NEUROPSYCHOLOGICAL OUTCOMES FROM DEEP BRAIN STIMULATION

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INTRODUCTION

Despite the success of levodopa-based treatment for Parkinson's disease (PD), over time many patients develop disabling motor side effects. One alternative for these patients is deep brain stimulation (DBS), which has been shown to be effective for treating the motor symptoms of PD. However, DBS is not without its own side effects profile. In particular, a high prevalence of neuropsychological effects has been observed in this patient population. Hence a significant problem for these patients is the titration of stimulation parameters to provide symptomatic relief without neuropsychological effects. And because these effects may take days or weeks to present, patients who experience these side effects must have their stimulation parameters revised many times. We are addressing this problem by combining patient-specific computational modeling with a data bank of neuropsychological outcomes in PD and essential tremor (ET) patients. Preliminary results from a recently completed prospective study of motor outcomes indicates that the stimulation targets of DBS vary on a per-symptom basis in the region of the subthalamic nucleus (STN). This was determined by constructing a probabilistic atlas of clinical outcomes that were correlated with model-predicted volumes of activation. In the present study, we are using a similar methodology to determine whether stimulation-induced activation of brain regions is correlated with changes in cognitive and neuropsychological outcomes. The central hypothesis of this work is that cognitive and psychological outcomes in PD (DBS target: subthalamic nucleus STN) and ET (DBS target: ventral intermediate nucleus (VIM)) patients are correlated with stimulation-induced activation of specific brain regions.

OBJECTIVES

1. Create a probabilistic atlas of neuropsychological outcomes from DBS
2. Use neuropsychological evaluation and patient-specific computational models to identify regions that, when activated during DBS, result in statistically significant changes in clinical outcomes

NEUROPSYCHOLOGICAL EVALUATION

We tested two groups as detailed in Table 1. Each patient had a battery of pre-operative and post-operative neuropsychological tests which were administered to measure a range of cognitive functions including intellectual capacity, complex problem solving skills, processing speed, verbal fluency, word finding, spatial skills, and learning/memory. The tests are summarized in Table 2. The primary outcome measure for this study is the difference between pre- and post-operative neuropsychological scores or subscores for each test. T-tests (p<.05) were used to identify significant differences in pre- versus post-operative scores after patients were grouped by disease and stimulation target.

Table 1 Patient Demographics

|	N	Sex	Years Education	Age at Diagnosis	Age at Surgery	Uni/Bilateral	Days from pre- to post-op Tests
Parkinson's disease	18	7F, 11M	14 +/- 3	49 +/- 11	66 +/- 8	16 Bi, 2 Uni	586 +/- 226
Essential Tremor	8	5F, 3M	14 +/- 2	49 +/- 15	67 +/- 9	4 Bi, 4 Uni	510 +/- 116

Table 2 Neuro-phsychological Tests

| Dementia Rating Scale (DRS)	Wechsler Abbreviated Scale of Intelligence	Wechsler Memory Scale - III	Wisconsin Card Sorting Test (WCST)
Attention	Vocabulary	Logical Memory I	Sorting
Initiation / Perseveration	Similarities	Logical Memory II	Perseverative errors
Construction	Block Design	Logical Memory Recall	Failure to maintain set
Conceptual reasoning	Matrix Reasoning	Faces I	Total errors
Memory		Faces II	
Auditory Verbal Learning Test (AVLT)	**Boston Naming Test (BNT)**	**Beck Depression Inventory (BDI)**	**Symbol Digit Modality Test (SDM)**
Summary	**Wide Range Academic Test (WRAT)**	**Wechsler Adult Intelligence Scale**	**Controlled Oral Word Association (COWA)**
Recall	**Judgement of Line Orientation (JLO)**	Digit Span	**Beck Anxiety Inventory (BAI)**
Recognition	**Animal Naming Test**	Letter-Number Sequencing	

PROBABILISTIC ATLAS

We used a previously published method to predict the volume of tissue activated (VTA) during DBS on an individual patient basis[1]. Pre- and post-operative images were coregistered each other and with an atlas brain. Hence, the electrode locations and VTAs for all patients were expressed in a common anatomical framework. Clinical scores for each test were assigned to each VTA for each patient at best therapeutic stimulation settings. Statistical analysis was performed on a per-voxel and per-test basis to identify regions where stimulation-induced activation was correlated with differences between pre- and post-operative neuropsychological test scores.

