

Temporo-spatial distribution of subthalamic oscillatory activity.

Ettore Accolla^{1*}, Andreas Horn^{2,3*}, Maria Herrojo-Ruiz⁴, Wolf-Julian Neumann²,
Andrea A. Kühn²

¹Neurology Unit, Medicine Department, HFR Cantonal Hospital and Faculty of Sciences, University of Fribourg, Fribourg, Switzerland.

²Department of Neurology, Charité University Medicine Berlin, Campus Virchow, 13353 Berlin, Germany.

³Berenson-Allen Center for Non-Invasive Brain Stimulation and Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

⁴Department of Psychology, Goldsmiths University of London, Lewisham Way, New Cross, London, UK.

*equal contribution

Sir,

We are very pleased to be given the opportunity of commenting the letter from Wojtecki et al.

They report very interesting data stemming from LFP recordings from anteriomedial 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 organisation.

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 to those questions should take into account evidence on both local oscillatory properties, which depend on local microcircuits, and global inter-site synchronization, which is a marker of long-range network interactions.

In Parkinson's Disease (PD) patients prominent beta-band oscillations have been consistently recorded from the dorso-lateral (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. 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. Moreover, their finding of significant beta-band 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 pallido-cortical beta-band coherence is predominantly found to motor cortical areas (Neumann et al., 2015). This pallido-cortical 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., in revision; abstract IBAGS 2017). Recent work underscores that beta coherence between the STN and primary motor cortex (M1) is also maximal at rest in PD 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 PD patients while OFF medication.

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

Collectively, 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 subthalamic nucleus (Hirschmann et al., 2011; Litvak et al., 2011), the thalamus (Marsden et al., 2000) and the pedunculo-pontine 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 generalised 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, particularly conflict resolution, and the relevance of this function in OCD pathogenesis: STN-medial prefrontal

cortex theta coherence was shown increased in high-conflict decision making (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.*, 2017a). 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 re-analysed the same dataset to map the predominant (normalised) frequency recorded from each contact pair to common stereotactic space. As illustrated in figure 1, the predominant frequency of the power activity in the dorsolateral part of the nucleus was in the upper range of the beta band (30-35Hz), while ventromedial portions showed higher power activity at lower frequencies within the beta (13-20Hz) band down to the alpha band.

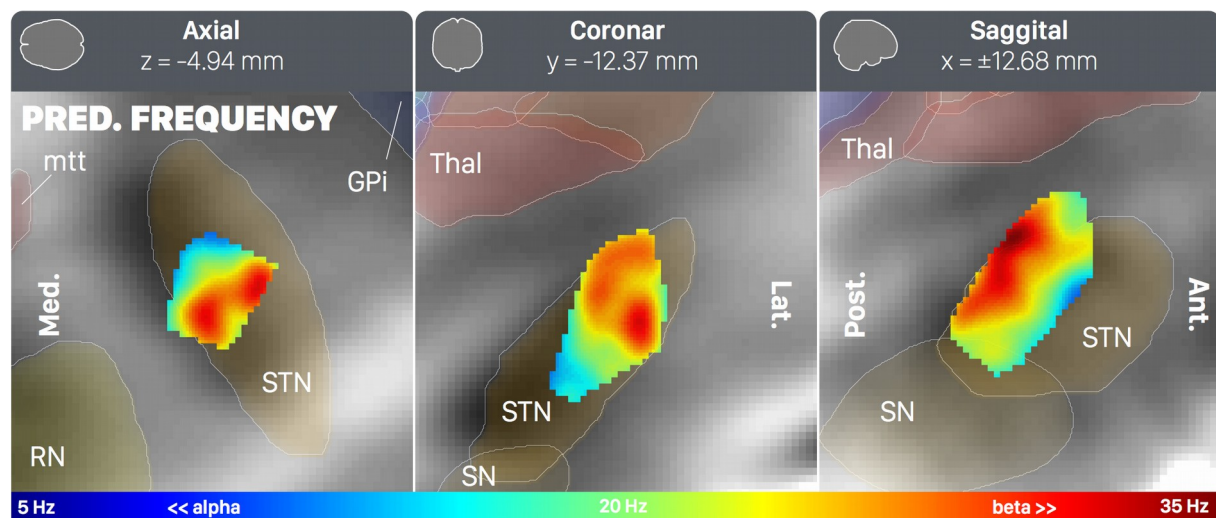


Fig. 1: Predominant frequencies of oscillatory activity recorded during rest in 54 patients (309 artifact free channels) were mapped to the subcortex in standard stereotactic space. Colors represent the frequency with the highest power recorded across the frequency band of 5 - 35 Hz (see color bar below).

