Toward future adaptive deep brain stimulation for Parkinson's disease: the novel biomarker — narrowband gamma oscillation

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases, affecting individuals especially over 60 years of age. In the next three decades, more than 12 million people will suffer from PD worldwide (Rocca, 2018). The characteristic symptoms of PD begin as a movement disorder including bradykinesia, resting tremor, rigidity, and postural instability. Among these symptoms, bradykinesia is considered to be the major feature in diagnosing PD. At early stages, the motor symptoms of PD can be traced back to the loss of dopaminergic neurons of the substantia nigra (Armstrong and Okun, 2020). The other known neuropathological hallmark of PD is the intracellular inclusions containing the aggregates of a-synuclein (Armstrong and Okun, 2020). Nevertheless, consensus exists that the dysfunction of the interconnected neural networks plays a fundamental role in the presence of clinical symptoms given the anatomical and functional interactions within the brain. The current most prevalent clinical treatment involves substituting dopamine with medication and suppressing pathological neural activity via deep brain stimulation (DBS).

DBS has been developed over the last thirty years to be an evidence-based standard therapy and has become a highly effective treatment option for PD (Muthuraman et al., 2018). The aim of DBS is to modulate neuronal oscillation by delivering high-frequency electrical stimulation to precise areas within the brain. This is done by implanting a wire with electrodes into a brain site, the common brain region used as the target for moderate and advanced PD is the subthalamic nucleus (STN). To date, the underlying physiological mechanisms of DBS in PD are still unclear. Among several proposed hypotheses, the most prevalent is the suppression of elevated neuronal activity by the DBS intervention. This was supported by the inhibitory neural activity recorded around STN during the stimulation. Furthermore, the direct cortical activation by the stimulation has been also reported in several animal studies based on neurotoxin-induced models of PD. Therefore, the therapeutic benefits of DBS seem to be not only the suppression of the aberrant neuronal activity but also the modulation of the cortical activity (Muthuraman et al., 2018). Recent studies showed promising results of DBS treatment even early in the course of the disease before the appearance of severe disabling motor complications (Porta et al., 2020). However, there are still several limitations of conventional DBS in terms of safety and efficiency. The major reason behind these limitations is the design of conventional DBS systems. Clinically available DBS devices for PD are "open loop" system that delivers constant electric currents to the targeted brain site. It does not respond to the fluctuation of the motor symptoms and causes potential side effects and shortens battery lifespan. Adaptive deep brain stimulation (aDBS), which acts in a responsive manner based on the presence of pathological neuronal oscillation or other biomarkers, has been clinically applied for epilepsy providing an opportunity to maximize the potential of DBS to PD (Beudel et al., 2020). The technical feasibility and efficacy for PD patients were investigated by several aDBS pilot studies, both unilateral and bilateral aDBS can lead to substantial motor improvement in terms of the unified PD rating scale and less energy consumption. Importantly, stimulation-induced side effects such as dysarthria, which were observed in conventional DBS, may potentially lessen as the reduced time of stimulation (Beudel et al., 2020). In order to apply aDBS, distinct and robust neuropathological biomarkers as the control signal combined with relevant physiological features need to be identified. Previous studies have shown that PD patients exhibit a prolonged duration at beta oscillation in the STN as the pathological neural activity during rest and may contribute to implementing aDBS (Gonzalez-Escamilla et al., 2020). Recently multiple studies reported the observations in gamma oscillation and the potential relation with beta activity within the cortico-BG network, such emerging feature may be crucial for clinical application of aDBS (Litvak et al., 2021). In this perspective article, we will summarize the known pathological neuronal activity and its potential to the future development of aDBS.

STN-DBS regulated beta and narrowband gamma oscillation in basal ganglia-cortical motor network: Neural oscillation in the beta frequency (13–35 Hz) is a rhythmic representation of neuronal synchronization found across the cortico-basal ganglia network. In healthy humans, cortical beta oscillatory activity is found to be a robust hallmark that is modulated by movements and suppressed by the predictive cue of upcoming action. In PD patients, the reduction of beta oscillation exhibits asymmetric in the two primary sensorimotor areas, the decrease was significantly higher over the left than over the right hemisphere (Gonzalez-Escamilla et al., 2020).

