Imaging-informed brain simulations predict personalized DBS response

Jil Meier[1,2], Marius Pille[1,2], Leon Martin[1,2], Timo Hofsähs[1,2], Anaïs Halimi[1,2], Johannes Busch[3], Jan Roediger[3], Lucia Feldmann[3], Roxanne Lofredi[3], Patricia Krause[3], Andrea Kühn[3], Petra Ritter[1,2]

[1] Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany
[2] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Neurology with Experimental Neurology, Brain Simulation Section, Berlin, Germany
[3] Charité – Universitätsmedizin Berlin, Department of Neurology, Movement Disorders and Neuromodulation Unit, Berlin, Germany

Abstract

Introduction: Deep Brain Stimulation (DBS) is a successful symptom-relieving treatment for Parkinson's disease (PD). However, the introduction of advanced directional DBS electrodes significantly expands the programming parameter space, rendering the traditional trial-and-error approach for DBS optimization impractical and demonstrating the need for computational tools. Our recently developed DBS model using The Virtual Brain simulation tool was able to reproduce multiple biologically plausible effects of DBS in PD (Meier et al., 2022), though a link with clinical outcome data was still missing.

Methods: In the current work, we extended our virtual DBS model toward higher resolution for the stimulus input, incorporating streamlines around the electrode and the electric field calculation, adapting a previous approach by (An et al., 2022). The region-based whole-brain simulations were set up with The Virtual Brain applying the generic two-dimensional oscillator as neural mass model and an averaged connectome from the Human Connectome Project S1200 release as underlying structural network. We simulated DBS of N=14 PD patients with available empirical data on monopolar ring and directional contact activations of N=392 different electrode settings (in total over all patients, with varying amplitudes between 0 and 3mA) of the 'SenSight' electrode with corresponding motor task outcome (Busch et al., 2023). The motor task involved maximum-velocity pronation-supination movements of the lower arm, with the movement velocity recorded using a handlebar-like device held in the patient's hand. To predict the motor task outcome for each individual setting, we fitted a linear model based on the first three principal components of the N=392 time-averaged DBS-evoked simulated responses.

Results: The whole-brain simulations are now sensitive to the exact three-dimensional location of the activated contact and the tested amplitude. Our prediction model based on the simulated or so-called *sweet dynamics* demonstrated a correlation between predicted and empirically observed motor task improvements due to DBS of $r=0.386$ ($p<10^{-4}$) in a leave-one-setting-out cross-validation (Figure 1A-B). Benchmarking revealed a trend toward better predictions with our *sweet dynamics* than imaging-based static methods such as the sweet spot ($r=0.16$, $p<0.05$) and sweet streamline ($r=0.26$, $p<10^{-4}$) approaches (Hollunder et al., 2024). Furthermore, our model outperforms the traditional trial-and-error method in predicting optimal clinical settings for individual patients, e.g. achieving an over 60% likelihood of identifying the optimal contact within the first two suggested contacts compared to a 25% likelihood for the trial-and-error method (Figure 1C).

Conclusions: We identified the *sweet dynamics* that show improved motor task outcome for individual electrode settings of PD patients. These simulated DBS-evoked responses can be used to find the optimal electrode settings via a novel network-dynamics-based computational method. In the future,

the developed framework can be used to optimize the electrode placement and settings *in silico* in individual patients prospectively. Our study showcases the potential benefit of whole-brain simulations for improving clinical routine.

