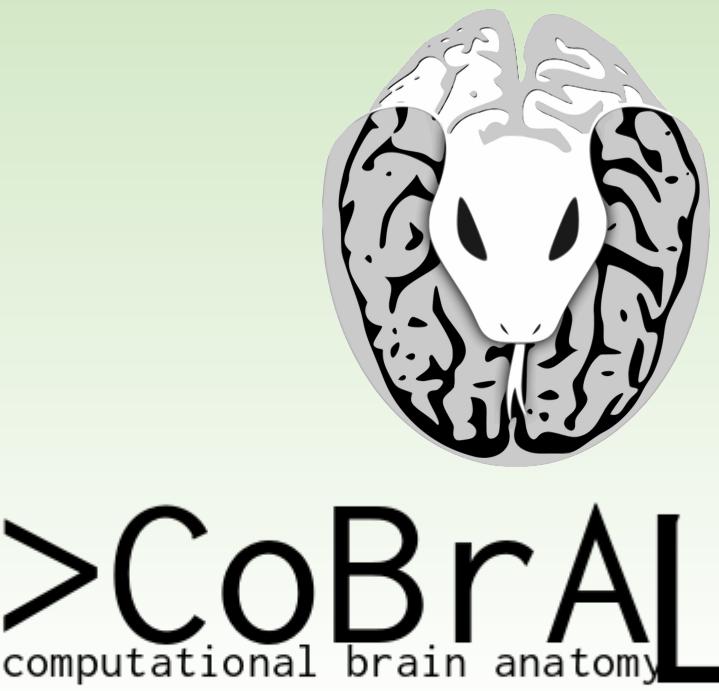


Acute Fornix Deep Brain Stimulation Remodels Brain and Improves Memory in Alzheimer's Mouse Model



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Introduction

- Deep brain stimulation (DBS) makes use of surgically implanted electrodes to deliver electrical stimulation to critical nodes compromised in neuropsychiatric disorders
- Originally a treatment for Parkinson's disease, DBS is being examined for Alzheimer's disease (AD), eating disorders, major depression and others
- DBS clinical trials for AD have yielded encouraging but mixed results, and suffer from the fact that only a narrow range of electrical parameters have been approved

Objectives

- Develop a pre-clinical, experimental paradigm capable of
 - evaluating DBS outcomes in terms of both anatomy and behaviour
 - exploring the full range of electrical parameters available
- Assess deep brain stimulation of the memory circuit as a proof of concept, mimicking clinical high-frequency regimens

Experimental Design

- 3xTg-AD hemizygous mice (APP Swedish, MAPT P301L, and PSEN1 M146V)
- Wild type controls C57/129S hybrids
- DBS or sham DBS targeting fornix using MRI-compatible carbon fibre-based electrodes
- Anatomical MRI 3 days before stimulation, 3 days post-stimulation, and 6 week follow up
- Weekly longitudinal water maze to assess memory and learning

	Wild Type	3xTg-AD
Stimulation	8M / 8F (16)	8M / 8F (16)
Sham Stimulation	8M / 8F (16)	8M / 8F (16)
No Electrodes	8M / 8F (16)	8M / 8F (16)

