Optimal Stimulation Sites and Networks for Deep Brain Stimulation of the Fornix in Alzheimer's Disease

INTRODUCTION

Alzheimer's Disease (AD) is the most common neurodegenerative disease burdening healthcare attention with an ineffective treatment to date. Deep brain stimulation (DBS) to the fornix is under investigation for mild AD with completed phase I and II trials, showing cognitive improvement in some patients and deterioration in others. An observed in other conditions treated with DBS, an explanation of these outcomes could lie in variance in electrode placement engaging distinct neural circuits.

OBJECTIVES

To identify optimal electrode location by investigating effects of stimulation on three levels: 1) Fibertract: White matter tracts traversing Electric-fields informed by a high resolution normative connectome.
2) Sweetspot: local-level voxel-wise analysis to identify an optimal stimulation site.
3) Network Mapping: whole-brain network effect informed by resting state fMRI data of 1000 treated with DBS under investigation for mild AD with completed phase I and II trials attention without an effective treatment to date.

RESULTS

These analyses demonstrated that:
1) Stimulation of Papez' circuit and stria terminals associated with cognitive improvement (R = 0.45 at p < 0.01).
2) Optimal stimulation site resided at the interface between fornix and bed nucleus of the stria terminalis (R = 0.30 at p = 0.001).
3) Modulating specific distributed brain networks accounted for optimal outcomes (R = 0.30 at terminalis (R = 0.29 at p = 0.016).

METHODS

Retrospective analysis of a multi-center cohort of 50 patients (20 female, mean age: 75.7 ± 7.9 years) underwent fornix-DBS to treat mild AD. Pre- and post-operative MRI scans of the participants were processed using the lead-DBS pipeline (lead-dbs.org), normalization and electrode localization were manually refined (NeuroSuite tool) and clinical outcomes were measured by changes in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog score). At the fibertract level, the subjects were randomly assigned to a Training cohort (n=30) or Test cohort (n=20). Streamlines correlated to clinical improvement were identified in the Training cohort (leave-one-out and K-fold approach) and then used to predict clinical improvement of the Test cohort (cross-prediction).

For the sweet spot and network mapping analyses, optimal sites and networks were investigated using the whole cohort results and were cross-validated with a leave-one-out approach and multiple K-fold approaches.

CONCLUSIONS

A potential optimal stimulation target for Alzheimer's Disease treatment with fornix-DBS is proposed.
1) Stimulation of Papez' circuit and bed nucleus of the stria terminals associated with cognitive improvement.
2) Optimal stimulation site: intersection between fornix and bed nucleus of the stria terminals.
3) Modulating specific whole-brain networks seems crucial for DBS-induced positive effects on cognition.