Personalized medicine in deep brain stimulation through utilization of neural oscillations

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The neural underpinnings for normal and abnormal basal ganglia functions and functional connectivities remain unknown, although several important pieces to the puzzle have emerged over 3 decades. First was the identification of segregated basal ganglia circuits.[1] This discovery was closely paralleled by the realization that these circuits communicated through the use of a special physiologic language,[2] which proved to be more complex than initially thought, as it was not the simple firing rate of neurons, but rather specific patterns of oscillatory neuronal discharges that were important.[3] The most recent realization is the oscillation model, according to which the oscillatory neuronal discharges in specific frequency bands dictate specific motor behaviors.[4]

In Parkinson disease, increased endogenous frequencies in the θ (4–10 Hz) and β (11–30 Hz) bands recorded from the subthalamic nucleus (STN) region are associated with worsening of motor symptoms. These bands have been referred to as antikinetic or bad frequency bands. In contrast, γ frequencies (31–100 Hz) are associated with motor improvements, and are referred to as prokinetic, or good frequency bands.[5] Complicating the picture, the peak frequencies in each of the 3 bands recorded from the STN region may vary widely among persons.[6] Tsang and colleagues,[7] in this issue of *Neurology*®, ask whether these specific oscillatory frequencies could be utilized to tailor a personalized approach to STN deep brain stimulation (DBS).

The current clinical practice of DBS is empirical, and utilizes a high-frequency >100 Hz signal for therapeutic stimulation of the STN region.[8] According to the oscillation model, therapeutic STN DBS in the γ (31–100 Hz) frequency band should artificially drive a prokinetic circuit. Stimulation in θ (4–10 Hz) and β (11–30 Hz) bands should worsen the motor response. These stimulation effects could possibly be more robust if STN DBS was delivered at specific frequencies that were individualized for specific patients and specific symptoms. In this proof of concept study, individually defined medication-dependent and movement-related peak frequencies across θ, β, and γ bands of stimulation were determined and applied, and correlated with potential related clinical motor responses. Individual frequencies were ascertained directly from the DBS leads following insertion into STN, sampled within the first month after surgery before connection to the final chest-based battery source. For each subject, the peak frequency was determined that showed a reduction in the antikinetic band (θ and β frequencies) and an increase in the prokinetic band (γ frequency) during medication "on" recordings, as compared to medication "off" periods. Similarly, peak frequencies that reduced the antikinetic and increased in the prokinetic band for movement periods as compared to premovement periods were recorded when subjects performed self-initiated and externally triggered wrist movements. These frequencies in the θ, β, and γ bands were called individualized frequencies. The authors cleverly employed DBS at these "individually" determined frequencies, and compared their results to the empirically chosen high-frequency stimulation that was utilized by the treating team. This testing was performed at a minimum of 3 months after the surgery in order to avoid postsurgical effects (implantation and microlesion effects).

The investigators concluded that the motor benefits of DBS at individual γ frequencies were comparable to those obtained with high-frequency stimulation. These findings were puzzling, as one would have hypothesized that stimulation at individualized prokinetic rhythms would have been superior to conventional high-frequency stimulation. The empirically determined high frequencies that were used for chronic stimulation did not reflect as harmonics of the prokinetic γ frequencies, and therefore the authors suggested an intriguing possibility that the basal ganglia circuit could have more than one prokinetic frequency band. If this suggestion proves true, it will have the potential to alter future therapeutic approaches.

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There were a few methodologic constraints that limited the interpretation of results. The voltages used for stimulation in the γ band were not exactly the same as the chronic high-frequency settings; this change introduced some difficulty in interpretation: to determine whether boosting γ frequency was the main mechanism driving STN DBS, the voltages used should have been similar for γ and high-frequency settings. Finally, the effects of bilateral and longer-term stimulation could not be determined in this study with acute experiment design. Whether stimulation at natural γ rhythms may prove better tolerated by the brain, and possibly have fewer side effects, remains for future work.

Another important conclusion was that stimulation in the lower frequency θ and β bands did not block the levodopa effects, and did not result in motor worsening. This finding was counterintuitive. One explanation could be the technical limitation of using single pulse stimulations as opposed to using trains of pulses, with potential failure to synchronize the intrinsic θ and β rhythms, so that the antikinetic effects of θ and β stimulation were absent. It is also possible that the θ and β rhythms could be simply markers of, but not major contributors to, motor symptoms.[9] This point will need to be clarified as the field moves forward.

The current oscillation model is missing some critical data for better understanding the therapeutic effects of STN DBS. The physiologic and pathologic frequencies associated with motor responses are complex. It may not be enough to merely drive a network at prokinetic or antikinetic frequencies, as there may also need to be synchronization with other relevant upstream and downstream structures. The current DBS technology has been evolving to allow direct monitoring of local field potentials from the lead, but the stimulation still does not selectively activate specific and desired components of the targeted neurons.[10] As the technical limitations dissipate, and the current gaps in knowledge are filled by studies such as this one by Tsang and colleagues, hopefully we will be able to move toward a personalized DBS approach that can be tailored to each patient's specific needs.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.
2. DeLong MR. Activity of basal ganglia neurons during movement. Brain Res 1972;40:127–135.
3. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 1994;117:877–897.
4. Hutchison WD, Dostrovsky JO, Walters JR, et al. Neuronal oscillations in the basal ganglia and movement disorders: evidence from whole animal and human recordings. J Neurosci 2004;24:9240–9243.
5. Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003;18:357–363.
6. Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exp Neurol 2009; 215:20–28.
7. Tsang EW, Hamani C, Moro E, et al. Subthalamic deep brain stimulation at individualized frequencies for Parkinson disease. Neurology 2012;78:1930–1938.
8. Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA. Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. Brain 1960; 83:337–350.
9. Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. Brain 2010;133:2007–2021.
10. McIntyre CC, Grill WM. Excitation of central nervous system neurons by nonuniform electric fields. Biophys J 1999;76:878–888.