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Long-lasting effects of subthalamic nucleus coordinated reset deep brain stimulation in the non-human primate model of parkinsonism: A case report

Dear Editor

Continuous, high-frequency isochronal (i.e., "traditional") deep brain stimulation (tDBS), is a standard treatment option for advanced-stage Parkinson's disease (PD). However, tDBS is limited by side effects [1] and its chronic nature can necessitate frequent battery replacement. To address these issues, a novel stimulation method, coordinated reset (CR)-DBS, was developed through computational modeling [2,3]. To date, however, data addressing its underlying electrophysiological effects are limited [3]. The goal of this study was to characterize the sub-acute and carryover motor and electrophysiological effects of CR-DBS in terms of both local field potential (LFP) power changes and brain connectivity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) non-human primate (NHP) model of parkinsonism.

Animal care complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and a protocol approved by the Cleveland Clinic Institutional Animal Care and Use Committee (IACUC). A 14-year-old adult female NHP (Macaca mulatta) was instrumented with a DBS lead in the subthalamic nucleus (STN) and a pair of twelve-contact electrocorticography (ECoG) arrays spanning from medial somatosensory to prefrontal cortex (Fig. 1A) as described previously [4,5]. The M1 region was identified as the contacts showing the lowest threshold for cortico-spinal activation, with localization confirmed by 3D reconstruction of the co-registered preoperative MRI and postoperative CT (Fig. 1B) [6]. The data presented in this work are novel and not derived from [7].

Each day, before stimulation, the animal was brought into the lab for measurement of behavioral and electrophysiological metrics, including 30 minutes performing a simple touchscreen-based reach task [4]. A custom stimulator was then mounted to the cranial implant, stimulation activated, and the animal returned to its home cage. After the four-hour stimulation period, the animal was returned to the lab, the stimulation device was removed, and data collection repeated. This process was repeated over five consecutive days [7]. Behavioral and electrophysiological data were collected once daily for an additional seven days after the stimulation period to characterize carry-over effects. This treatment block was replicated four times over a period of 12 months with periodic evaluation of behavioral and electrophysiological metrics between each session to ensure return to pre-treatment baseline. To characterize electrophysiological differences between CR-DBS vs tDBS effects, the animal received tDBS using the same schedule design. The animal also performed the behavioral task while tDBS was delivered to further establish the efficacy of tDBS [7]. The animal was treated with tDBS while completing the touch screen task across five separate days at the same time during the day as the twelve-day schedule. (See Supplementary Fig. S1 for details on DBS conditions).

Spontaneous LFP data were recorded with the awake animal seated in a commercial primate chair. Data from the four treatment blocks (5 stimulation days to 7 post-stimulation days each) yielded 45min recordings (split into 3min each for analysis, recorded pre- and post-stimulation, and once during post-stimulation days) collected from the baseline period for the separate tDBS and CR-DBS sessions recorded across the one year period. Recordings were grounded and referenced to the cranial head post, and digitized at 24,414.0625Hz (Tucker Davis Technologies, Alachua, FL). Bipolar referencing in M1 was achieved by medio-lateral subtraction of the pair of adjacent contacts situated over M1 of the cortical array ipsilateral to the implanted STN lead. Data were subsequently down-sampled (~6 kHz) and pre-processed as reported previously [5]. (For more details on the preprocessing, see supplementary material, section 1.1).

Fig. 1C and D reveal differences in M1 oscillatory power and cortico-cortical coherence (which is where we found significant network changes) between the untreated parkinsonian state and data acquired immediately following cessation of stimulation. The effects of DBS immediately following cessation of stimulation on each day of the treatment phase were compared to the pre-stimulation baseline using the nonparametric Mann-Whitney-Wilcoxon statistical inference testing (significance threshold: $p < 0.05$, and Bonferroni-corrected for multiple comparisons), and the results were averaged. Following both DBS conditions, therapeutic benefit was accompanied by a decrease (%change) in M1 power and cortico-cortical. As shown in Fig. 1E, CR-DBS produced overall sub-acute changes of PSD and coherence changes at the same level of those produced by tDBS (changes induced by both DBS therapies were not statistically significant as per the same Mann-Whitney-Wilcoxon test above with significance threshold: $p < 0.05$) with the effects of CR-DBS persisting into the long-term carry-over period.