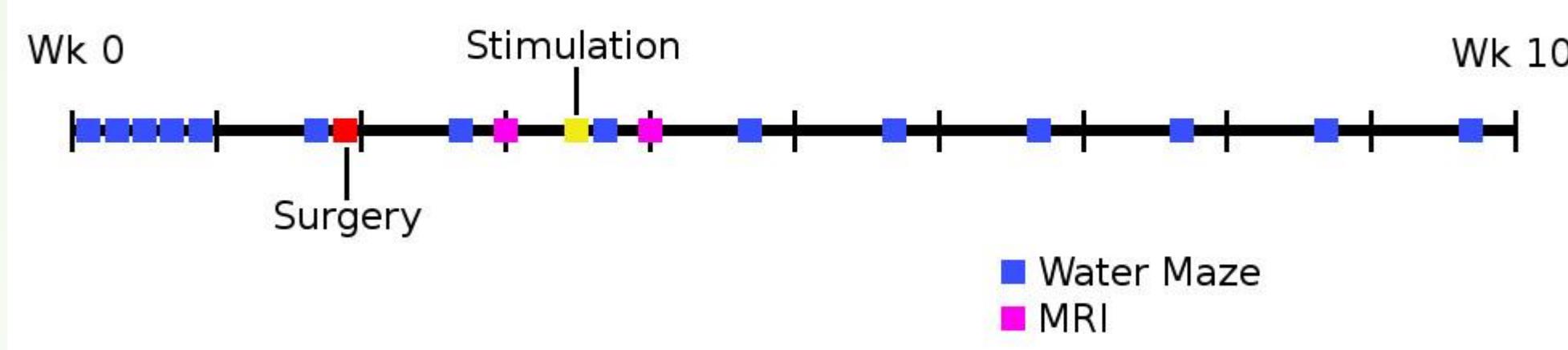


Figure 1. Experimental groups (top) and timeline (bottom). Alzheimer's model 3xTg mice and background strain wild types were subjected to either 1 hour of DBS, 1 hour of sham DBS or did not have any electrodes implanted to begin with. The subject number for each group is given as Male/Female (**Total**). The experimental timeline is shown in weeks (ticks) from start of experiment.

