Gene Therapy and Subsequent Deep Brain Stimulation for Parkinson's Disease

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Background

Parkinson's Disease

- Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting the elderly population
- Characterized by tremor, rigidity, akinesia, bradykinesia, postural instability
- Pathologic: Neuronal degeneration of dopaminergic cells, Lewy bodies and neurites
- Treatment involves dopamine replacement therapy, surgical intervention, and gene therapy

GAD gene Therapy

- Introducing glutamic acid decarboxylase (GAD) through via adeno-associated virus (AAV)
- STN hyperactivity in PD creates toxic levels of glutamate

GAD catalyzes synthesis of GABA, which decreases hyperactivity of the STN

Deep Brain Stimulation

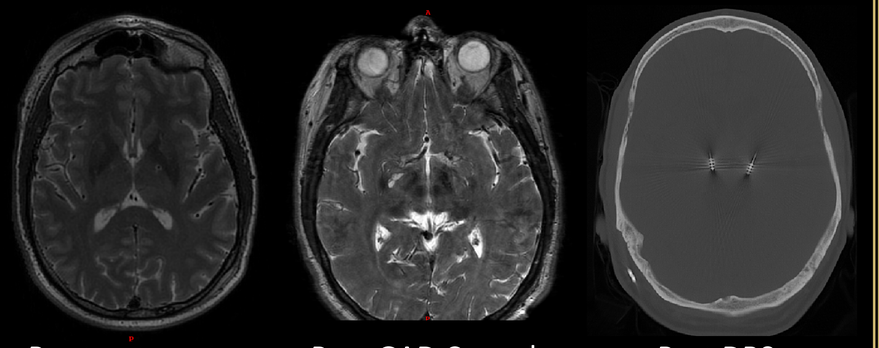
- Placement of electrodes into a targeted region of the brain
- The subthalamic nucleus (STN) is a common target in DBS
- Stimulation is adjustable for contacts and other variables

Objectives

- Both dopamine replacement therapy and DBS address the physiological symptoms of PD
- We studied the outcomes of patients who initially had GAD treatment and subsequently underwent DBS
- Largest cohort of GAD+DBS patients to date

Methods

Figure 1: Surgical Neuro-imaging



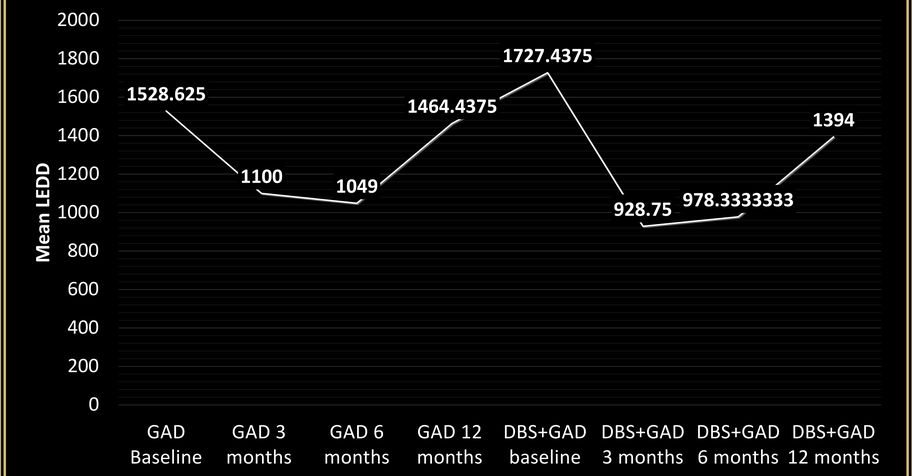
Pre-treatment | Post-GAD Cannula | Post DBS

Surgical Treatment

- Five (of 11) patients received GAD bilaterally in the STN
- All patients received bilateral DBS electrode implantation in the STN
- 3-, 6-, and 12-months post GAD and DBS surgery **LEDD (**Levodopa equivalent dose) & **UPDRS** (Unified Parkinson's Disease Rating Scale) were collected

Results

FIGURE 2: MEAN LEDD (LEVODOPA EQUIVALENT DOSES) GAD + DBS COMBINED THERAPY COHORT



- Troughs in mean LEDD values at 3-and 6-month timepoints in both GAD and GAD+DBS cohorts

Results (cont.)

Table 1: Descriptive Statistics of GAD LEDD Data

Descriptive Statistics	GAD Baseline	GAD 3 months	GAD 6 months	GAD 12 months
Valid	4	1	4	4
Missing	0	3	0	0
Mean	1529	1100	1049	1464
Std. Deviation	421.9	NaN	364.1	504.0
Minimum	1192	1100	532.0	1000
Maximum	2075	1100	1380	2175

Table 2: Descriptive Statistics of GAD and DBS LEDD Data

Descriptive Statistics ▼	DBS+GAD baseline	DBS+GAD 3 months	DBS+GAD 6 months	DBS+GAD 12 months
Valid	4	4	3	4
Missing	0	0	1	0
Mean	1727	928.8	978.3	1394
Std. Deviation	615.1	504.0	674.7	1331
Minimum	1000	465.0	500.0	500.0
Maximum	2275	1575	1750	3375

- Results show that mean patient LEDD dose values were significantly lower ($p<.05$) at 3- and 6-months post DBS(t -test)

Table 3: Descriptive Statistics of GAD and DBS of UPDRS Data

Descriptive Statistics	UPDRS DBS +GAD baseline	UPDRS DBS +GAD 3mo	UPDRS DBS +GAD 6mo	UPDRS DBS +GAD 12mo
Valid	4	4	5	5
Missing	1	1	0	0
Mean	25.25	22.25	19.00	23.40
Std. Deviation	10.59	5.188	7.176	10.62
Minimum	14.00	15.00	9.000	15.00
Maximum	39.00	26.00	25.00	40.00

- UPDRS motor scores were significantly lower at 6 months post DBS ($p<.05$) (t-test)

Looking Forward

- ANOVA analysis on UPDRS and LEDD data
  - At baseline and 3,6,12-month follow up
- Further analysis of neuroimaging data will reveal GAD volume of coverage/infused within targets
- Compare findings with DBS only matched cohort
- Positive outcomes in patients who received both treatment modalities signify the <u>treatments are compatible together</u>

References

Rossi, A., Berger, K., Chen, H., Leslie, D., Mailman, R. B., & Huang, X. (2018). Projection of the prevalence of Parkinson's disease in the coming decades: Revisited. Movement Disorders, 33(1), 156-159. doi:10.1002/mds.27063