We analyzed the time course of pre-DBS changes in the theta and beta band PSD and coherence values by displaying the values from the electrophysiological recordings each morning over the 12-day experimental window. In both frequency bands, a clear, step-wise pattern of change in response to CR-DBS was observed across the 5-day treatment period. Persistent carry-over effects (%

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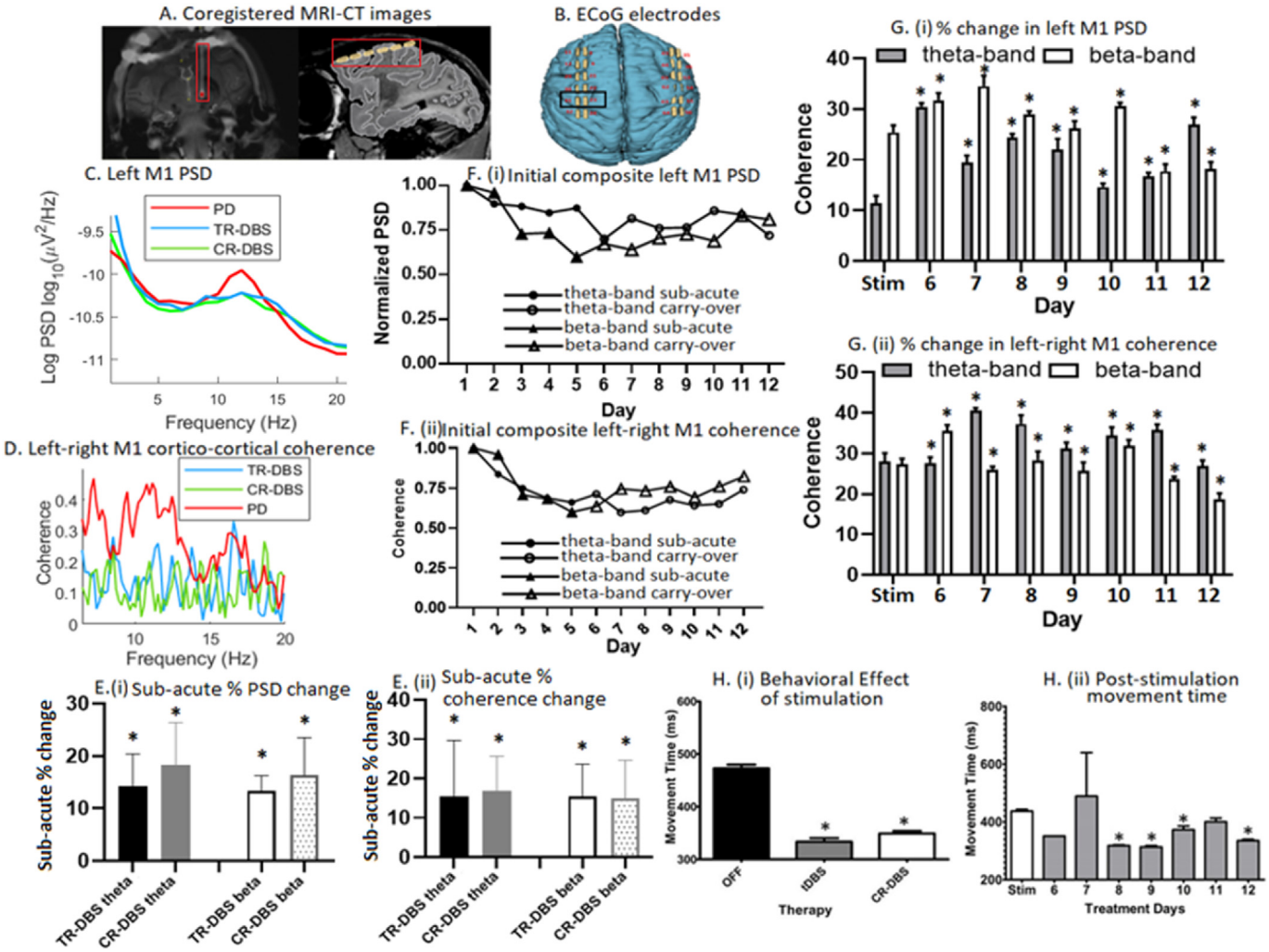

