Reply: Oscillatory coupling of the subthalamic nucleus in obsessive compulsive disorder

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Sir,

We are very pleased to be given the opportunity of commenting the letter from Wojtecki *et al.* (2017). They report very interesting data stemming from local field potential (LFP) recordings from anteromedial subthalamic nucleus (STN) in a patient undergoing deep brain stimulation (DBS) for an obsessive compulsive disorder (OCD). Their findings offer an important contribution to our understanding of cortico-subcortical circuits' organization.

Regarding the common interpretation of basal ganglia functioning, two key questions remain partially unanswered: are oscillation frequencies function-specific? Is function (and predominant frequency) topographically segregated? Inductive approaches to human brain data, by their nature charged with variability and uncertainty, have led to an implicit 'yes' answer to both of these questions. However, a proper answer should take into account evidence on both local oscillatory properties, which depend on local microcircuits, and global intersite synchronization, which is a marker of long-range network interactions.

In patients with Parkinson's disease, prominent beta-band oscillations have been consistently recorded from the dorsolateral (motor) STN. Beta oscillations have been given mainly a motor significance within the nucleus, particularly because beta spectral power is increased in the OFF medication state, and correlates with the severity of motor symptoms (Kühn *et al.*, 2006). In their OCD patient, Wojtecki *et al.* show that beta oscillations are not restricted to the motor STN, or to the parkinsonian condition. The increase in beta power in the posterior trajectory, however, is in line with the motor STN as the source of beta in the present patient. Hence, the reported coherence between the STN and sensorimotor cortex does not contradict the notion of beta oscillations being—at least predominantly—of motor significance within the cortex-basal ganglia loop. This is further supported by our recent studies in patients with dystonia where pallidocortical beta-band coherence is predominantly found to motor cortical areas (Neumann *et al.*, 2015). This pallidocortical beta-band coherence is significantly reduced with movement, and the degree of beta-band coherence correlates with reaction times, which further supports a role in motor

behaviour (van Wijk *et al.*, 2017, in press). Recent work underscores that beta coherence between the STN and primary motor cortex (M1) is also maximal at rest in Parkinson's disease patients, and is greatly attenuated during movement (Canessa *et al.*, 2016). Accordingly, we believe that beta-band activity within the basal ganglia-cortical circuits is relevant for normal physiological functions and is not confined to the parkinsonian state, despite being pathologically enhanced in Parkinson's disease patients while OFF medication.

Interestingly, dopaminergic medication and DBS seem to have different effects on cortico-subthalamic coupling. While dopaminergic medication increased cortico-subthalamic coherence (Litvak *et al.*, 2011), DBS decreased cortico-subthalamic (Oswal *et al.*, 2016) and cortico-cortical coupling (Weiss *et al.*, 2015) and phase amplitude coupling (de Hemptinne *et al.*, 2014). Dopamine may therefore enhance physiological interaction, whereas DBS interferes with cortical synchronization.

Taken together, the evidence does not lead to the conclusion that beta oscillations *per se* are related to motor processing alone, but only that they have a distinctive significance within the motor system, as they are consistently found to mediate synchronization between cortical motor regions and major subcortical motor hubs including the internal pallidum (Neumann *et al.*, 2015), the STN (Hirschmann *et al.*, 2011; Litvak *et al.*, 2011), the thalamus (Marsden *et al.*, 2000) and the pedunculopontine nucleus (Jha *et al.*, 2017). One influential account on physiological and pathophysiological beta activity may be summarized in the hypothesis that beta activity is related to the maintenance of the current cognitive or motor state (Engel and Fries, 2010). Yet an even more general proposal is that cortico-basal ganglia beta oscillations reflect the gating functions in these circuits (Leventhal *et al.*, 2012), such that a reduction in the amplitude of beta oscillations would reflect an 'open' basal ganglia state that enables processing of new cues. In line with this, a recent study conducted in patients with major depressive disorder revealed a reduction in beta power in the subgenual cingulate cortex related to emotionally salient stimuli (Huebl *et al.*, 2016), suggesting that beta activity can similarly reflect gating functions in limbic circuits. Thus, the function of beta activity can be generalized to a certain extent, although it likely also depends on the observed circuit.

In line with the conclusions from our paper, Wojtecki *et al.* find beta activity outside the motor functional zone of the STN, in an antero-medial location. These data indicate that neural populations oscillating at different predominant frequencies are spread over the nucleus length, yet maintaining a topographical concentration according to function. This interpretation strengthens the notion that STN is a crucial node in the integration among different cortico-subcortical loops. In this line, Wojtecki's finding of theta coherence between the antero-medial STN and the anterior cingulate is particularly interesting when considering the role of theta oscillations in decision-making, notably conflict resolution, and the relevance of this function in OCD pathogenesis (Zavala *et al.*, 2016).

We recently showed that there is a frequency-specific topographical distribution of oscillatory activity within the subthalamic nucleus at rest (Horn *et al.*, 2017*a*). We confirmed that significantly higher beta power was recorded in the dorsolateral than ventromedial STN and that this region was structurally more strongly connected to primary motor cortices. Inversely, alpha power was stronger in a ventromedial location, and more strongly connected to frontal and limbic areas.