Patient Specific Model
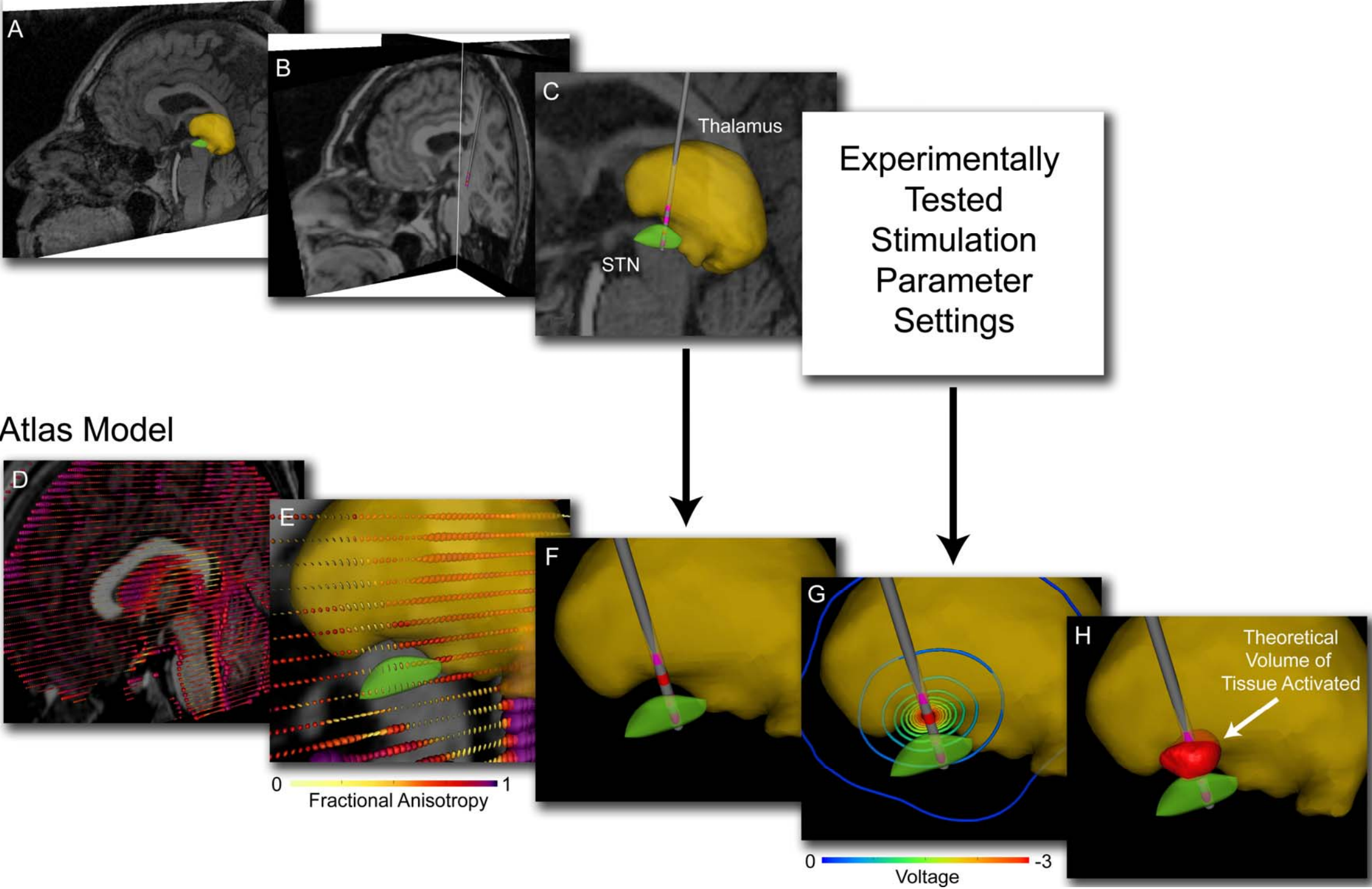
Atlas Model

Patient-specific DBS models A) Pre- and B) post-operative images were fused and registered to C) a 3D atlas brain (thalamus – yellow volume; STN – green volume). D,E) The atlas brain included both anatomical and diffusion tensor imaging data and was used to predict neural activation from the stimulation protocol. G) The voltage distribution and H) theoretical volume of tissue activated (VTA) was calculated for F) each electrode position.
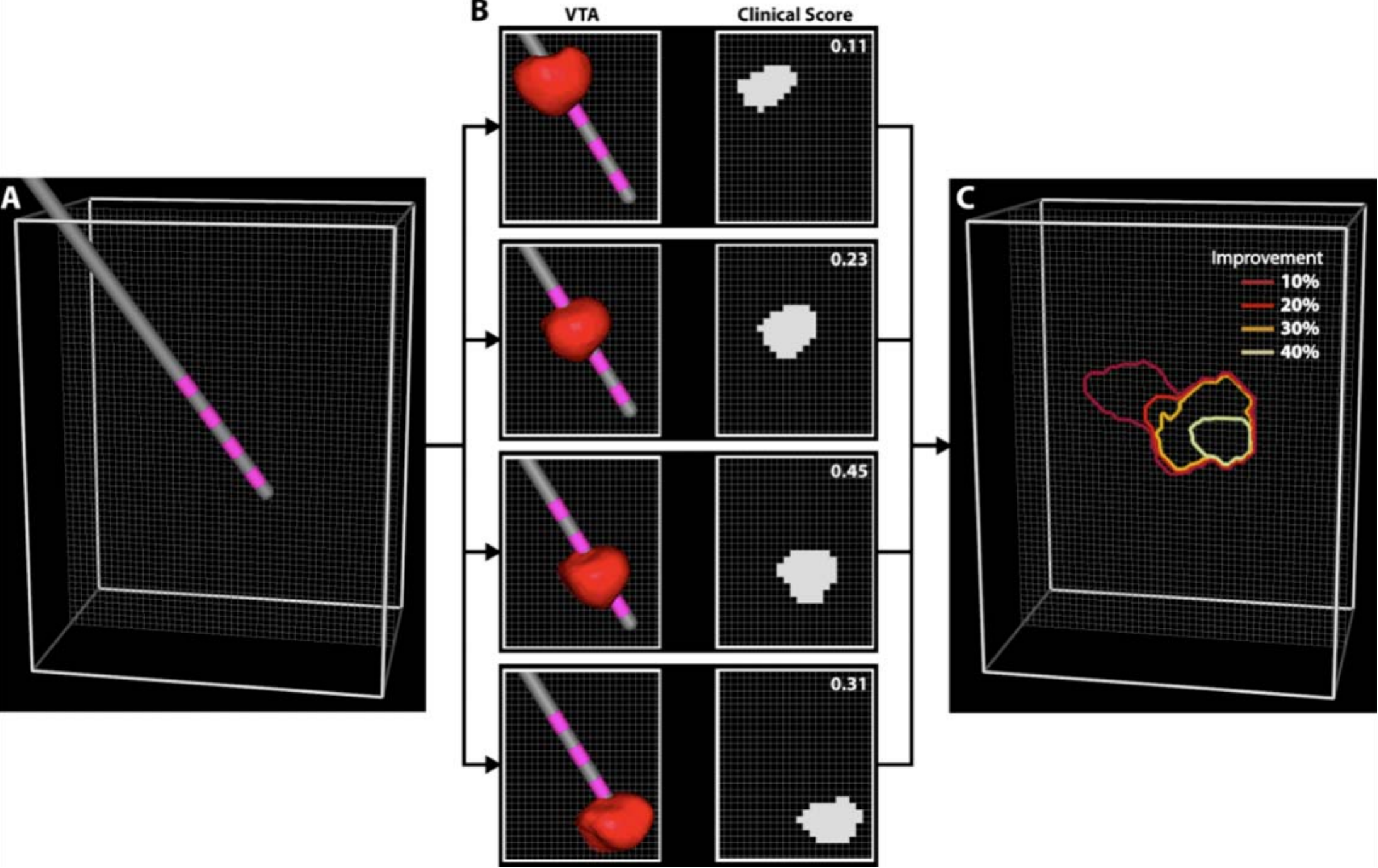

Probabilistic atlas generation A) A 3D lattice with 1 mm³ voxels was constructed to encompass all of the VTAs for all patients. For clarity, only one cross-sectional slice of the lattice is shown. B) An example VTA is shown for each contact with stimulation settings -4 V, 60 sec, 130 Hz. Voxels within the VTA were assigned the corresponding normalized clinical score as indicated. C) The probabilistic atlas was created from the average clinical score for each voxel.