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; 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 the STN.

Given the relatively low amount of beta power in the anterior STN, which could be explained by the natural decrease of oscillatory power with an increased distance to a dorsolateral source, one could assume that its function is again entailed with motor, but to an equally 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).

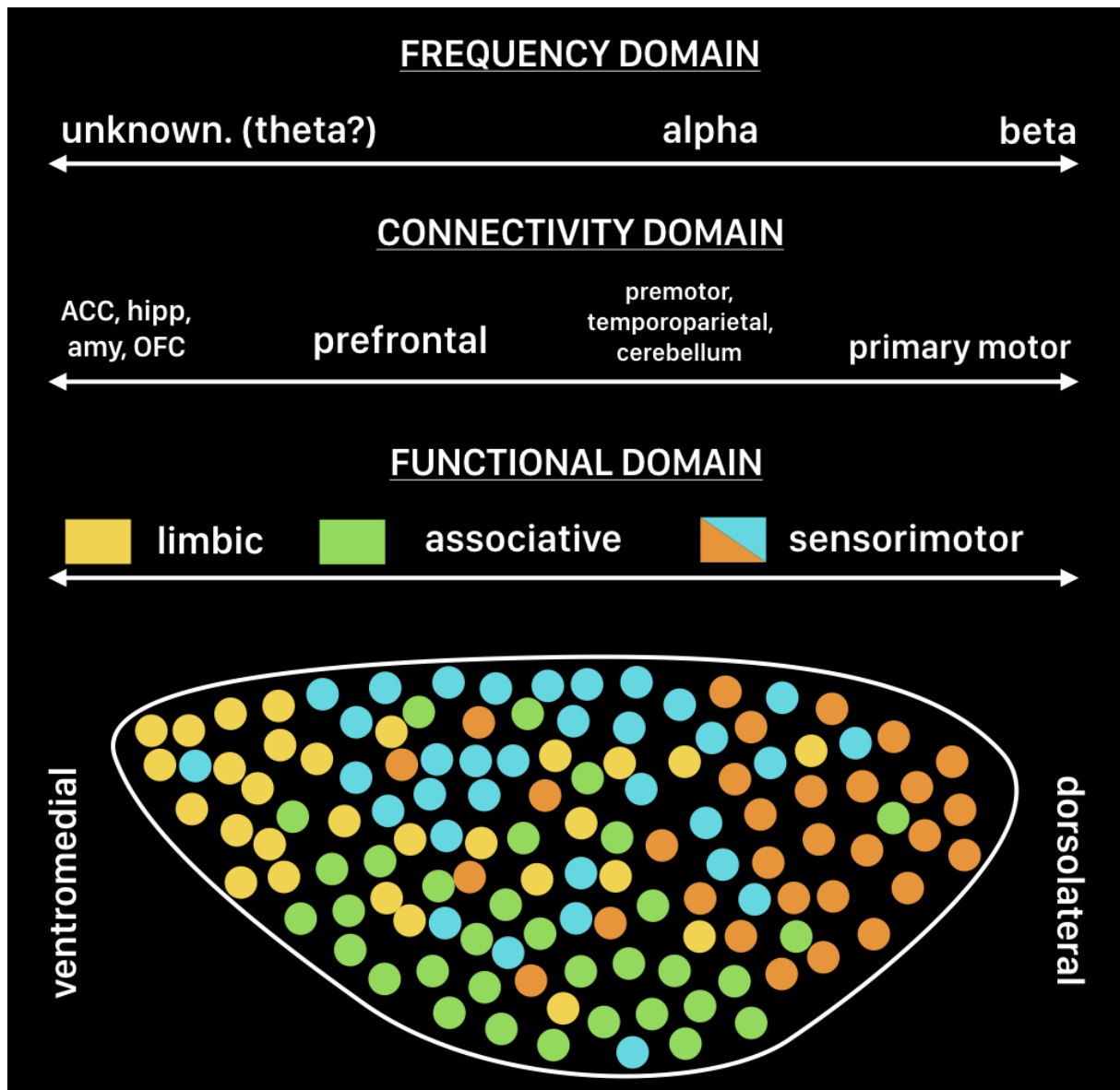


Fig. 2: Hypothetical conclusion of a potential distribution of STN function, recorded frequency at rest and connectivity. Going from dorsolateral to ventromedial within the nucleus, beta power and connectivity to the sensorimotor cortex gradually declines (Accolla *et al.*, 2016; Horn *et al.*, 2017) (Ewert *et al.*, 2017; Horn *et al.*, 2017b).

In conclusion, the results obtained from this OCD patient support the validity of a nuanced affirmative answer to both the above questions: frequency and localisation 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.

References

- Accolla EA, Dukart J, Helms G, Weiskopf N, Kherif F, Lutti A, et al. Brain tissue properties differentiate between motor and limbic basal ganglia circuits. *Hum. Brain Mapp.* 2014
- Accolla EA, Herrojo Ruiz M, Horn A, Schneider G-H, Schmitz-Hübsch T, Draganski B, et al. Brain networks modulated by subthalamic nucleus deep brain stimulation. *Brain J. Neurol.* 2016; 139: 2503-2515.
- Engel AK, Fries P. Beta-band oscillations--signalling the status quo? *Curr. Opin. Neurobiol.* 2010; 20: 156-165.
- Ewert S, Pletting P, Chakravarty MM, Kühn AA, Horn A. Toward defining deep brain stimulation targets in MNI space: A subcortical atlas based on multimodal MRI, histology and structural connectivity. *Neuroimage 2017* (epub ahead of print).
- Hirschmann J, Özkurt TE, Butz M, Homburger M, Elben S, Hartmann CJ, et al. Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. *NeuroImage* 2011; 55: 1159-1168.