To further evaluate the spatial and frequency-specific distribution, we reanalysed the same dataset to map the predominant (normalized) frequency recorded from each contact pair to common stereotactic space. As illustrated in

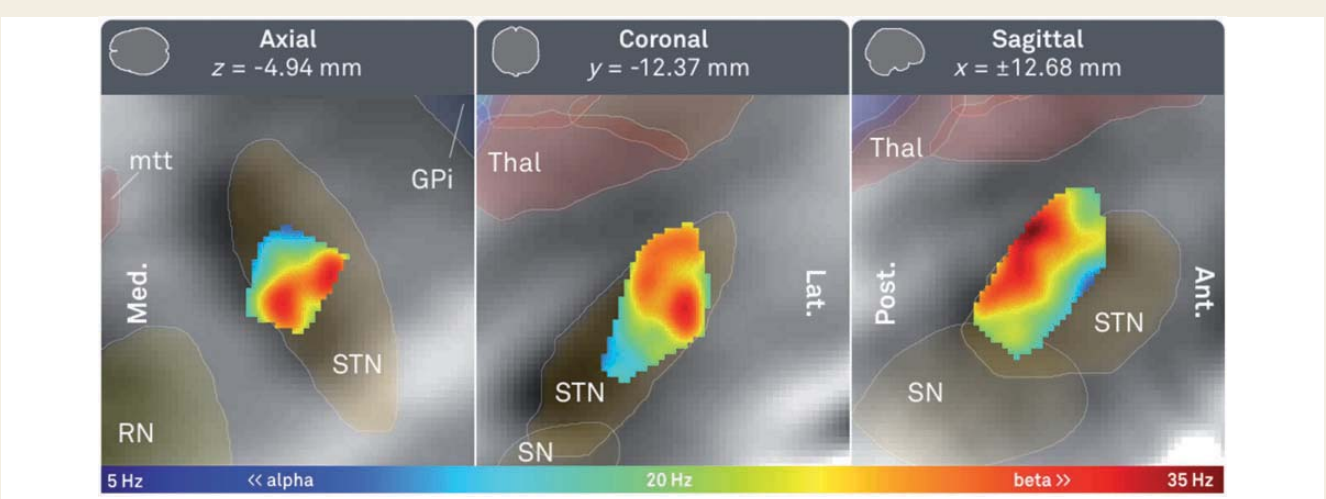

Figure 1 Predominant frequencies of oscillatory activity recorded during rest in 54 patients (309 artefact-free channels) were mapped to the subthalamic area in standard stereotactic space. Colours represent the frequency with the highest power recorded across the frequency band of 5–35 Hz (see colour bar below). GPi = internal globus pallidus; mtt = mamillo-thalamic tract; RN = red nucleus.

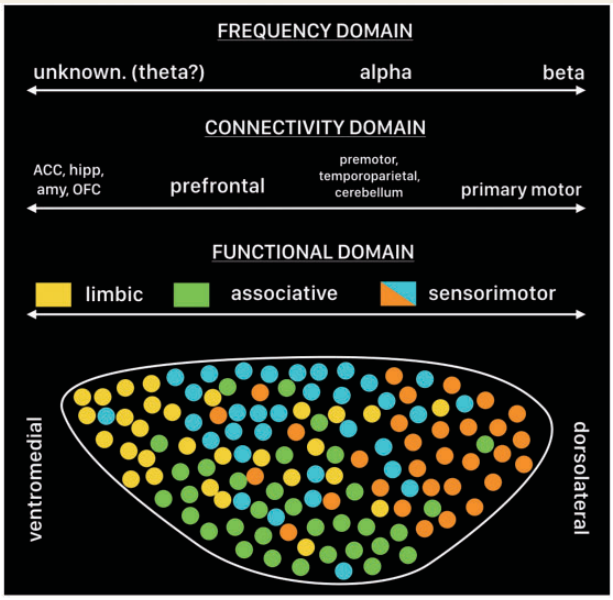

Figure 2 Hypothetical conclusion of a potential distribution of STN function, recorded frequency at rest and connectivity. ACC = anterior cingulate cortex; hipp = hippocampus; amy = amygdala; OFC = orbitofrontal cortex. Going from dorsolateral to ventromedial within the nucleus, beta power and connectivity to the sensorimotor cortex gradually declines (Accolla *et al.*, 2016; Ewert *et al.*, 2017; Horn *et al.*, 2017*a*, *b*).

Fig. 1, the predominant resting frequency power activity was within the high beta band in the dorsolateral parts of the nucleus, while ventromedial portions showed higher activity in gradually lower frequencies down to the alpha band.

Combining these findings with the letter by Wojtecki *et al.*, we draw the following conclusions: (i) enhanced beta power is found in a parkinsonian state (at rest) within large portions of the STN but it is more strongly present in its dorsolateral portion; and (ii) connectivity between the STN and sensorimotor cortex is consistently reflected in measures of beta-band coherence, irrespective of the specific spatial origin within the STN.

Given the relatively low amount of beta power in the anterior STN, one could assume that local beta oscillations are still involved in sensory-motor processing, but to an accordingly lesser degree. The gradual transition from motor to cognitive/limbic functional domains (Accolla *et al.*, 2014) could reflect the relative decrease of beta power and connectivity to primary sensorimotor areas (Fig. 2).

In conclusion, the results obtained from this OCD patient support the validity of a nuanced affirmative answer to both the above questions: frequency and localization are only partially function-specific. Working models and hypotheses maintain their usefulness, when one acknowledges the complex cortico-basal ganglia interactions and the inherent limitations of human invasive recordings that are confined to patients. On the other hand, this line of research opens up new avenues for understanding human basal ganglia function and improve treatment options.

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