RESULTS

Parkinson's Disease Group Statistics

PD patients who received STN stimulation showed significant test score differences for:
• Wechsler Abbreviated Scale of Intelligence: Vocabulary
• Wechsler Memory Test - III: Learning/Memory II
• Auditory Verbal Learning Test: Sum; Del
• Letter Number Sequence
• Symbol Digit Modality Test
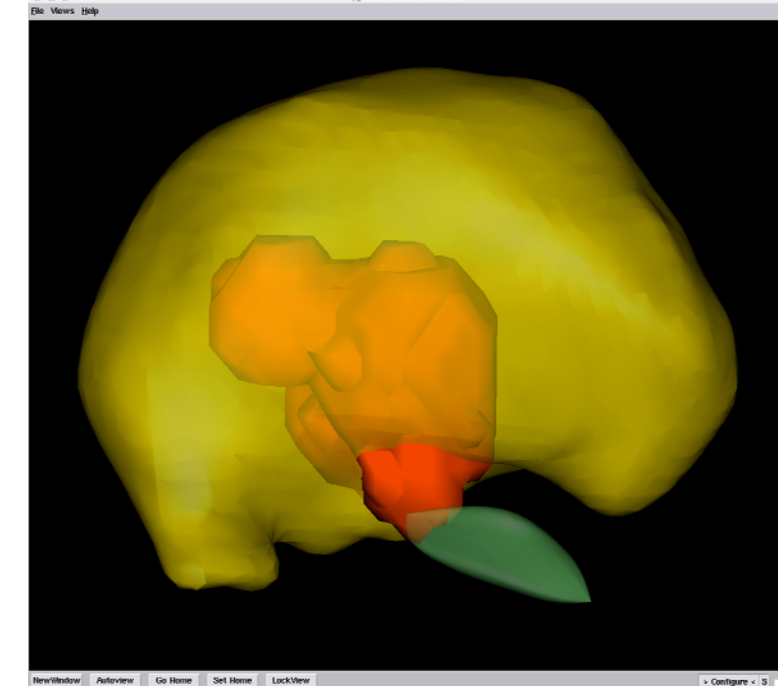• Controlled Oral Word Association
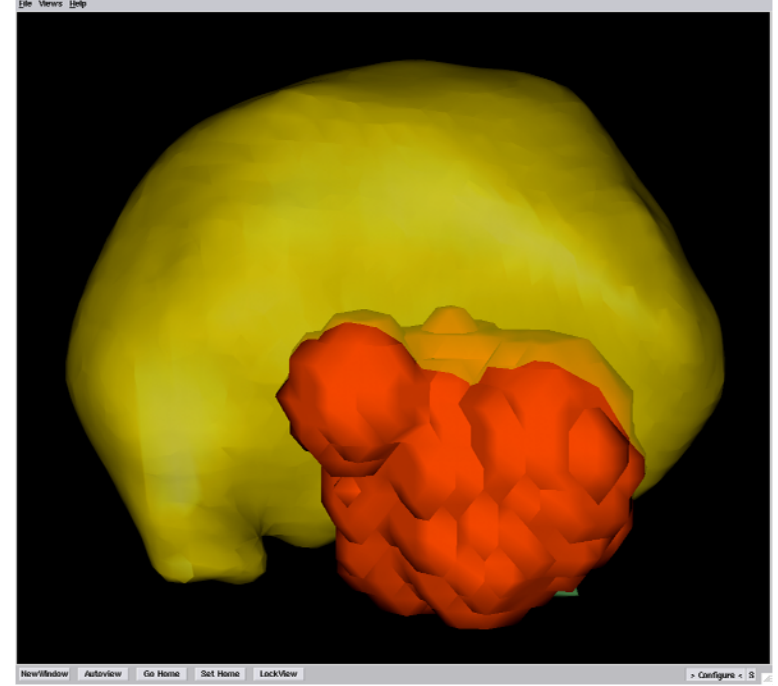
Activation Volumes for all PD patients

Essential Tremor Group Statistics

ET patients receiving VIM stimulation showed significant test score differences for:
• Symbol Digit Modality Test
• Wisconsin Card Sorting Test:
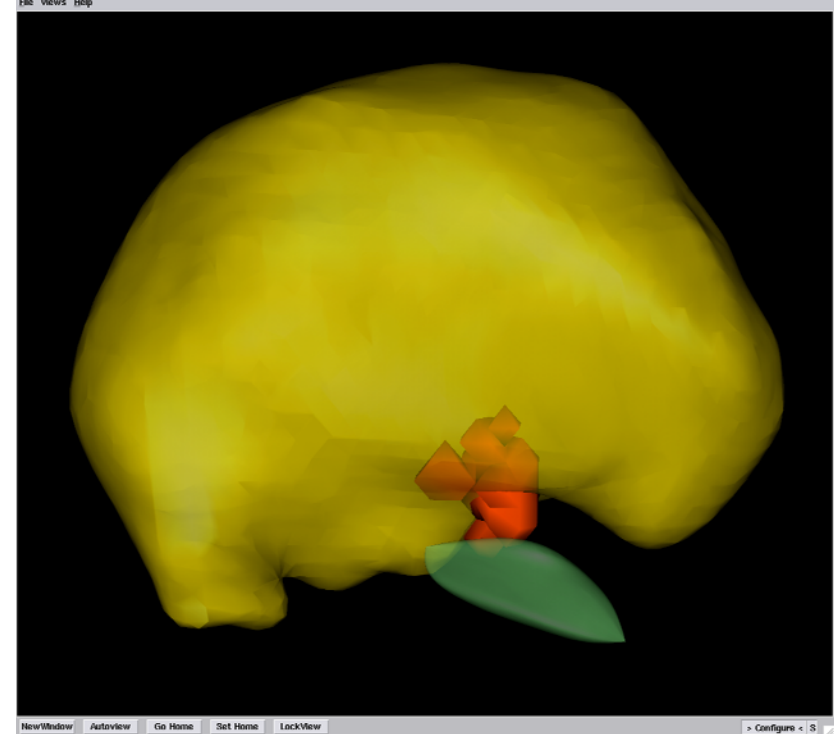 • Perseverative Errors
  • Total Errors

Activation Volumes for all ET patients

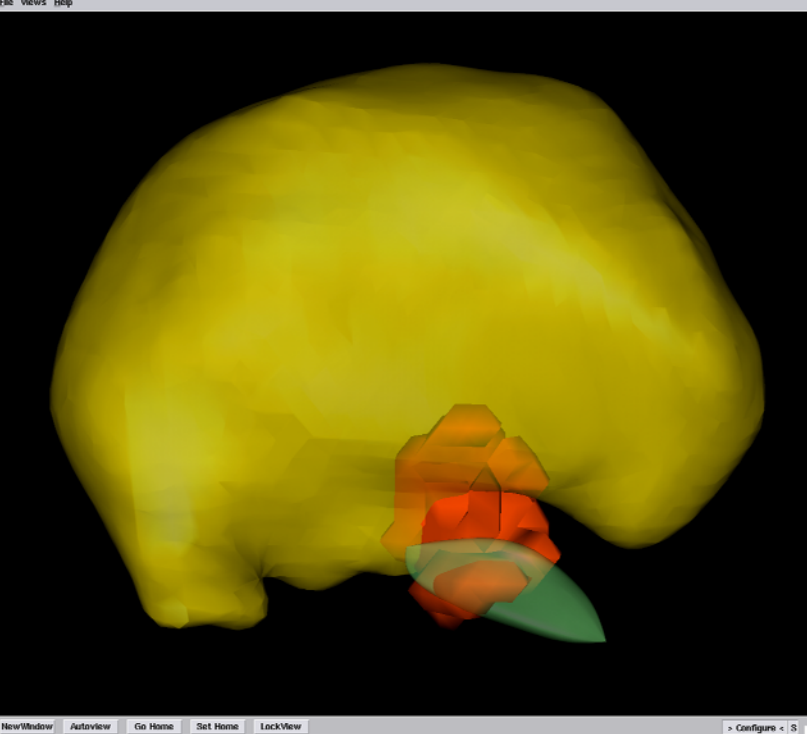### Probabilistic Atlas: Regions With Significant Pre-Post Neuropsychological Score Differences

