Subthalamic stimulation evoked cortical responses relate to motor performance in Parkinson's disease

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established therapy for Parkinson's disease (PD) [1]. However, determining the optimal stimulation setting can be a time-consuming trial-and-error process. Thus, there is a need to define non-invasive biomarkers, for instance through the analysis of DBS-evoked cortical responses (CR) [2]. Previous studies indicate that CR with latencies of 2–10 ms — resulting from antidromic hyperdirect pathway activation — are higher for stimulation contacts that elicit a therapeutic effect [3]. Still, neither the direct relationship to objective measures of motor performance nor the precise cortical distribution of CR have been studied so far. Making use of magnetoencephalography (MEG), we aimed to analyze the cortical distribution of stimulation evoked responses and relate them to objective quantitative parameters of motor performance.

22 patients with PD were asked to tap 10 times their right index finger onto their thumb as large, fast and regular as possible with a periodicity of about 2 ms [2]. These responses might be generated by a recurrent activation of layer V pyramidal neurons in M1 following their antidromic activation [7]. Both responses (R5 and R20) involve M1 and could therefore result from recurrent activation of layer V neurons after antidromic cortical activation. Moreover, higher R5 and R10 responses in M1 and SMA were significant predictors of tap frequency (Fig. 1 H, J, K), such that greater R5 and R20 responses predicted greater consistency in finger tapping frequency (R5: M1: b = -8.60 ± 3.12, p = 0.043; SMA: b = -8.60 ± 2.99, p = 0.043; R20: M1: b = -16.10 ± 4.13, p = 0.005; SMA: b = -8.59 ± 3.16, p = 0.043). The R10 response in M1 was a significant predictor of tap frequency (Fig. 1 I), with greater CR related to greater tap frequencies (b = 0.23 ± 0.09, p = 0.043).

In this study we identified distinct CR patterns associated with different latencies. The R5 response involved M1 and SMA, while the R10 response was confined to M1 and the R20 response again included the SMA, MFG and IFG. Interestingly, the R10 response in M1 was a significant predictor of finger tap frequency while the R5 and R20 related to a more regular movement profile. This might indicate a fine-grained discrimination of movement by these responses.

Tap variability reflects the motor task's consistency, the number of hesitations, and errors. This translates to impaired movement initiation — a cardinal element of akinesia. Meanwhile, tap frequency relates to bradykinesia. The relationship between CR and tap variability but not tap frequency might indicate, that CR amplitudes are markers of pathway activation related to movement initiation and inhibition rather than bradykinesia, which is better reflected by local oscillatory beta-band activity within the subthalamic nucleus [6].

CR between 2 and 10 ms occur at three distinct latencies with a periodicity of about 2 ms [2]. These responses might be generated by a recurrent activation of layer V pyramidal neurons in M1 following their antidromic activation [7]. Both responses (R5 and R10) involve M1 and could therefore result from recurrent activation of layer V neurons after antidromic cortical activation. Moreover, higher R5 and R10 responses in M1 and SMA were indicative of better finger tapping performance. In animal models...
of PD antidromic spiking of M1 layer V neurons as well as CR in M1 related to improved motor symptoms [8]. Therefore, the R5 and R10 responses in our study could reflect antidromic spiking (R5) and its after-effects (R10).

CR at longer latencies (>20 ms) may represent an orthodromic synaptic transmission via the basal ganglia-thalamo-cortical loop [3]. Our identified CR at 21.8 ms localize within MFG, IFG, and SMA. This is consistent with a polysynaptic activation involving various functional areas of the basal ganglia-thalamo-cortical network.

One common limitation of MEG studies with DBS patients is the change from clinically-used monopolar to bipolar DBS to reduce stimulation related artefacts [9]. CR of less than 3 ms might still be contaminated by the monopolar stimulation artefact. Another limitation of our study is the exclusive focus on finger tapping as the behavioural marker of motor performance. While earlier studies relied on a limited cortical coverage, we reveal a cortical distribution of responses that aligns with the basal ganglia-thalamo-cortical network. Our study identifies a relationship between CR evoked by subthalamic stimulation and motor performance — an important prerequisite to use CR as biomarkers for clinical programming in the future.

Authors’ roles

BHB, RKS, CJH, AS, and EF contributed to the design of the study; BHB, RKS, and EF contributed to the acquisition and analysis of data; BHB and EF contributed to drafting the text and preparing the figures. RKS, CJH, EF, and AS reviewed and revised the manuscript for intellectual content.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AS received consultant and speaker fees from Medtronic Inc., Boston Scientific and Abbott. CJH received honoraria from Abbott. BHB, RKS and EF declare that they have no known competing interests.

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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.2023.02.014.

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