Fig. 1. A. Co-registered pre-operative MRI and post-operative CT depicting the trajectory and location of the DBS lead targeting the STN (coronal view, center of contact region of DBS lead marked with a red star), and the relative location of the ECoG array over the ipsilateral hemisphere (sagittal view, contacts highlighted in yellow). **B.** 3D reconstruction of cortex and ECoG array (M1 LFPs were derived from bipolar re-referencing of sites 31 and 23). **C.** Mean Left M1 PSD (zoomed in to 5–20Hz to show the theta and beta peaks characterized here as they showed significant changes in PD with DBS therapy), and **D.** Mean left-right M1 cortico-cortical Coherence. **E.** The mean (±SD) sub-acute change in the left M1 PSD, and the left-right M1 cortico-cortical coherence values for each treatment condition across the five treatment days relative to the pre-stimulation day. **F.** The initial composite (i) left M1 PSD values, (ii) left-right M1 coherence values, from recordings taken each morning across the 12-day experimental period. **G.** The mean (±SD) change in the left M1 PSD, and left-right M1 cortico-cortical coherence during the treatment phase and CR-DBS post-treatment carry-over period relative to the pre-stimulation day. *Significantly different from baseline ($p < 0.05$). **H.** Changes in reach behavior, (i)) The Effect of DBS therapy on MT immediately after stimulation during the treatment phase only, (ii) The mean (±SD) sub-acute change in MT during the CR-DBS treatment phase and post-treatment carry-over period in another dataset. *Significantly different from baseline ($p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

change in power) were observed in both bands for up to a week post-stimulation (Fig. 1F). (For more detailed individual plots, see Supplementary Fig. S2). Moreover, we observed that the %changes of PSD and coherence in the theta and beta bands persisted up to a week post-stimulation (Fig. 1G). The carry-over DBS effects on each day of the post-treatment phase were compared to the baseline before stimulation using the nonparametric Mann-Whitney-Wilcoxon statistical inference testing (significance threshold was set at $p < 0.05$). The similar trend of changes in the STN PSD and the M1-STN coherence are reported in the Supplementary Figs. S3 and S4.

Fig. 1H (i) shows the sub-acute effect of traditional- and CR-DBS on mean movement time (MT) immediately after stimulation during the treatment period. Longer MT were observed in the OFF-therapy condition, whereas both tDBS and CR-DBS showed MT reductions. In addition to its sub-acute effect, CR-DBS further showed long-term carry-over motor benefits in terms of behavioral performance. Fig. 1H (ii) summarizes changes in MT during the reach phase of the motor task immediately after CR-DBS across both the stimulation and post-stimulation phases. Although some variability was observed, MT was significantly decreased on days 1, 2 and 4 during the treatment phase. Persistent carry over motor benefits were also observed that lasted up to about a week following cessation of DBS therapy.

In this study, we observed that, despite its lower duty cycle and reduced pulse amplitude compared to tDBS, STN CR-DBS was associated with sub-acute motor effects similar to those observed during tDBS, but with the added advantage of providing carryover benefits following cessation of stimulation. CR-based approach has been previously shown, computationally, to shift networks from attractors with strong synaptic connectivity and strong neural synchrony to attractors with weak synaptic connectivity and weak

synchrony [8–10]. This indicates that CR-induced desynchronization lowers the rate of coincidences and, in turn, mediated by spike timing-dependent plasticity (STDP), an unlearning of abnormal synaptic connectivity and, in turn, of abnormal neuronal synchrony. Our findings in the parkinsonian MPTP provide further independent, in vivo evidence of that desynchronizing effect, with both sub-acute and long-lasting effects on both behavior and cortical physiology.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.04.005.

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