Results - Memory Improvement

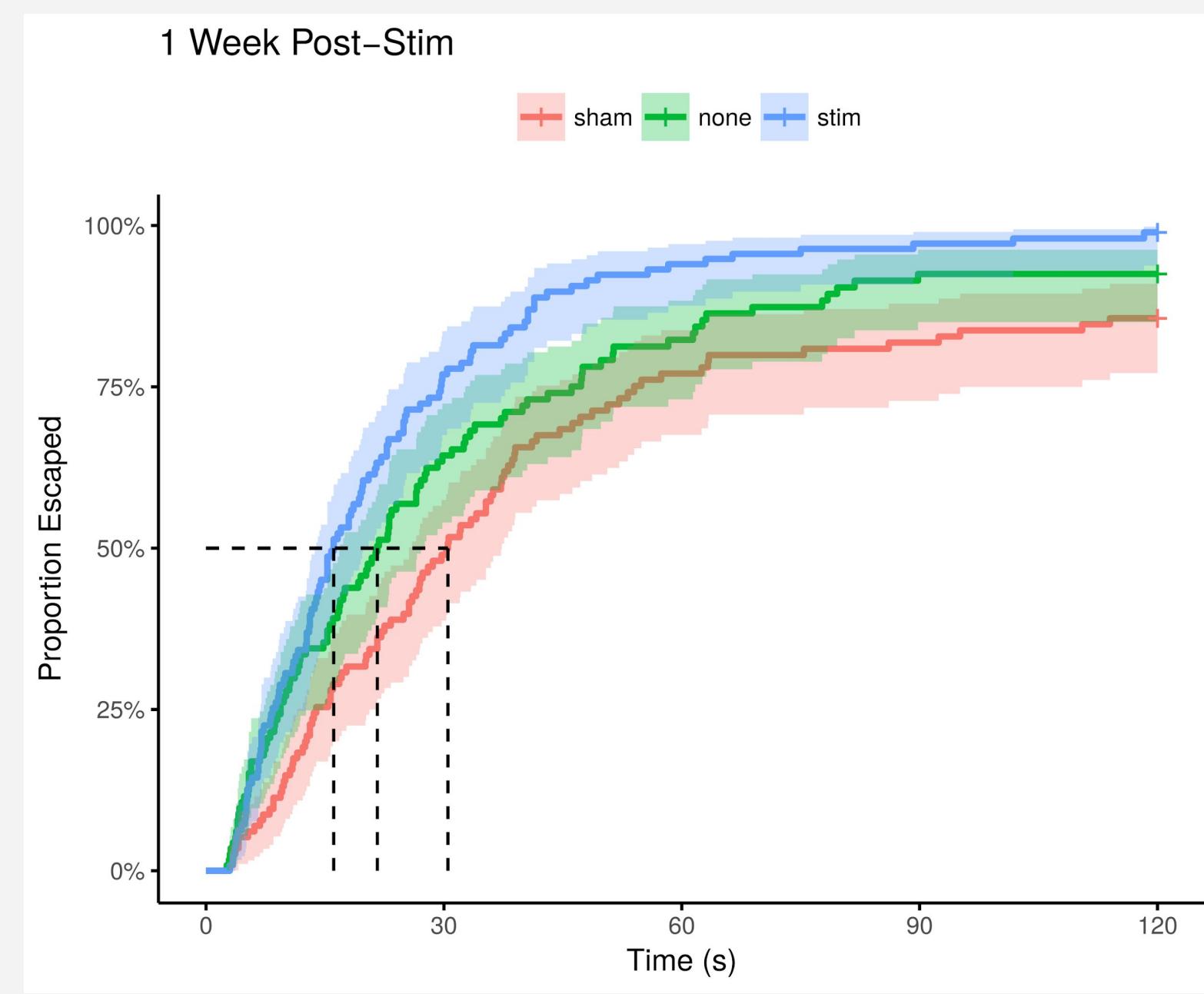


Figure 2. Stimulated mice outperform both sham ($p < 0.01$) and no electrode ($p < 0.05$) control groups 1 week after receiving stimulation. Inverted survival curves depict the proportion of mice successfully completing the water maze over time in non-naïve trials with a maximum of 120 s allowed. Lightly shaded areas around each curve show 95% confidence intervals. Dashed lines show times at which 50% of each experimental group completed the task. Sex and genotype did not contribute significantly to outcomes at this time.

