate to parkinsonian motor deficit (Hammond et al., 2007). PD patients also have an aberrant pattern of beta band desynchronization when attempting to move. Deep brain recordings in PD patients have shown that the subthalamic nucleus displays the same beta oscillations as the coherence found between motor cortex MEG, EEG, or local field potentials (Levy et al., 2002). In keeping, beta oscillations can be suppressed by deep brain stimulation of the subthalamic nucleus or by dopamine replacement therapy, and this suppression has been correlated to improvement of motor symptoms, likely through a modulation of activity in the basal ganglia-thalamo-cortical circuits (Kühn et al., 2006).

In PD, the whole motor cortex-basal ganglia networks may be held abnormally in a 15–30 Hz oscillatory state, which are the same coherent frequencies as those detected between motor cortex and

muscle during postural maintenance in healthy humans (Farmer et al., 1993). Johari and Behroozmand (2021) in this issue of *Clinical Neurophysiology* assessed beta band power and motor reaction time in PD compared to healthy controls. They measured limb and speech motor reaction time tasks in patients with mild-to-moderate PD during the ON-state to find that PD subjects had slower responses than controls, independently of stimulus timing and response modality. Externally cued limb movements have little influence of internal timing mechanisms; by contrast, speech has a significant internal component. The two experimental conditions were compared. The pattern of pre-movement beta band desynchronization (associated with action start) was modality-independent in both PD patients and controls, suggesting that homologous neural mechanisms regulate motor timing during both speech production and upper limb movement. As expected, however, both were slower in PD subjects.

Pre-movement beta band desynchronization correlated with motor reaction times in control subjects, but not in PD patients. Both PD and control subjects showed faster responses for hand movement vs speech production independent of stimulus timing, a likely influence of internal timing mechanisms. Although beta power desynchronization occurred in PD patients before, during and shortly after the onset of motor responses, the desynchronization pattern in PD patients was different from that of controls. The low beta (13–18 Hz) and the high beta (18–25 Hz) components varied differently in PD and control subjects.

Subcomponent analysis has shown that beta band activity can be sub-divided into low (13–20 Hz) and high (21–35 Hz) frequency components, where the low-beta band shows a greater decrease in power than the high-beta component in response to dopaminergic treatment (Lopez-Azcarate et al., 2010, Priori et al., 2004). The data collected by Johari and Behroozmand (2021) also suggest that high beta band power desynchronization and resynchronization correlate more specifically to hand movements than to speech production, particularly in PD patients. Their modulation may provide specific signatures for externally vs internally cued movements. Pre-movement desynchronization of high beta band activity was predominantly correlated with reaction times during hand movement, whereas speech motor responses were mainly correlated with low beta band neural desynchronizations. Further confirmation is warranted for this beta band sub-analysis.

Cueing network rhythms has important practical relevance for PD patients. The beta band is not the only frequency of relevance

in PD. Modulations induced by dopaminergic medication have also been observed in the theta-alpha range (4–12 Hz) (Alonso-Frech et al., 2006, Oswal et al., 2013) and at gamma band frequencies ($\approx$ 60–90 Hz) (Litvak et al., 2011, Williams et al., 2002). Moreover, there are indications for altered cross-frequency amplitude correlations between the theta and beta/gamma bands during movement (Herz et al., 2014) and between the beta and gamma bands in spontaneous activity (Fogelson et al., 2005). This implies that an integral perspective on activities throughout the entire frequency spectrum may be necessary to fully understand parkinsonian pathophysiology.

It has also been reported that gamma oscillations (60–90 Hz) are associated to PD dyskinesia (Swann et al., 2016), suggesting that the beta and gamma bands may provide two physiologic signatures, respectively identifying the bradykinetic and dyskinetic states. Patients with deep brain stimulation device implants provide a special setting for testing active modulation of these two frequency bands. Devices are evolving from the original open-loop design to a closed-loop structure where sensing is provided by recording specific frequencies. Several companies are actively pursuing brain computer interface technology and developing new neural implants. Adaptive closed-loop stimulation systems that integrate feedback signals will ideally be able to rapidly respond to real-time changes in brain rhythms by changing stimulation settings and inducing consequent functional changes. We are still in the early stages of this promising trajectory. The main concerns currently refer to the ability in reading reliable signature signals, correlating them with clinical phenomenology, and controlling interference related to movement preparation and execution.

Attractive though the above considerations seem, important inconsistencies remain which will need to be addressed through further experimentation. Still, the road is now set for listening to the internal rhythms of the brain, recording and interpreting their significance. The overarching goal is to improve the motor and non-motor conditions in PD patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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