All results are for PD except as noted. Red volumes indicate statistically significant activation regions for each test.
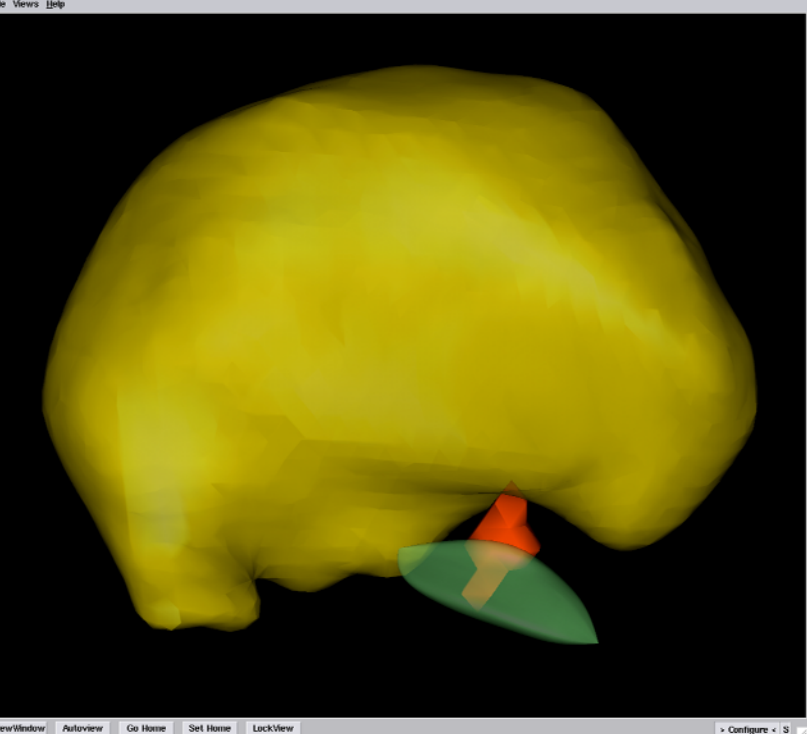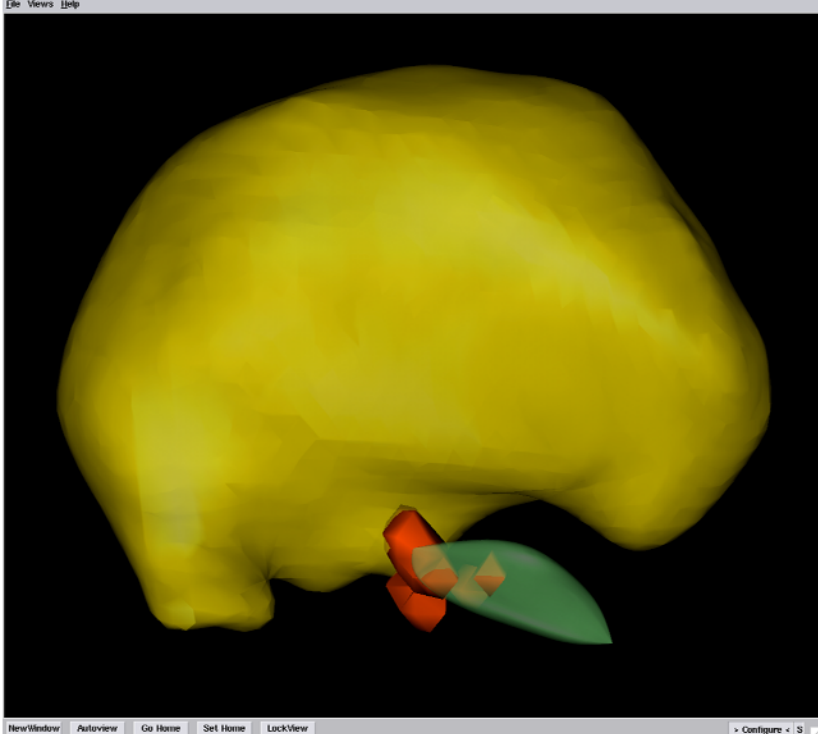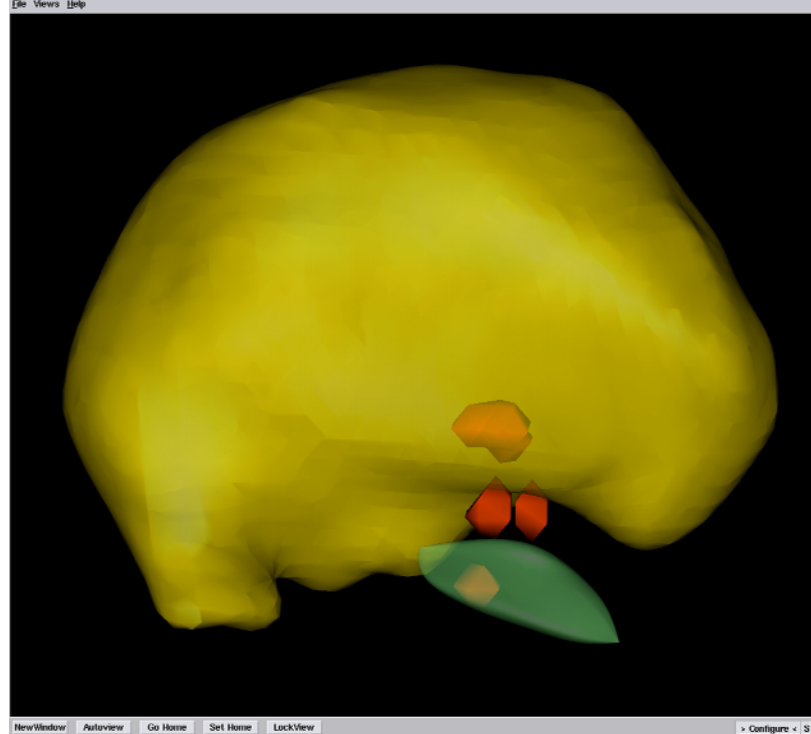

