Using Structural and Functional Connectivity to Predict Response to Deep Brain Stimulation in Patients with Advanced Parkinson’s Disease

Lucy Li1, Jennifer Muller1, Sara Thalheimer3, Mackenzie D Silverman1, Mahdi Alizadeh4, Tsao-Wei Liang4, Kelly Layton4, Daniel Kremens1, Victor Romo1, Feroze B. Mohamed1, Chengyuan Wu1
1Thomas Jefferson University, Philadelphia, PA

Introduction

- Parkinson’s Disease (PD) affects more than 1 million people in the U.S., with about 60,000 new cases identified each year.8
- PD is a neurodegenerative disorder characterized by loss of dopamine-secreting neurons in the substantia nigra, resulting in gradual motor impairment as well as non-motor problems as the disease progresses.40
- Cardinal motor symptoms include tremor, bradykinesia, rigidity, and postural instability, while non-motor complications include dementia, depression, and anxiety.6
- Currently, levodopa (precursor to the neurotransmitter dopamine) or a dopamine agonist is recommended as the first drug of choice for motor symptomatic treatment of PD.57
- Long-term levodopa use, however, has been associated with higher risk of motor complications, such as dyskinesia and motor fluctuations. Motor complications are estimated to occur in at least 50 percent of patients five to ten years post-treatment.9
- It is clear that there are varying degrees of response to levodopa in patients with advanced PD. This loss of effective responsiveness to levodopa is one of the most difficult aspects of treating PD, and is an important factor when determining patient selection for deep brain stimulation (DBS).4
- DBS is a surgical treatment to reduce motor symptoms in patients when drugs become ineffective.2
- Because of the motor complications and varying long-term effectiveness of levodopa in patients, it would be beneficial to determine neuroimaging biomarkers that can predict patient response to DBS as a form of treatment earlier on.
- However, there is still a limited understanding of the underlying neural mechanisms of DBS and whether it creates long-term effects on brain connectivity.11
- Better understanding of the role DBS plays on the functional and structural brain networks in PD can allow for deeper investigation into the pathogenesis of PD and lead to more effective treatment.

Objective

- It is hypothesized that motor performance in PD reflects adjustments in a network of interacting neural circuits, that contribute to motor control.6
- Functional and diffusion tensor imaging (DTI) neuroimaging techniques may reveal insights into functional and structural neural network changes in PD.
- In this project, we aimed to investigate how changes in functional and structural connectivity may relate to patient response to DBS, through the examination of large-scale brain network changes.

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Methods

- Ten patients with advanced Parkinson’s Disease were included in this study. Patients were evaluated for their preoperative UPDRS-III score on medication prior to DBS implantation and then evaluated for their postoperative UPDRS-III score on medication after DBS implantation (eight bilateral GPI-DBS and two bilateral STN-DBS) to determine their percent improvement in UPDRS-III score after surgery. Patients also underwent preoperative DTI and resting-state fMRI scans to acquire data for structural and functional connectivity analysis respectively. 120 brain regions from the AAL atlas were nonlinearly registered to both structural and functional scans. Structural tracts from DTI were reconstructed using Camino4, and fMRI data was preprocessed using GRETNA12. GRETNA was used to create 2D correlation matrices representing the connection strength between different regions, and network analysis was performed to compute both global and local graph theory metrics. Metrics were correlated with UPDRS-III percent improvement using Matlab to identify significant correlations to UPDRS-III improvement following DBS.

Results

- Combined structural and functional graph theory metrics highlighted 32 structures to be significantly correlated (mean p=0.027) with UPDRS-III improvement (tables 1 and 2). Many of these structures, such as precuneus and postcentral, have been previously described as major hubs in PD.3
- Connections to the cerebellum and precuneus were found to be significantly correlated with UPDRS-III improvement across several metrics for both structural and functional connectivity.

Conclusions

- In this work, we combined DTI, fMRI, and graph theory analysis to evaluate improvement with DBS. We identified several imaging biomarkers that are robust predictors for UPDRS-III improvement.
- This work warrants investigation into the compensatory effect of the cerebellum and precuneus as well as other potential biomarkers for identifying DBS candidates.
- By identifying both structural and functional neuroimaging biomarkers in patients who have responded well to deep brain stimulation, we can predictively select candidates to increase the effectiveness of this treatment option.

References