PAPER OF THE MONTH 05/2024

TRR 295 ReTune

Deep brain stimulation of symptom-specific networks in Parkinson's disease.

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Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for Parkinson's disease (PD). However, its effects on gait and other axial symptoms have been variable, even including detrimental effects of electrical stimulation under certain circumstances. One reason could be that we generally target the same brain region to treat different symptoms of the disease. A more optimal strategy for maximal improvement in clinical outcomes of DBS could be to fine tune targeting such that subcortical tracts are stimulated that maximally associate with symptom-specific improvement.

Here, we developed a 3D stereotaxic model of four cardinal motor symptoms in PD – tremor, bradykinesia, rigidity, axial symptoms and to explore the relationship between tracts and symptoms. Data used to calculate the tract model was kindly shared by three centres of DBS – Würzburg, Berlin and Amsterdam with a total of 129 patients who had undergone DBS for PD at the STN. To determine these relationships, we used the DBS fiber filtering approach, along with a newly created DBS pathway atlas which was curated and validated by expert neuroanatomists in this work. Using this approach, we observed that tremor improvements were associated with stimulation of tracts connected to primary motor cortex and cerebellum, while axial symptoms are associated with stimulation of tracts connected to the supplementary motor cortex and brainstem. Bradykinesia and rigidity improvements were associated with the stimulation of tracts connected to the supplementary motor and premotor cortices, respectively. To validate the tract model, we used two independent cohorts – first, a dataset of 93 patients from Wurzburg and Beijing, in which our model was able to significantly predict empirical improvements ($R = 0.37$, $p = 0.0006$). Second, to test for symptom specificity, we used monopolar review data kindly shared by colleagues in Cologne, in which $N = 10$ patients had undergone meticulous monopolar review. The tract model predicted symptom specific outcomes.

Finally, we fully leveraged the symptom tracts by introducing an algorithm called Cleartune that utilizes the symptom library and suggests stimulation parameters which are predicted to lead to maximal improvement given an individual patient's baseline symptom profile. To this end, we prospectively tested the applicability of Cleartune in five patients treated at the University Hospital Würzburg. Cleartune was able to suggests settings that resulted in better improvements than the standard of care settings in four out of five patients; in the fifth one, improvements were comparable.

In conclusion, this symptom-response tract model and the Cleartune algorithm may be helpful toward developing patient-specific treatment options using DBS in patients with PD.

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