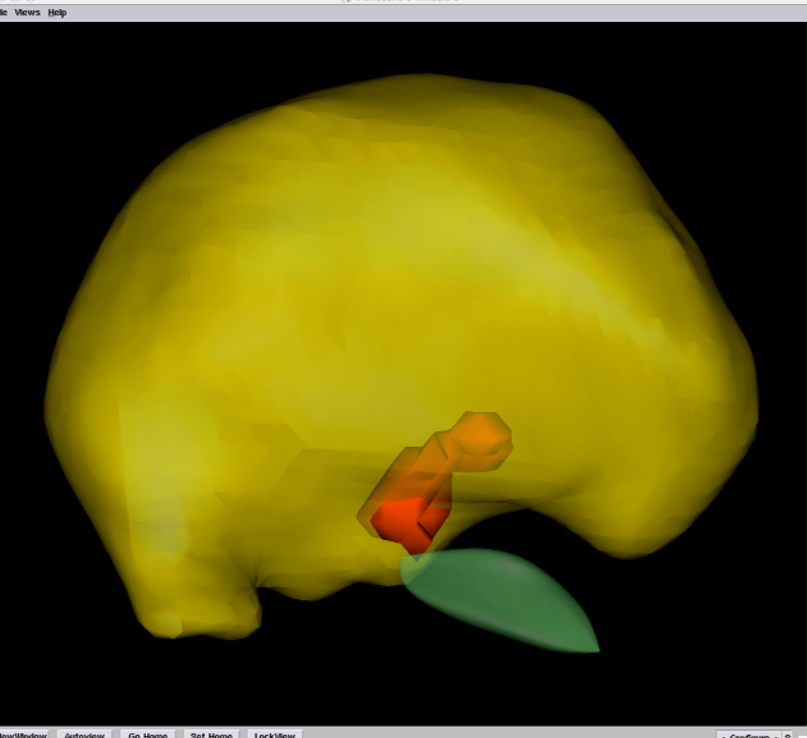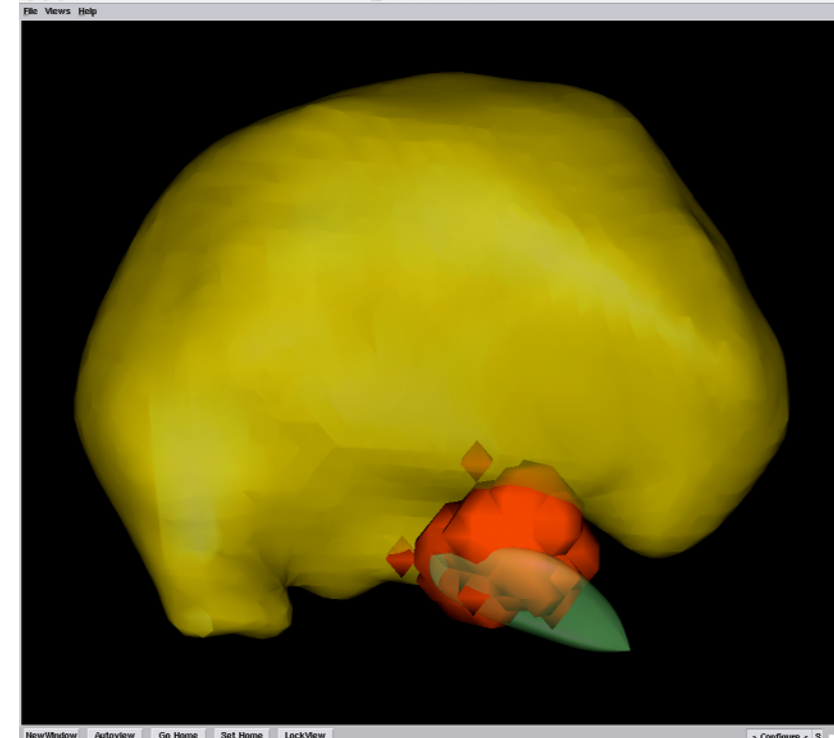Dementia Rating Scale | Wechsler Memory Test - III LM I | Wechsler Memory Test - III LM II | Wechsler Memory Test - III FACES I | Wechsler Memory Test - III FACES II
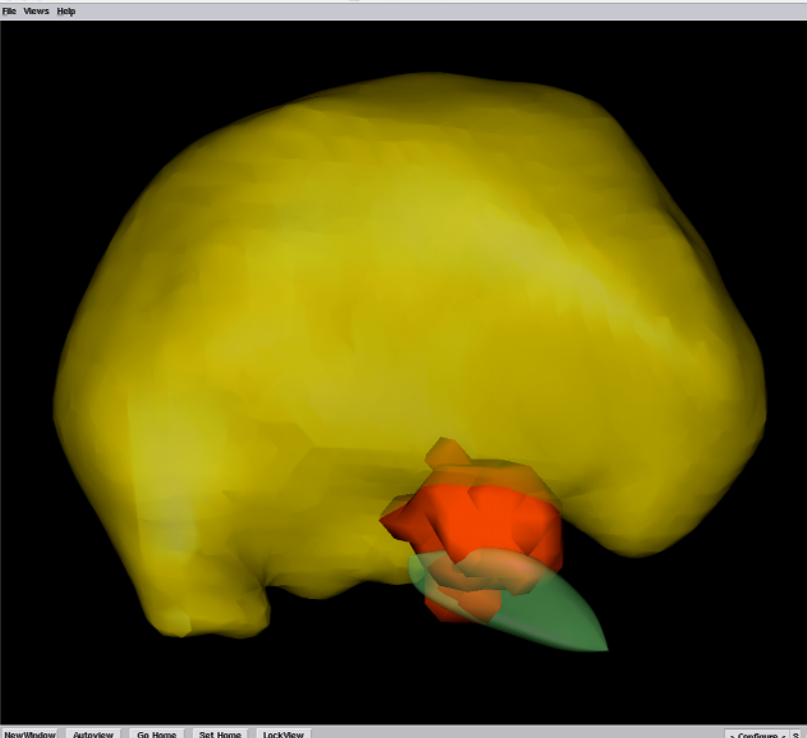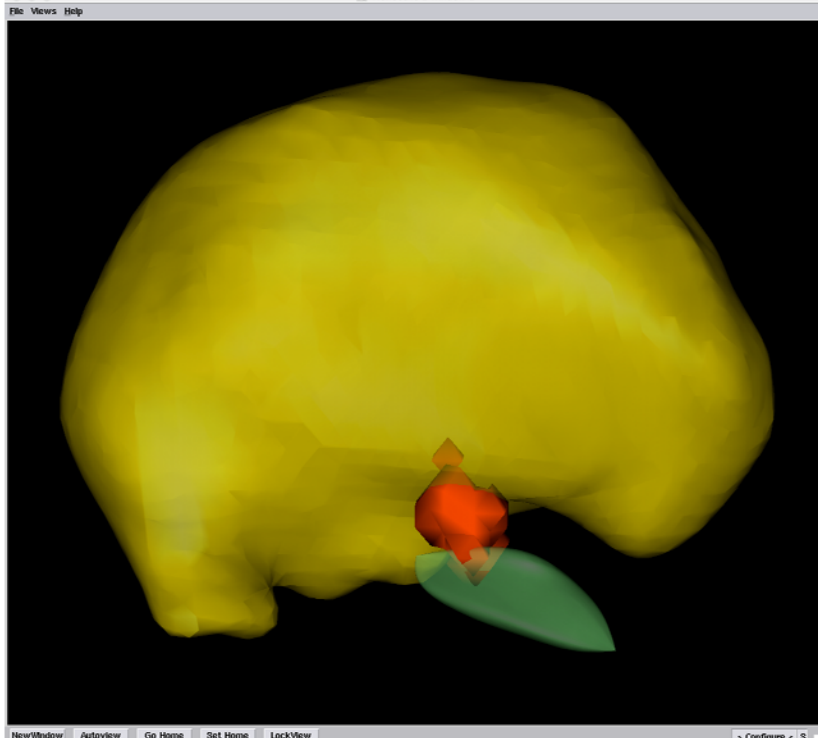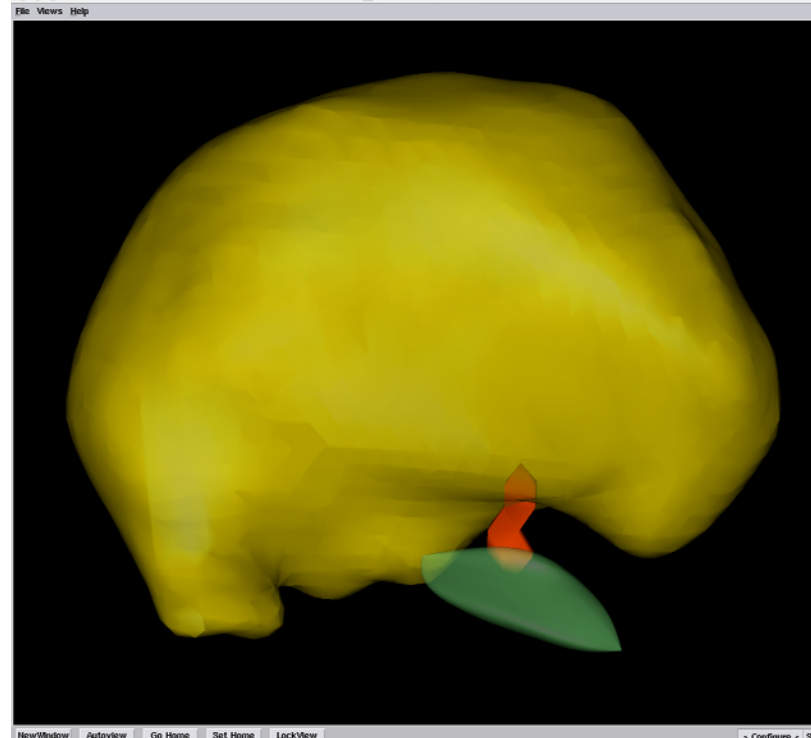