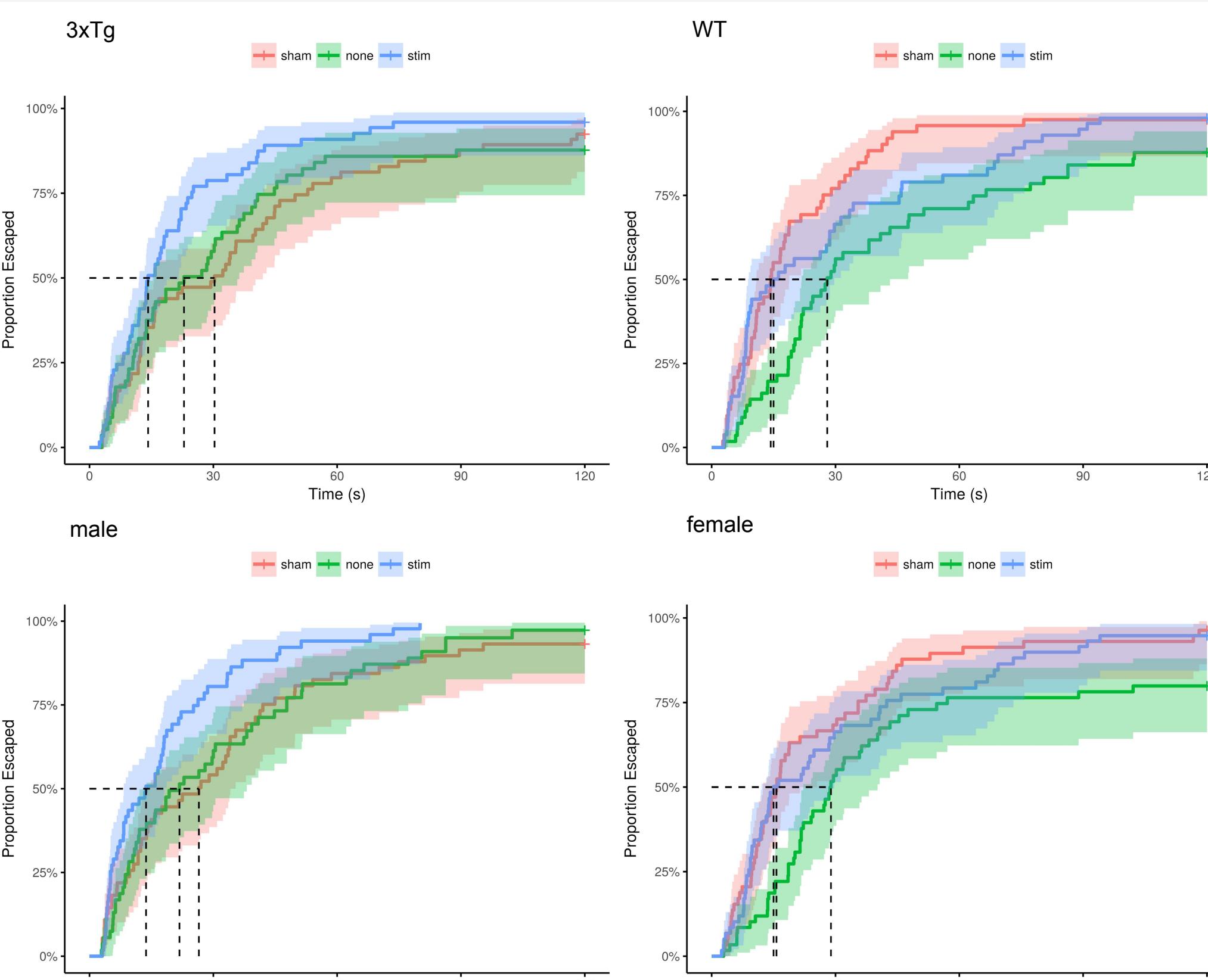


Figure 3. Stimulated mice outperform controls 4 weeks after receiving stimulation. The effect was modulated by both genotype (split top row, $p < 0.05$) and sex (split bottom row, $p < 0.05$).

Methods-Imaging

- 5% induction, 1.5% maintenance isoflurane anesthesia
- 7T Bruker Biospec magnet, 3D-FLASH scan, 100 μ m isotropic voxels, matrix of 180x160x90
- TR = 20 ms, TE = 4.5 ms, FA = 20°
- MnCl₂ contrast enhanced, fat suppression on
- Analysis with deformation-based morphometry (fig. 6)

