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Methylphenidate effects on a clinically informative oscillatory signal within the subthalamic nucleus in Parkinson's disease during deep brain stimulation programming

To the Editor:

Local field potentials (LFPs) within the beta frequency (13–30 Hz) from the subthalamic nucleus (STN) of Parkinson's disease (PD) patients exhibit strong correlation with symptom severity and are reduced with dopaminergic medications [1–3]. Clinical consensus supports the use of beta frequency power as a reliable biomarker for DBS programming including contact selection, directionality and parameter adjustments [4]. Deep brain stimulation (DBS) implantable pulse generators (IPGs) now permit simultaneous stimulation and recording of LFP activity of brain target without external devices. Although beta power LFP response to dopaminergic medications is well-established, the effects of others commonly used in the treatment of PD have not been reported. This understanding is essential as clinicians use beta power LFPs to guide DBS programming and as next-generation closed-loop systems may use the same signals to automate stimulation. We describe a significant suppression of beta power due to methylphenidate, and subsequent programming adjustments after cessation of the medication.

A 63-year-old right-handed man with an 11-year history of PD underwent bilateral STN DBS (Percept PC™, electrode model B33005, Medtronic, Inc., Minneapolis MN, USA). The patient's PD medications included carbidopa/levodopa 25/100mg 3 tabs (3x per day), carbidopa levodopa CR 25/100mg (at bedtime), amantadine 200mg (2x per day), methylphenidate 5mg (2x per day), clonazepam 0.5mg (at bedtime), and melatonin 10mg (at bedtime). At initial programming, carbidopa/levodopa and amantadine were held for 12 hours (overnight) while he continued all other medications including methylphenidate. Initial programming was conducted using BrainSense™ Survey – a bipolar assessment of LFP power for all available contact pairs. During the survey (~1.5 min duration), the patient sat motionless and quiet. An analysis of the difference in LFP power microvolts peak (μVp) within the beta range for all paired contacts did not indicate any difference for the right or left electrodes (Fig. 1A; +MPH). The power spectrum information in beta range did not evince a prominent peak for any contact pair. In addition, there was no beta peak identified in recording the two middle contacts by sensing from the neighboring contacts using the BrainSense™ Signal Test, for either electrode. Consequently, there was minimal beta power recorded from the contacts. Therefore, a monopolar review was performed of the therapeutic window (initial onset of clinical efficacy to stimulation-induced adverse effect), by gradually increasing amplitude (mA) while maintaining pulse width (60μsec) and frequency (130Hz) for each contact level. Stimulation using the middle two contacts (Left: 1ABC and 2ABC, Right: 9ABC and 10ABC) was equivalent in rigidity and bradykinesia suppression. Further, although tremor may have improved at lower amplitude with stimulation of the more ventral contacts, difference in amplitude for tremor suppression between 1ABC to 2ABC and 9ABC to 10ABC were both ~0.5mA. There was minimal stimulation-induced adverse effects differences between the middle two contacts for both electrodes. The patient was subsequently discharged on L STN: 1ABC- case+: 2.5mA/60μsec/125Hz; R STN: 9ABC- case+: 2mA/60μsec/125Hz.

The following day, the patient reported a change in personality, feeling more emotionally labile and anxious. Motorically, the patient also reported dyskinesias. Stimulation amplitude was reduced to eliminate dyskinesias; although personality changes persisted. Consequently, methylphenidate was stopped 3 days following initial programming as this was prescribed for fatigue, a symptom he was not describing at the time, and there was concern that it may be contributing to the personality changes. He returned to clinic 10 days from his initial programming session and on the same medications at discharge, except carbidopa/levodopa was reduced to 2 tabs (3x per day) and methylphenidate was stopped. Carbidopa/levodopa was taken ~3 hours before his second programming session. BrainSense™ Survey was repeated following the protocol performed at initial programming, and showed clear differences across contact pairs within the beta frequency with a peak at 20.5 Hz and 19.5 Hz for the left and right lead, respectively (Fig. 1A). Likewise, using BrainSense™ Signal Test for both leads demonstrated peak beta bands of the middle contacts. The left STN peak frequency was at 21.5Hz, with power as follows: 1ABC (1.86μVp), 2ABC (2.76μVp), 1ABC and 2ABC (1.29μVp); right STN peak frequency was at 20.5Hz, with power as follows: 9ABC (1.89μVp), 10ABC (2.03μVp), 9ABC and 10ABC (1.41μVp). Informed by beta power, the patient was subsequently re-programmed using contacts 2ABC and 10ABC. Programming was targeted to eliminate tremor and rigidity as well as to suppress the beta peak (21.4 Hz ± 2.5 Hz) through passive streaming (Fig. 1B). He was discharged on: L STN: 2ABC- case+: 1.5mA/60μsec/125Hz; R STN: 10ABC- case+: 2mA/60μsec/125Hz. The patient was re-evaluated 18 days thereafter and he reported complete resolution of stimulation-induced mood changes as well as minimal tremor and no sensation of rigidity.