More insights into the beta activity in PD patients were attained by local field potential (LFP) recordings from implanted electrodes with temporal externalization or wireless approaches (Litvak et al., 2021). LFP signals recorded from the STN during resting-state confirmed that the aberrant beta activity in PD patients is time-locked and turned out to be remarkably robust even over periods of years (Little and Brown, 2014). The role of exaggerated beta synchrony was revealed by low beta frequency stimulation at the STN that resulted in the slowing of movements in PD patients. Moreover, such elevated beta synchrony exceeded its anatomical borders and may affect the entire cortico-basal ganglia network that is highly related to the severity of motor symptoms in PD patients (Gonzalez-Escamilla et al., 2020). Current clinical motor improvement in PD patients via DBS is achieved with high-frequency stimulation typically at 130 Hz to the STN, which suppressing the elevated beta synchrony. However, the efficacy is limited by side effects including cognitive and speech dysfunction. Some of these side effects may involve not only the suppression of exaggerated beta activity but also change in neural oscillation at gamma frequency (Little and Brown, 2014).

Cortical phase-amplitude coupling between beta and gamma frequency was investigated by de Hemptinne et al. (2013). LFPs recorded from the primary motor cortex (M1) among PD patients showed the phase of the beta band was excessively coupled to the amplitude of broadband gamma frequency (50–200 Hz). Further cross-frequency coupling (CFC) analysis revealed the abnormal CFC between the STN beta power and broadband gamma rhythm in M1. As M1 has long been implicated in the pathophysiology of PD and appeared to be one of the consistent brain areas reported in several task-based PD studies (Herz et al., 2021), it is evident that the immoderate coupling within M1 may be the representation of the cortical modification of the immoderate synchronization within the motor cortico-basal ganglia network.

Note that the broadband gamma may be responsible for several independent processes and can be modulated by voluntary movement, therefore it is important to distinguish it from finely tuned gamma (FTG), the neuronal rhythm between a narrow band 60–90 Hz, which might play a role in adverse effects caused by PD treatment. One such effect is dyskinesia that characterized by involuntary muscle movements including choreiform and diminished voluntary movements, associated with dopaminergic medication and/or DBS. Even though therapy combined with medication and DBS showed a greater effect on motor severity than either treatment alone (Muthuraman et al., 2018), the risk of treatment-induced dyskinesia may be additive due to that dyskinesia clinically is not only associated with medication but may be induced by DBS. Swann et al. (2016) demonstrated that the entrainment of oscillation within the narrowband gamma when dyskinesia is present during DBS, which offers a potential explanation for stimulation-induced dyskinesia. In addition, such association showed its potential to distinguish the presence of dyskinesia, supported by the logistic regression-based classifier with the cortical gamma power and the phase coherence between motor cortex and STN as the predictors (Swann et al., 2016). Thus, we can see evident inclination that narrowband gamma oscillation between

cortex and subcortical modulators may be new possible biomarker for aDBS.