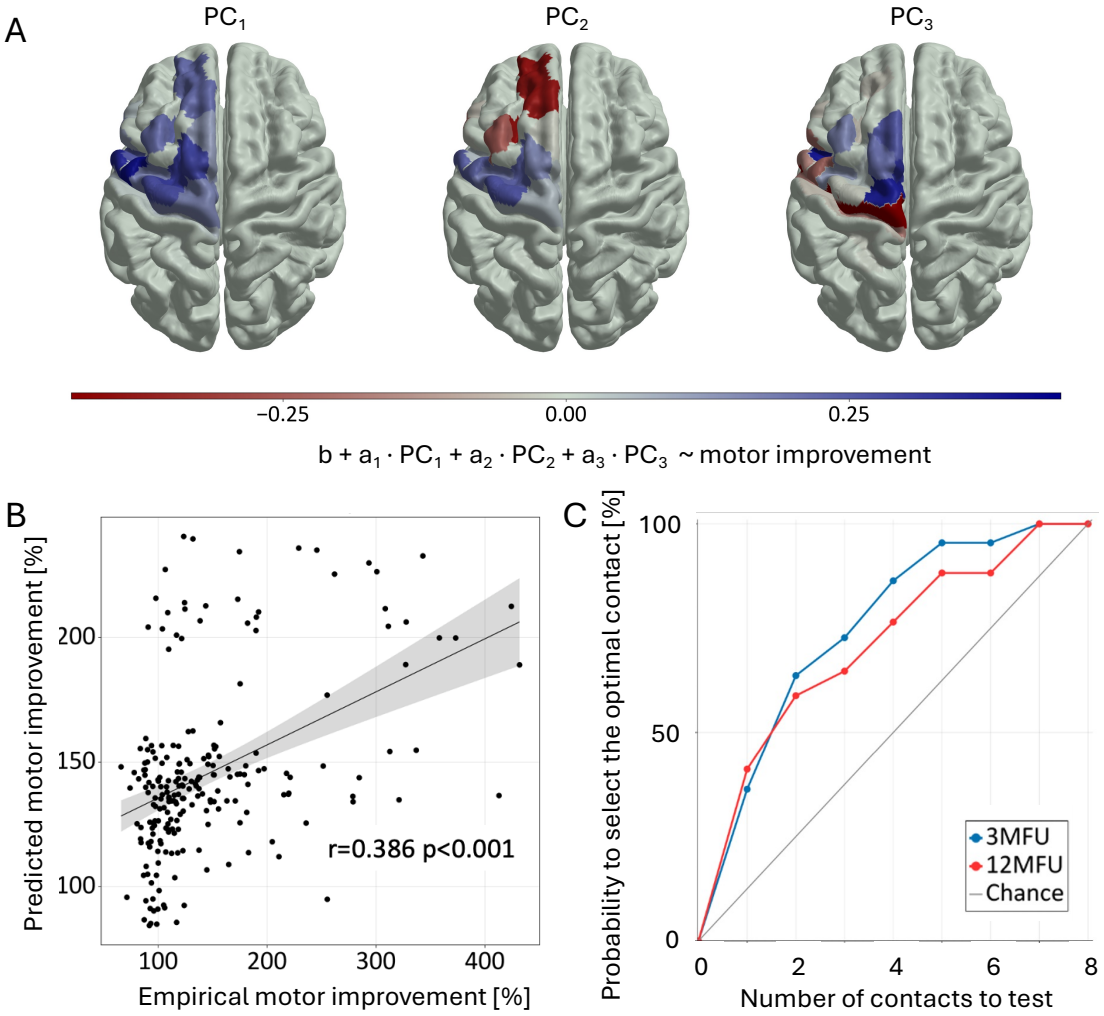

Figure 1: Sweet dynamics predict clinical motor improvement. (A) Correlation between predicted motor improvement based on the sweet dynamics model and empirical motor improvement in a leave-one-out cross-validation. Percentages on the axes represent the relative improvement of the velocity during the motor task compared to DBS switched-off. (B) The sweet dynamics model is based on a linear combination of these three principal components (PCs) of stimulus-evoked simulated activity. Red-colored regions represent decreased, blue-colored increased activity after DBS. (C) Probability to select the optimal individual contact at the three- and 12-month-follow-up (MFU) visits based on traditional trial-and-error method (grey line) and sweet dynamics model (blue and red line).

References

An, S., Fousek, J., Kiss, Z. H., Cortese, F., van Der Wijk, G., McAusland, L. B., ... & Protzner, A. B. (2022). High-resolution virtual brain modeling personalizes deep brain stimulation for treatment-resistant depression: Spatiotemporal response characteristics following stimulation of neural fiber pathways. *Neuroimage*. https://doi.org/10.1016/j.neuroimage.2021.118848

Busch, J. L., Kaplan, J., Bahners, B. H., Roediger, J., Faust, K., Schneider, G. H., ... & Kühn, A. A. (2023). Local Field Potentials Predict Motor Performance in Deep Brain Stimulation for Parkinson's Disease. *Movement Disorders*. https://doi.org/10.1002/mds.29626

Hollunder, B., Butenko, K., Neudorfer, C., Dougherty, D. D., Richardson, R. M., Ostrem, J. L., ... & Li, N. (2024). Mapping dysfunctional circuits in the frontal cortex using deep brain stimulation. *Nature Neuroscience*. https://doi.org/10.1038/s41593-024-01570-1

Meier, J. M., Perdikis, D., Blickensdörfer, A., Stefanovski, L., Liu, Q., Maith, O., ... & Ritter, P. (2022). Virtual deep brain stimulation: Multiscale co-simulation of a spiking basal ganglia model and a whole-brain mean-field model with The Virtual Brain. *Experimental Neurology.* https://doi.org/10.1016/j.expneurol.2022.114111