- Horn A, Neumann W-J, Degen K, Schneider G-H, Kühn AA. Toward an electrophysiological 'sweet spot' for deep brain stimulation in the subthalamic nucleus. *Hum. Brain Mapp.* 2017
- Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, Schmitz-Hübsch T, Nickl R, Kupsch A, Volkmann J, Kühn AA, Fox MD. Connectivity predicts deep brain stimulation outcome in Parkinson's disease. *Annals of Neurology* 2017b; epub ahead of print.
- Huebl J, Brücke C, Merkl A, Bajbouj M, Schneider G-H, Kühn AA. Processing of emotional stimuli is reflected by modulations of beta band activity in the subgenual anterior cingulate cortex in patients with treatment resistant depression. *Soc. Cogn. Affect. Neurosci.* 2016; 11: 1290-1298.
- Jha A, Litvak V, Taulu S, Thevathasan W, Hyam JA, Foltynie T, et al. Functional Connectivity of the Pedunculo-pontine Nucleus and Surrounding Region in Parkinson's Disease. *Cereb. Cortex N. Y. N* 1991 2017; 27: 54-67.
- Leventhal, D. K., Gage, G. J., Schmidt, R., Pettibone, J. R., Case, A. C., & Berke, J. D. (2012). Basal ganglia beta oscillations accompany cue utilization. *Neuron*, 73(3), 523-536.
- Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, et al. Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain J. Neurol.* 2011; 134: 359-374.
- Marsden JF, Ashby P, Limousin-Dowsey P, Rothwell JC, Brown P. Coherence between cerebellar thalamus, cortex and muscle in man: cerebellar thalamus interactions. *Brain J. Neurol.* 2000; 123 (Pt 7): 1459-1470.
- Neumann W-J, Jha A, Bock A, Huebl J, Horn A, Schneider G-H, et al. Cortico-pallidal oscillatory connectivity in patients with dystonia. *Brain J. Neurol.* 2015; 138: 1894-1906.
- Zavala B, Tan H, Ashkan K, Foltynie T, Limousin P, Zrinzo L, et al. Human subthalamic nucleus-medial frontal cortex theta phase coherence is involved in conflict and error related cortical monitoring. *Neuroimage 2016*; 137: 178-187.