Results - Anatomical Remodelling

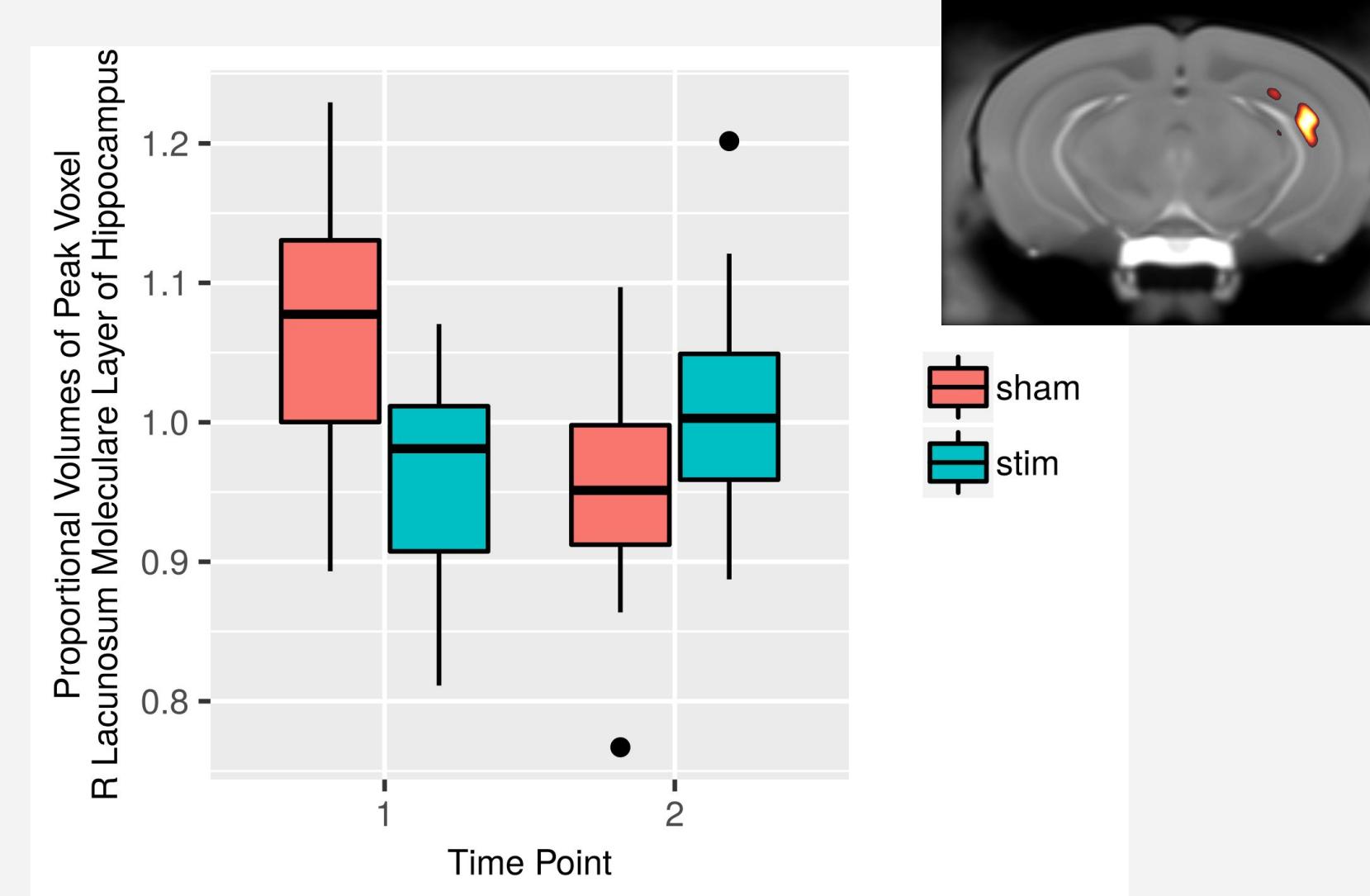


Figure 4. Short term volume changes. 3xTg mice experience significant volumetric changes from baseline (time point 1) to 3 days after receiving stimulation (time point 2). A t-statistic map is shown on the right highlighting one such area in the hippocampus after correcting for a false discovery rate of $q < 0.05$. The relative volumes in the peak voxel of this area are displayed on the left by group. This area, along with locations in the orbital cortex, olfactory bulb and somatosensory cortex register larger local volumes relative to controls ($q < 0.05$) while smaller volumes appear in crus 2 of the cerebellum ($q < 0.05$). Wild type mice register no significant differences between treatment groups, while sex is not a significant factor.

