CIRCUIT LEVEL MODULATION OF AROUSAL USING CENTRAL THALAMIC DEEP BRAIN STIMULATION

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INTRODUCTION

Deep brain stimulation (DBS) is an established therapy for movement disorders such as Parkinson's disease and essential tremor, and its effectiveness is being assessed for a variety of other conditions. One potential indication is central thalamic DBS (CT-DBS) for treatment of severe to moderate traumatic brain injury (TBI). The effectiveness of CT-DBS has been shown in a previous human study (Schiff et al, 2007), and the mechanisms for this therapy are being explored in primate and rodent models (NIH R01 NS067249). In previous studies we showed that CT-DBS causes an increase in arousal in mice implanted with bilateral DBS leads (Quinkert et al, 2010, 2012). In this study we used computational models and a connectivity atlas to identify common cortical regions that are modulated during effective CT DBS in injured (TBI group) and non-injured (Intact group) mice. We were motivated by the fact that there is widespread agreement that the effects of DBS are critically dependent on stimulation location. However, these variables are not often quantified. There are a few reasons why we would expect DBS lead location to have a significant effect on outcomes. First, there are limits to surgical accuracy in lead placement, and as a result there is inherent variability in lead location. Second, electrical current from DBS spreads in all directions and can impinge upon many anatomical regions, especially for a nucleus that is as rich in function as the thalamus. Lastly, lead location and stimulation settings (e.g. amplitude, pulse width) interact to determine the extent of stimulation. Hence, we used a previously published computational model to quantify stimulation location in each animal. We then built a probabilistic stimulation atlas (PSA) to identify regions where stimulation is significantly correlated with changes in behavior. Lastly, we used the Allen Mouse Brain Connectivity Atlas to identify cortical regions with the highest projection density from effective stimulation sites.

OBJECTIVE & HYPOTHESIS

The objective of this study was to use computational models and connectomics to identify cortical regions with thalamocortical projections that were stimulated during effective CT DBS. We hypothesized that variability in behavioral performance was due to differential modulation of thalamocortical circuits among the animals.

METHODS

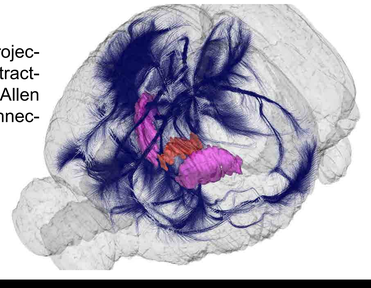
Animals: Monopolar stainless steel electrodes (Plastics One, 0.3mm diameter with 0.5mm stripped from the electrode tip) were implanted bilaterally into the central thalamus of mice using a Kopf stereotaxic apparatus. Coordinates used were as follows: anterior–posterior, -1.70 mm from bregma; lateral, ±0.75 mm from midline; and depth, -3.00 mm from the surface of the brain. Two groups of mice received CT DBS. Intact: non-injured mice (n=10). TBI: injured mice (n=13) received a closed head injury.

Behavioral Evaluation: Three behavioral data measures were collected. Counts: whole body activity counts, collected by a transmitter and representing changes in field strength between the transmitter and receiver as the mouse moves. Horizontal activity: fidgeting movements, collected by the home cage Accuscan system and representing the number of infrared beams broken in the horizontal plane. Total Distance: ambulation, collected by the home cage Accuscan system and representing non-repeating infrared beam breaks in the horizontal plane. Data was analyzed to determine the sums of activity 10 minutes before, 10 minutes during, and 10 minutes after stimulation with activity during and after stimulation normalized to activity before stimulation.

Determination of Stimulation Location: DBS lead location was determined from post-mortem histology. Computational models were used to predict the volume of tissue activated for each electrode location in each animal using a previously published method (Butson et al, 2007). A probabilistic stimulation atlas (PSA) was constructed by voxelizing the mouse brain, and determining the voxels that were affected by each VTA (Butson et al, 2011). Behavioral outcome scores were applied to the voxels in each VTA, and all data was compiled into a PSA by averaging all scores at each voxel and locating the regions where stimulation had the strongest behavioral effect(s).

