Do Effects of DBS on Network Activity in Parkinson's Disease Vary Based on Phenotype?

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Introduction

Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease affecting over 10 million people worldwide. PD is characterized by a loss of dopaminergic neurons impairing the basal ganglia which regulates fine motor control.

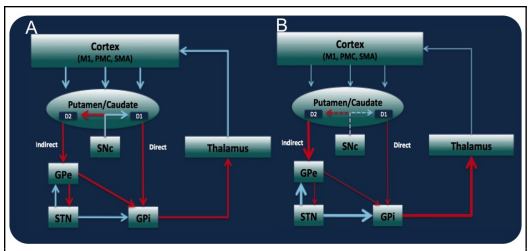

Figure 1. Depiction of the current accepted pathway in both a normal condition (A) and PD condition (B). In (A) there is a balance between the direct and indirect pathways leading to correct motor control. In (B) the depletion of dopamine triggers the indirect pathway to become dominant, impairing the motor cortex.

Tremor and akinesia-rigidity (AR) phenotypes are two common groupings based on motor symptoms. Both subthalamic nucleus (STN) and globus pallidus interna (GPi) DBS effectively treat different PD phenotypes, however, the physiological effects are unknown.

fMRI

Conditional DBS labeling allows patients to undergo an MRI with their DBS turned ON, allowing for the possibility to visualize blood oxygen level dependent (BOLD) changes that occur with DBS.

Hypothesis

The tremor dominant phenotype of PD will exhibit different, identifiable changes in brain activation compared to the akinesia rigidity phenotype.

Methods

Subjects were placed into either a tremor or AR cohort based off of Unified Parkinson's Disease motor subunit scores (UPDRS-III).

Subjects completed 1 fMRI scan with IPG devices cycling (30s ON/OFF) and synchronized to the scanner using a custom electronics box (e-box).

Model-based voxel-wise general linear model (p=0.05 FWE, cluster voxels =50) were used to determine regions altered by DBS using SPM12 and a 2-sample t.test was performed on the areas of interest. A ROI connectivity analysis was also used to verify connections between specific brain regions.

Results

Comparisons of Tremor vs. AR at different regions of interest

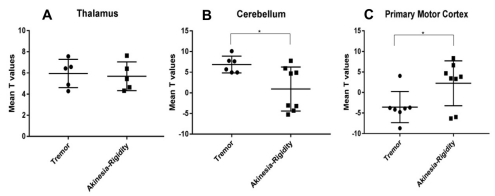

Figure 2. A t.test was performed on t-values generated by the GLM to compare regions of interest between the tremor and AR cohorts. The graph shows mean ±SD. There was no difference in the thalamus (A) and a significant difference between the cerebellum (B) and M1 (C), (p=0.77, 0.025, 0.034, respectively).

Table 1. Patient Demographics

	Tremor	AR
Sample size	N=8	N=11
Females,males	1,7	2,9
Mean age (range)	67.75 (59-78)	62.7 (54-70)
STN, GPi	6,2	5,6

Table 1 shows patient demographics in the tremor and AR cohorts including: sample size, number of females and males, mean age and location of implantation.

An example of an individual tremor subject

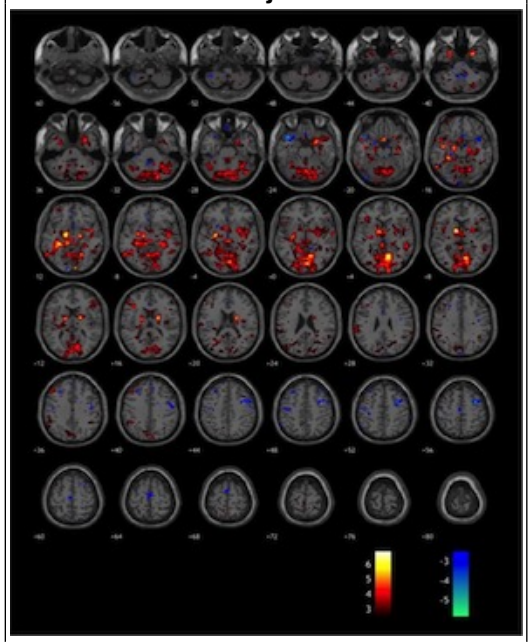

Figure 3. An individual tremor subject showed that activation occured in the cerebellum, thalamus, striatum and deactivation in the primary motor cortex (p=0.05).

Group analysis

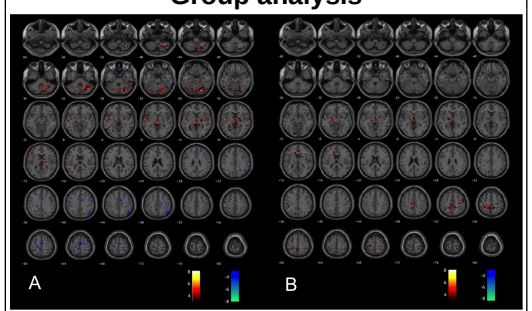

Figure 4. A) The tremor cohort shows activation observed in the cerebellum, thalamus, putamen and deactivation in M1. B) The AR cohort showed activation observed in the thalamus and M1.

Connectivity analysis for tremor and AR cohorts

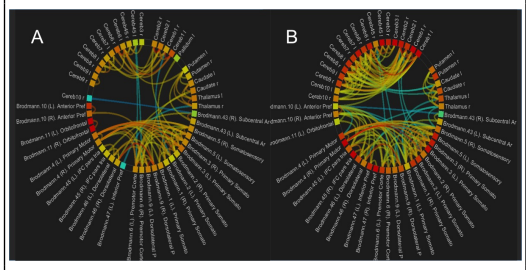

Figure 5. A) The tremor cohort showed more connections between the cerebellum and motor areas (ie. putamen and premotor cortex) than the AR cohort (B) showed (p=0.05).

Conclusions

The activation in the cerebellum with deactivation in M1 in the tremor cohort may suggest the use of the cerebello-thalamo-cortical (CTC) pathway. The CTC pathway suggests STN has indirect glutamatergic projections into the cerebellum. When DBS is utilized, it may activate the cerebellum causing an increase in long intracortical inhibition, deactivating M1.

In the AR cohort, we observed differences in the cerebellum with consistent M1 activation. Those in the AR cohort may use the current accepted pathway. The deactivation present in the cerebellum may be due a loss of purkinje cells found in PD. The CTC pathway however, suggests a feedback mechanism with indirect glutamatergic connections from M1 to the cerebellum. With M1 being stimulated, it may be activating the cerebellum in some patients through this feedback mechanism.

References

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