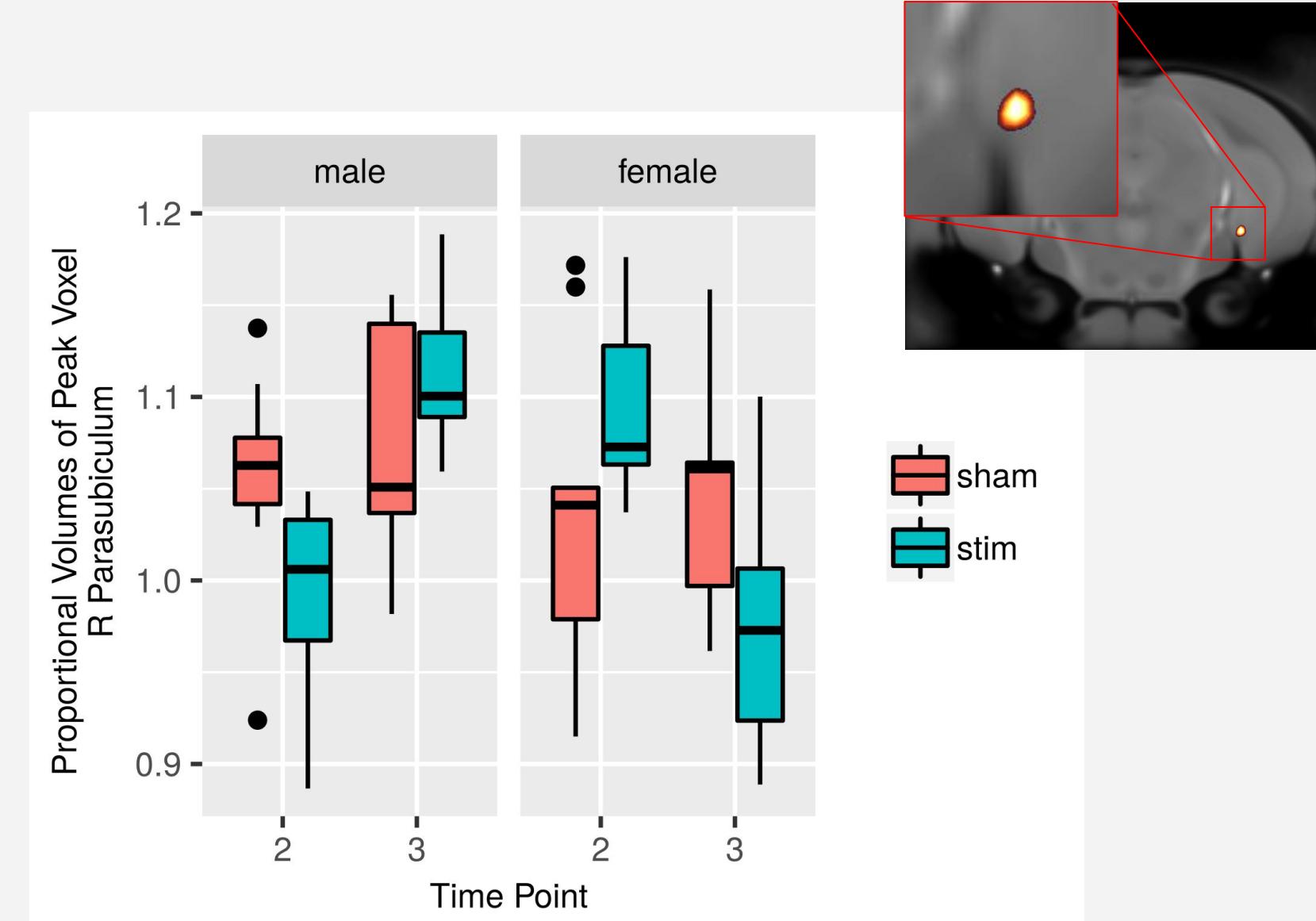


Figure 5. Long term volume changes. Both wild type and 3xTg mice experience significant, sex-dependant volumetric changes between 3 days and 6 weeks post stimulation (time points 2 and 3). A t-statistic map is shown on the right highlighting one such area in the subiculum of wild type mice after correcting for a false discovery rate of $q < 0.01$. The relative volumes in the peak voxel of this area are displayed on the left by group and sex. This area, along with locations in the olfactory bulb ($q < 0.05$) register larger local volumes relative to controls ($q < 0.05$) in male, wild type mice while larger volumes also appear in the olfactory bulbs of male, 3xTg mice ($q < 0.05$) when stimulated.