As ascertained by previous studies, it is proposed to study PD on a network-level when investigating the effect of DBS. Recently, the relation between beta and narrowband gamma oscillation was further investigated by Muthuraman et al. (2020). Brain activity reconstructed via beamforming approach and taking the volume of tissue activated as the reference region (**Figure 1A**) revealing both source power and CFC between multiple cortical regions including M1, Premotor cortex, supplementary motor area, posterior parietal cortex at the clinical effective DBS frequency in the STN during rest as shown in **Figure 1B**. Clinically effective DBS exhibited a negative relation with significantly reduced beta power and concurrently increased gamma power in M1, Premotor cortex, supplementary motor area, STN, and CER. This implies that while the absence of stimulation, the gamma and beta oscillations may act independently, DBS might induce a negative association between the two oscillations, thereby maintaining a balance between these brain activities supporting dynamic processing. Interestingly, the beta power reduction only appeared in STN while stimulating the brain site with either low (110 and 140 Hz) or high frequency (150 and 180 Hz), suggesting that motor symptoms alleviation depends on the network-wide effect rather than solely reducing STN beta power. In addition, the power-to-power CFC between cortical regions and volume of tissue activated revealed clusters that lie between narrowband gamma coupled with the stimulation frequency (130 and 160 Hz) as can be seen in **Figure 1C**, suggesting the intrinsic FTG activity associated with clinically effective DBS frequency, which may be driven by an entertainment mechanism. This potential entrained FTG activity during clinically effective DBS may be also engaged in suppressing beta activity. Another possible explanation for the gamma power is that the attenuated beta activity by DBS allows the gamma activity to reappear in the cortico-basal ganglia circuitry. Either way, maintaining the balance between beta and gamma activities within the cortico-basal ganglia network could improve on-demand information processing therefore alleviate motor symptoms (Muthuraman et al., 2020).

Conclusion and future perspective: Globally, PD is the second most common neurodegenerative disorder following AD, with a significantly consequent decrease in the quality of life among the patients. Over the past decades, several effective PD treatments and therapy have been widely studied and developed (e.g., levodopa, safinamide). However, due to the gradually diminishing effectiveness of the medication in PD patients, surgical intervention (e.g., DBS) is often implemented to further alleviate motor symptoms and positively modulate non-motor sequels (Muthuraman et al., 2018). To maximize the potential of DBS, reliable neuropathological biomarkers have to be defined in order to implement the closed-loop intervention such as aDBS. As described in this perspective article, several studies have shown the aberrant beta activity that is robust over a long period of time in PD patients. However, the beta oscillation

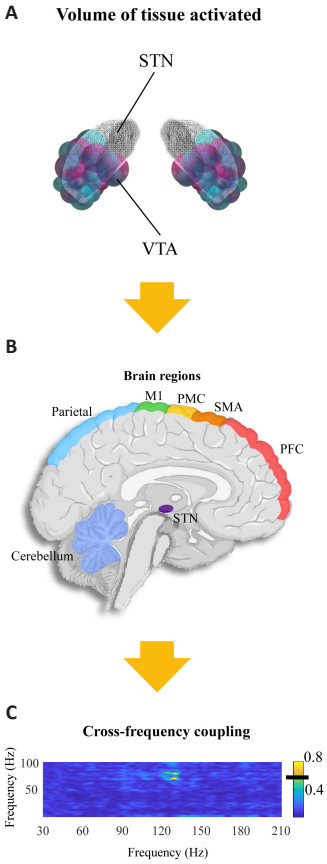

Figure 1 | Cross-frequency analysis revealed DBS entrained narrowband gamma oscillation. (A) Voxels identified by VTA analysis as a reference for the clinical stimulation condition. (B) Six coherent sources that were used for cross-frequency analysis. Additionally, the posterior parietal cortex was included as a control region. (C) Cross-frequency coupling between the VTA reference signal and the cortical region showed clusters between narrowband gamma (60–80 Hz) and the power at the stimulation frequency in the VTA. Reprinted with permission from Muthuraman et al. (2020). M1: Motor cortex; PFC: prefrontal cortex; PMC: premotor cortex; SMA: supplementary motor area; STN: subthalamic nucleus; VTA: volume of tissue activated.

can be modulated by voluntary movement as well as broadband gamma oscillation, which may present as a barrier and challenge for its use in aDBS. It is important to not confuse the narrowband gamma oscillation with the canonical movement-related broadband gamma activity that occurs at the onset of movement and may be as a part of ordinary cortical activity. Although the role of gamma oscillation in movement thus far still needs to be further explored, the emerging narrowband gamma entrainment during DBS may be the alternative biomarker and shape the future of aDBS.

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