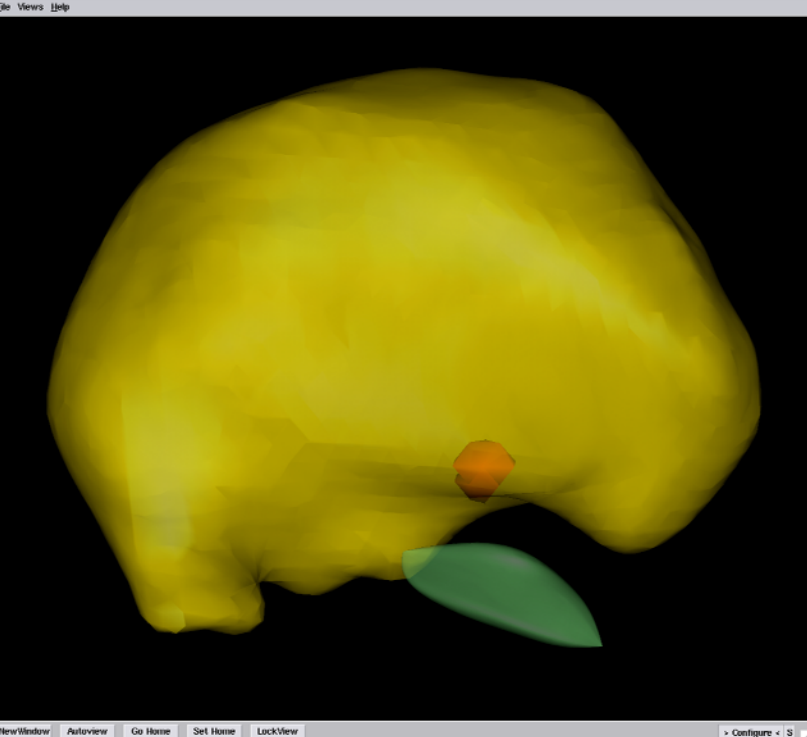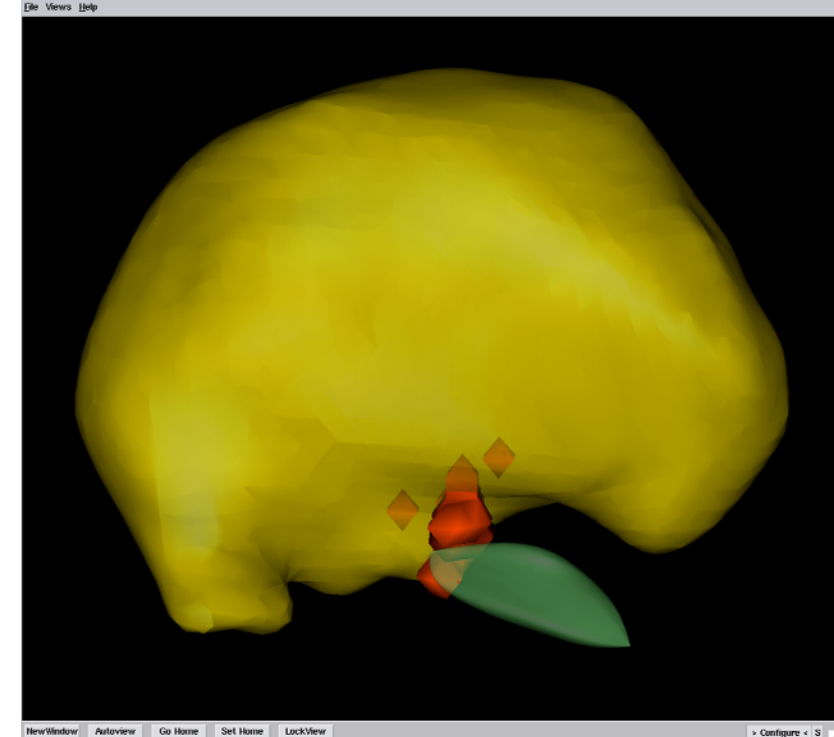Boston Naming Test | Auditory Verbal Learning Test Sum | Auditory Verbal Learning Test Recall | Auditory Verbal Learning Test Recognize | Wechsler Abbreviated Scale of Intelligence Block Design
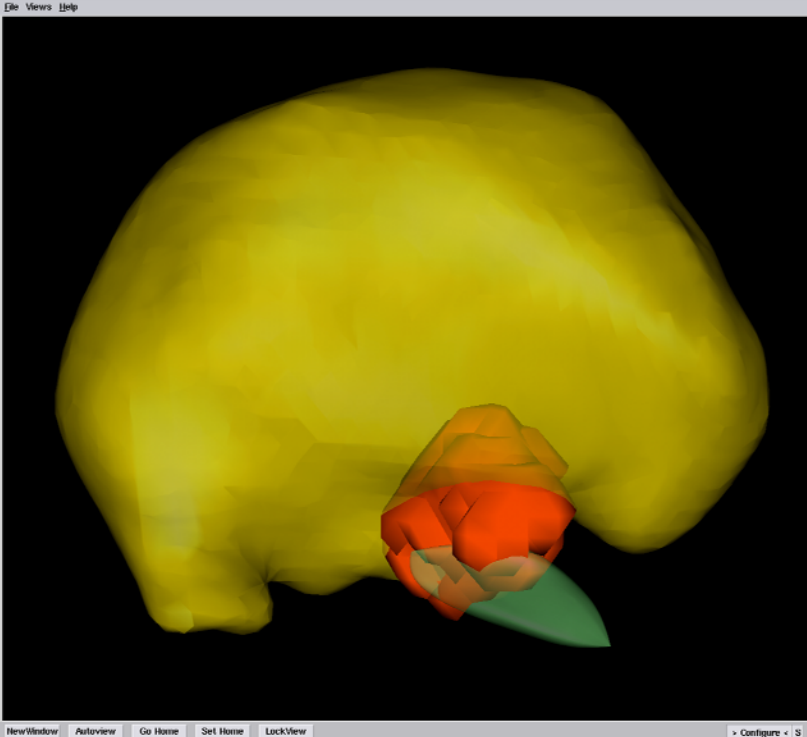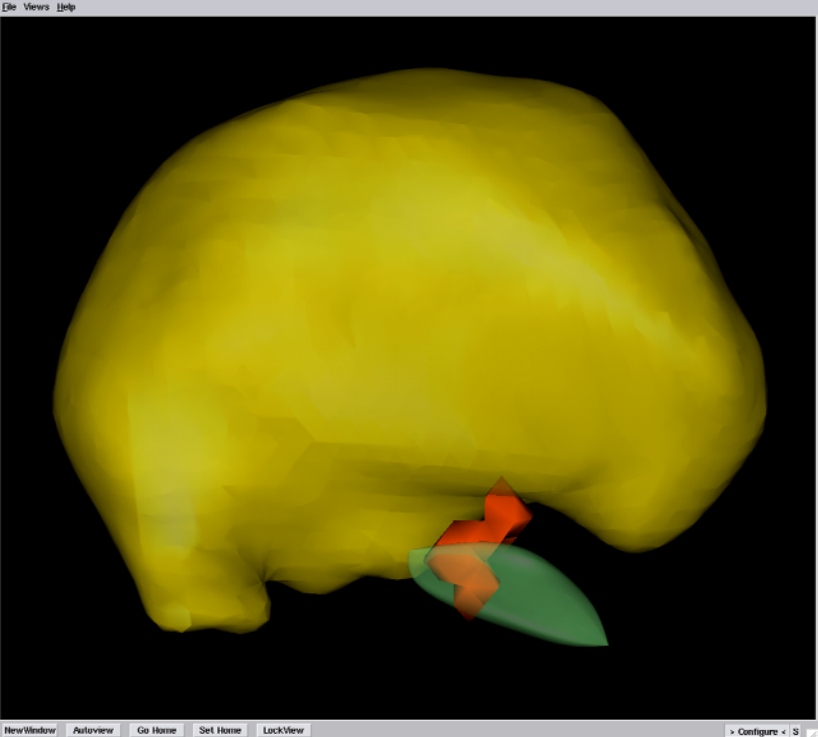
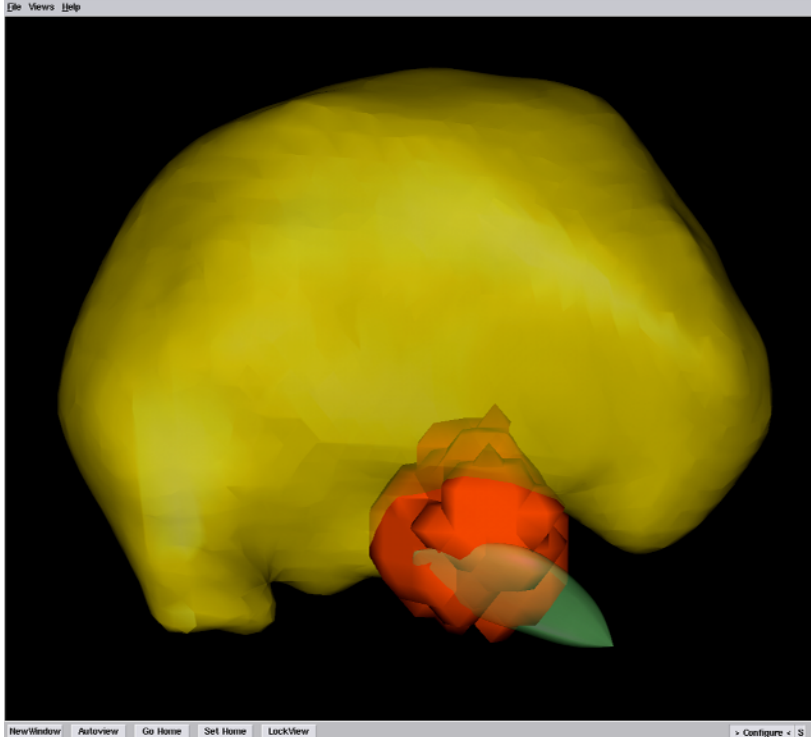