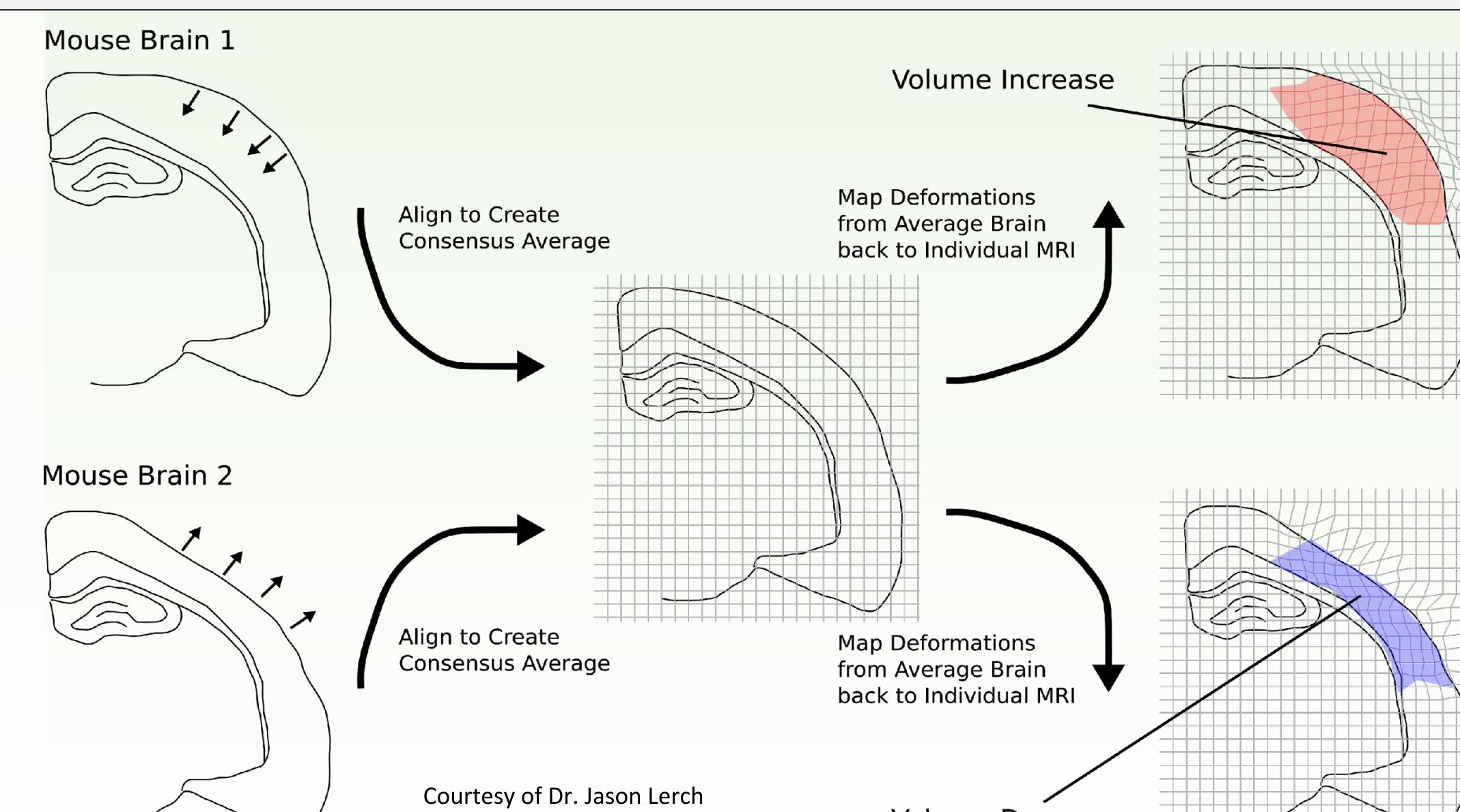


Figure 6. Deformation-based morphometry uses the deformation of individual images to an average to estimate local volumes in those images.

Methods-Stimulation

- 2 monopolar, carbon fibre electrodes
- implanted bilaterally +/- 0.75 mm at bregma, depth of 3.75 mm, perpendicular to skull plane
- Target: body of fornix and fimbria
- Mice are awake, unrestrained
- 1 hour stimulation, monophasic, 100 Hz, 100 μ A, ~3 V, pulse width of 100 μ s
- Left side negative, right side return (positive)



Figure 7. Mice with implanted electrodes (left), and while attached to the pulse generator (right). Electrodes are designed to anchor alligator clips to each mouse, while the pulse generator's swivel rings to allow mice to roam freely during stimulation.

Methods-Behaviour

- Longitudinal Morris Water Maze with changing platform assessed on one day, every week
- 4 trials of 120 s on testing days to find platform
- Learning assessed by Cox Proportional Hazards model with predictors of sex, genotype, trial number and mouse speed

Discussion

- Preclinical regimens offer a framework for evaluating DBS in terms of anatomical and behavioural outcomes
- DBS benefits AD model mice in memory tasks, along with healthy mice to a lesser degree
- DBS is associated in structural changes that have quick onset and persist for at least 6 weeks
- DBS effects are temporally specific and may depend on disease burden, sex
- Future work will include investigation of different stimulation regimens

Acknowledgements and Contact Info



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