 DOI: 10.3217/978-3-85125-962-9-187

At-home, embedded closed-loop deep brain stimulation using data-driven neural physiomarkers alleviates residual motor symptoms in Parkinson's disease

S. Cernera[1*], C.R. Oehrn[1], L.H. Hammer[1], J. Yao[1], M. Shcherbakova[1], A. G. Hahn[1], S. Wang[1], C. Belkoura[1], J.L. Ostrem[1], C. N. Smyth[1], S. Little[1], P. A. Starr[1]

[1]University of California, San Francisco, CA, USA

*521 Parnassus Ave, San Francisco, CA. E-mail: stephanie.cernera@ucsf.edu

Introduction: Deep brain stimulation (DBS) is a surgical therapy for patients with Parkinson's disease. However, standard-of-care continuous DBS may be associated with residual motor fluctuations, especially as patients transition throughout their levodopa medication cycle. Closed-loop DBS can automatically respond to motor fluctuations by adjusting stimulation amplitude in response to a neural physiomarker – a neural signature which reflects either medication state or motor symptoms. Prior closed-loop studies have been limited to perioperative environments that may not reflect naturalistic settings [1], and predefined frequency bands that may not be optimal physiomarkers for patient-specific symptoms [1], [2]. We sought to derive individualized neural physiomarkers based on at-home neural recordings and symptom monitoring, while implementing embedded closed-loop DBS in the home environment.

Materials, Methods and Results: Participants (n=5) were implanted with permanent subthalamic and sensorimotor cortical leads connected to a second-generation bidirectional device (Medtronic Summit™ RC+S). The RC+S has the capability of sensing neural signals while simultaneously delivering therapeutic stimulation [2]. We recorded local field potentials from the subthalamic nucleus and sensorimotor cortex via a patient-facing graphical user interface [2] and paired recordings with wearable monitors that assessed motor symptoms [3], [4] while participants performed activities of daily living. The most discriminative physiomarker of medication state or symptom was derived for each participant using a linear discriminant classifier with sequential forward feature selection [5] and cluster-based analyses controlling for stimulation effects on the neural signal [6]. During at-home implementation, we randomized testing days between continuous and closed-loop DBS while participants were blinded to the condition. At the end of each testing day, participants rated the number of awake hours and severity of their most bothersome motor symptom. These varied between individuals and included dyskinesia, bradykinesia, tremor, and dystonia. Data-driven physiomarker identification also varied between individuals and included cortical gamma (64-66 Hz and 64-70 Hz), subthalamic alpha/beta (11-15 Hz), subthalamic gamma (64-66 Hz), and cortical theta/alpha (2-10 Hz). Across participants and testing days, the average percentage of awake time spent with the most bothersome symptom decreased during closed-loop DBS compared to continuous stimulation (14.37% vs 35.82%, $p < 0.01$), as did the average severity of the symptom (1.72 vs 2.70, $p < 0.05$; scale 0-10).

Discussion: These results provide single-blinded evidence that embedded, neural-driven closed-loop DBS can reduce residual motor symptoms - both time and severity - compared to standard-of-care continuous stimulation.

Significance: Closed-loop DBS is translatable to the home environment and is facilitated by multi-site signal detection (cortex as well as basal ganglia). Future steps of this protocol involve the first long-term, at-home double-blind comparison between closed-loop and continuous stimulation.

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