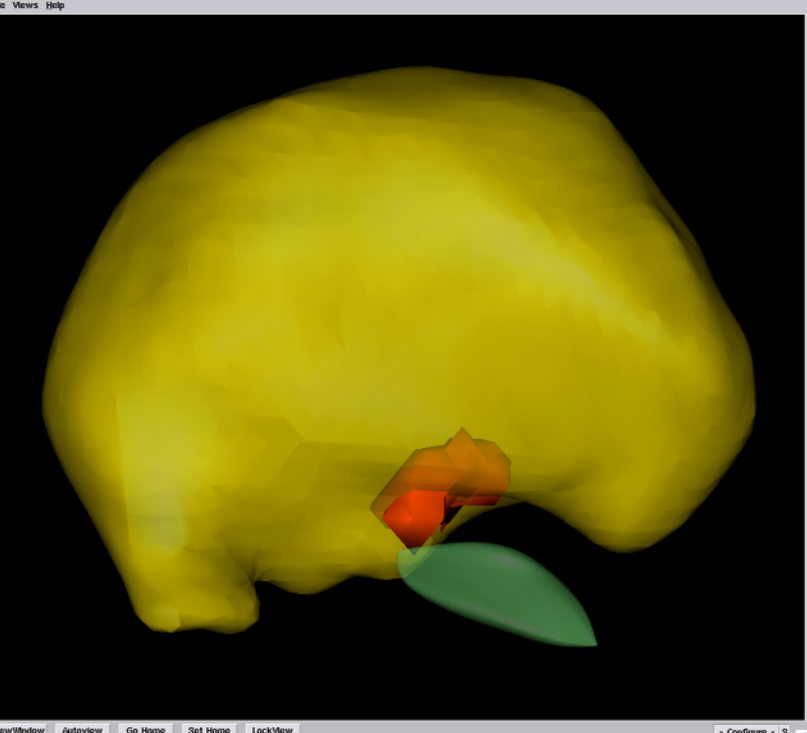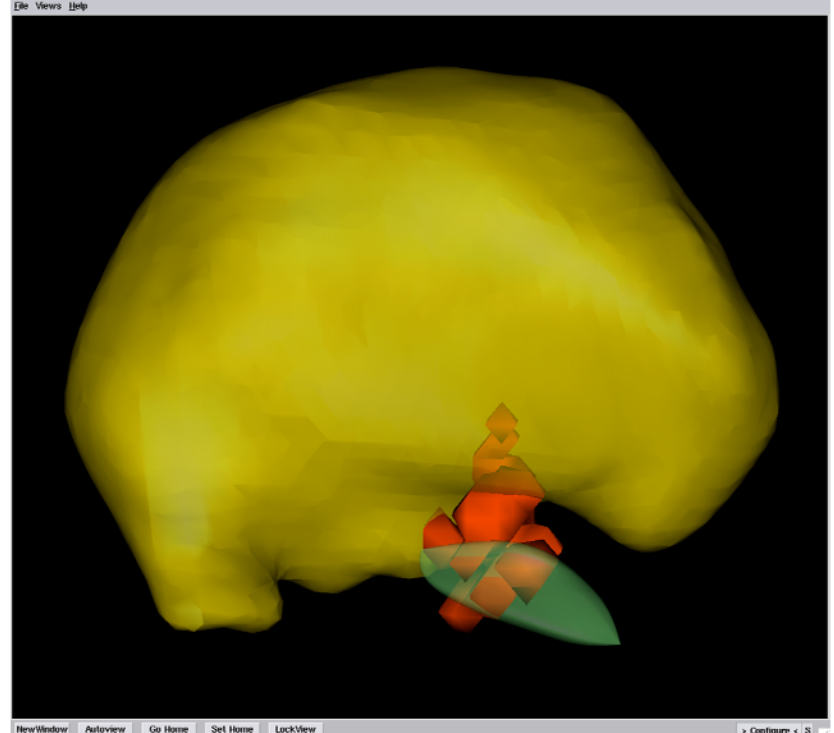Wide Range Academic Test Raw Score | Judgment of Line Orientation | Controlled Oral Word Association | Wisconsin Card Sorting Test Failure to Maintain Set | Symbol Digit Modality Test
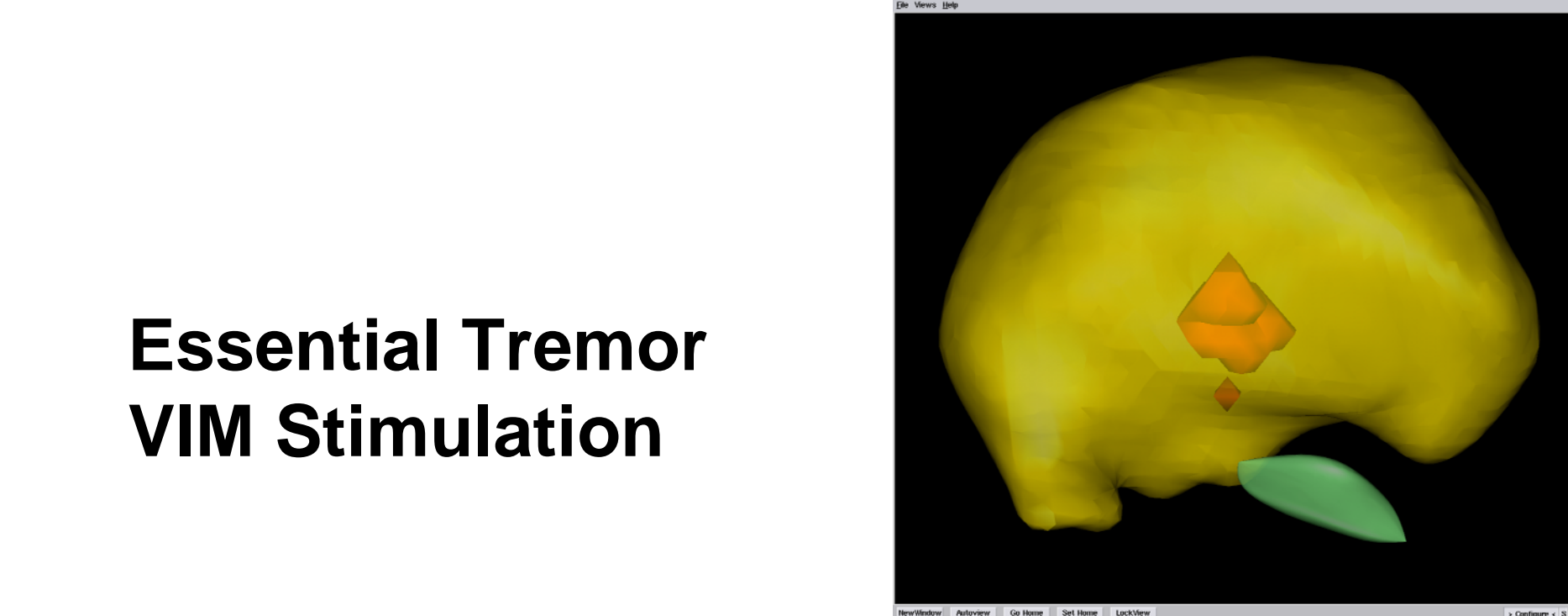
Wechsler Adult Intelligence Scale Digit Span | Wechsler Adult Intelligence Scale Letter Number Sequence