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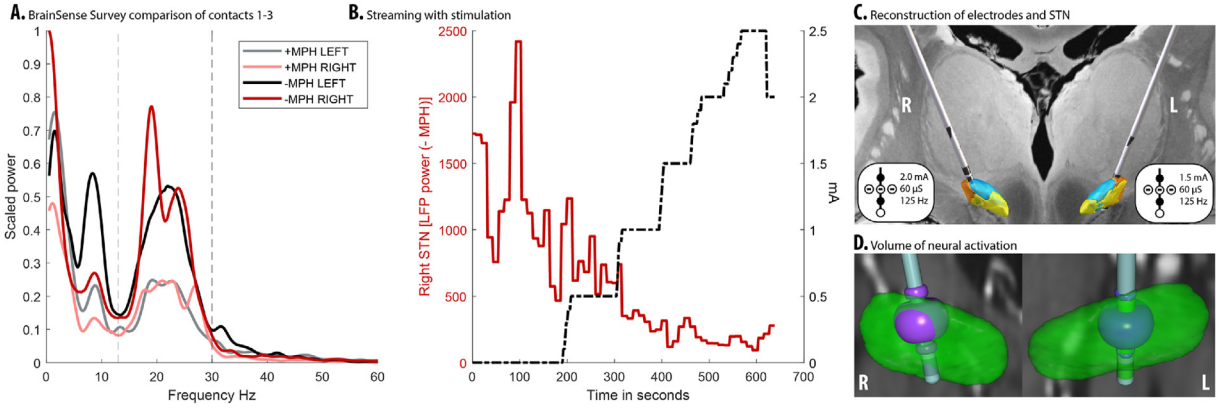

Fig. 1. A: BrainSense Survey™ of the LFP frequency differences between contacts 1 and 3 performed at initial programming on methylphenidate (MPH) (lighter color shade) and at second programming session off methylphenidate (darker color shade). B: Passive streaming within the right STN of the beta frequency 20.5Hz (red) in conjunction with increase of stimulation amplitude (black). C: Lead-DBS coronal view of contact location with the STN, motor area (brown), associative (aqua), limbic (yellow). D: SureTune™ analysis shown in medial sagittal view with the volume of neural activation of stimulation parameters programmed at the second programming session. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Lead localization indicated that contacts 1ABC and 9ABC were within or bordered the associative area of the STN while contacts 2ABC and 10ABC were within the dorsolateral region corresponding with the motor area of the STN (Fig. 1C) [5]. The volume of neural activation of contacts 2ABC and 10ABC using Medtronic SureTune™ 4 Software further confirmed that stimulation was localized within the dorsolateral region of the STN (Fig. 1D).

Methylphenidate may be used in PD to treat fatigue and gait impairment [6,7]. Methylphenidate is a stimulant that inhibits reuptake of norepinephrine and dopamine. The effects of methylphenidate on dopamine transporter SPECT imaging (DaTscan) resulting in false positive reduced tracer uptake have been reported [8,9]. In addition, it appears that beta frequency of the motor cortex in healthy individuals may be reduced with methylphenidate [10].

Between the initial and the second programming sessions methylphenidate was stopped, leading to conclusion that this medication dramatically suppressed STN beta frequency LFPs. Furthermore, beta power should have been greatest at initial programming with levodopa held overnight while not during the second programming session. This report demonstrates that methylphenidate can greatly affect beta power within the STN. Beta power analysis aided in selection of optimal contacts and stimulation amplitude. Future studies need to verify these findings and evaluate the effects of other medications on beta power, especially as this is being used as a biomarker for parkinsonism in DBS programming and in developing adaptive DBS.

Declaration of competing interest

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