Cortical Projections Density: We used the PSA to identify regions where stimulation was associated with the largest improvement in behavioral performance (top 20%). We then searched the Allen Mouse Brain Connectivity Atlas for experiments in which tracer studies originated in those regions in *wild type* mice. We added the projections from each experiment to our computational model and finally identified the cortical regions with highest projection density.

Four axonal projections of the 55 extracted from the Allen Mouse Brain Connectivity Atlas.



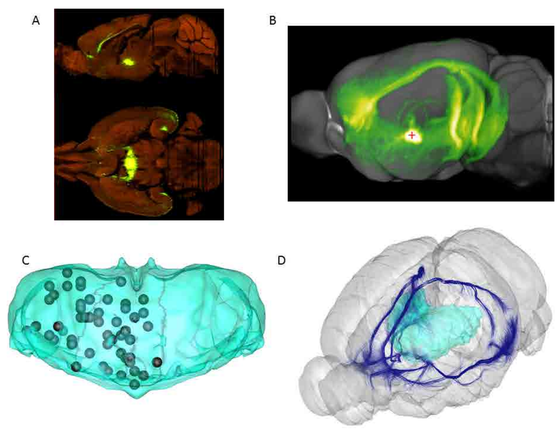


Figure 1: A) 2-photon fluorescence of viral tracer for a single injection. B) 3-D reconstruction of fluorescence imaging for a single injection. C) All injection locations, 55 total, inside the thalamus used to build fiber projection databank. D) Conversion of 3-D fluorescence into fiber projections for a single experiment. We used 55 of these reconstructions that cover a substantial amount of fiber projections from thalamus to cortex. A,B,D are all from the same experiment.

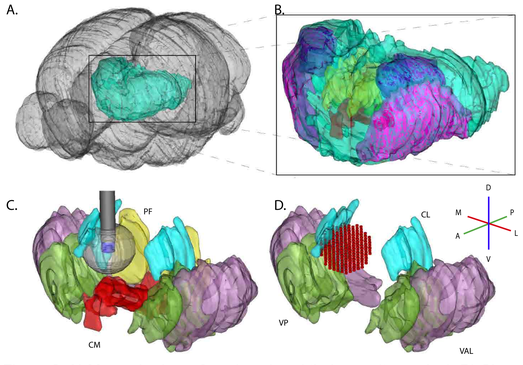
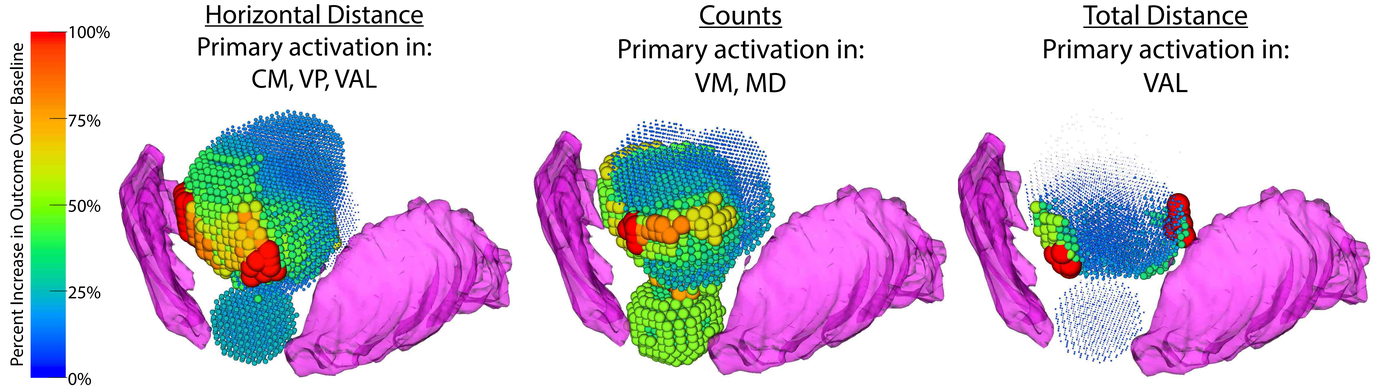