Essential Tremor VIM Stimulation

Wisconsin Card Sorting Test Perseverative Errors

CONCLUSION

The group statistics for the PD and ET samples used in this study are consistent with recently reported neuropsychological patient outcomes in DBS patients[2,3]. Changes in neuropsychological scores from pre- to post-operative testing could be attributed to several possible sources: DBS; aging; changes in medication subsequent to DBS; progression of the disease. In this study we have assumed that these changes were primarily attributable to DBS, and used computational methods to determine regions where activation was significantly correlated with changes in test scores on a per-voxel and per-test basis. Many of the regions that showed significance were in the posterior portion of the STN, as well as ZI/H2 and thalamus. In addition, many overlapped with target regions for therapeutic DBS. We recently started a prospective movement disorders databank which is designed to examine these findings in a larger patient sample. Our goal is to use this information for pre-operative surgical targeting and post-operative stimulation parameter selection to minimize adverse outcomes for DBS patients.

REFERENCES

1. Butson CR, Cooper SE, Henderson JM, McIntyre CC, Patient-specific analysis of the volume of tissue activated during deep brain stimulation, NeuroImage, 34(2):661-670, 2007.
2. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI, Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson disease: a meta-analysis, Lancet Neurol, 2006; 5: 578-88.
3. Okun MS et al, Cognition and Mood in Parkinson's Disease in Subthalamic Nucleus versus Globus Pallidus Interna Deep Brain Stimulation: The COMPARE Trial, Ann Neurol, 2009; 65:586-95.