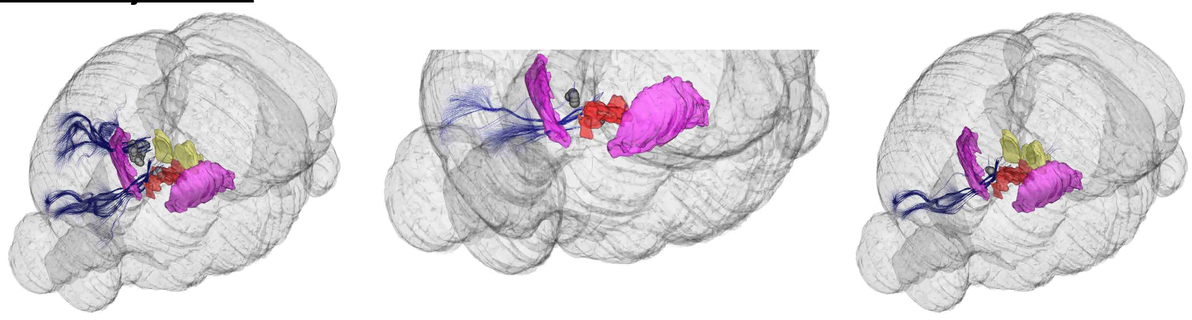
Figure 2: A) Mouse brain surface (gray) and thalamus (turquoise). B) Close up of thalamus and subnuclei. C) Electrode and DBS contact with VTA at a single stimulation location/setting (gray). D) Activated Voxels (red blocks) within the VTA. Abbreviations: central medial (CM); central lateral (CL); lateral dorsal (LD); mediodorsal (MD); paracentral (PCN); parafascicular (PF); reticular (RT); ventral anterior-lateral complex (VAL); ventral posterior complex (VP); ventral medial nucleus (VM). Note: some nuclei are ommited for clarity in parts C and D

RESULTS

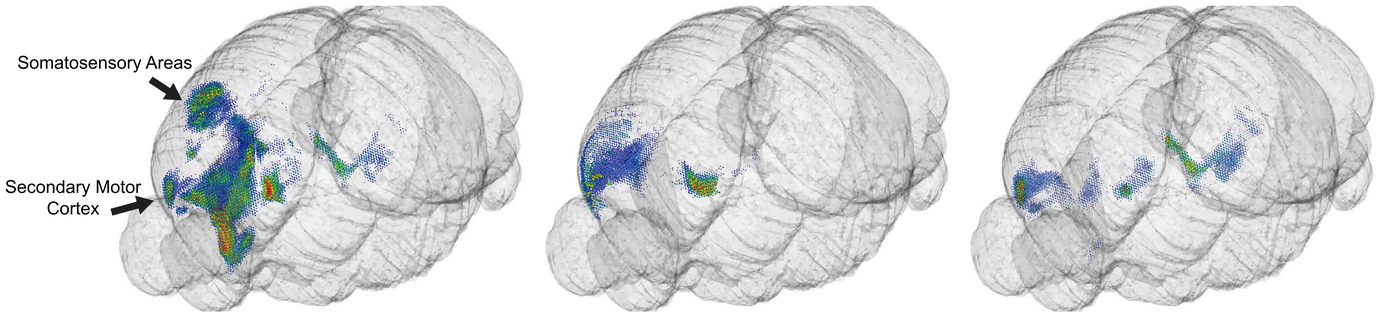
Probabilistic Stimulation Atlas of Behavioral Scores



Axonal Projections



Projection Density in Cortex



CONCLUSIONS

We identified thalamic subnuclei where stimulation is correlated with changes in behavioral outcomes: CM, VP, VAL, VM & MD. These observations are consistent with observations made in CT-DBS in primate. Further, we identified common cortical regions with high projection density among the animals stimulated in the most effective thalamic regions: secondary motor cortex, somatosensory area, striatum. The identification of these regions provides three important pieces of information. First, it allows quantitative comparison of outcomes across species for CT-DBS (rodent, primate and human). Second, it quantifies an important potential source of variability in the arousal response to stimulation, and provides targeting information for future CT-DBS studies. Third, mapping the projection density onto cortical regions could provide additional insights into the potential mechanisms of CT DBS.

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