High-frequency deep brain stimulation of the fornix improves memory consolidation and causes network-level neuroanatomical remodelling in an Alzheimer's mouse model

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Introduction

- Deep brain stimulation (DBS) delivers electrical stimulation via implanted electrodes to brain circuits compromised by neuropsychiatric disorders
- Currently used to treat Parkinson's disease (fig. 1)
- Under investigation for a host of other disorders such as major depression and obesity
- The potential of DBS to treat symptoms of Alzheimer's disease such as memory loss is not well explored

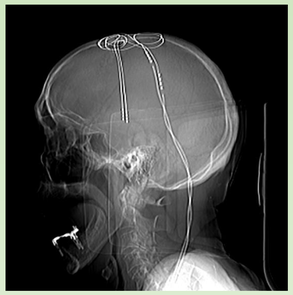

Figure 1. A CT scan of a Parkinson's patient with implanted DBS electrodes. Electrode stimulation is believed to disrupt the firing of over-excited cells, preventing the aberrant signalling that causes tremors. Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 19518

Objective

- To assess deep brain stimulation of the memory circuit as a therapeutic option in treating Alzheimer's disease in a novel, longitudinal imaging and behavioural experiment

Experimental Design

- 3xTg-AD hemizygote mice (APP Swedish, MAPT P301L, and PSEN1 M146V)
- Stimulation or sham stimulation targeting fornix using carbon electrodes
- MRI 3 days before, 3 days post-stimulation, and 6 week follow up
- Weekly longitudinal water maze to assess memory and learning

	Age 10–11 wks	Age 23–26 wks
Stimulation	9M / 8F (17)	3M / 4F (7)
Sham Stimulation	8M / 9F (17)	4M / 4F (8)

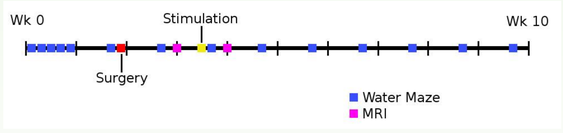

Figure 2. Experimental groups (top) and timeline (bottom). Mice of two age categories (starting age given) were subjected to either 1 hour of DBS or sham DBS. The subject number for each group is given as **M**ale/**F**emale (**Total**). The experimental timeline is shown in weeks (ticks) from start of experiment.

Results-Adult Mice

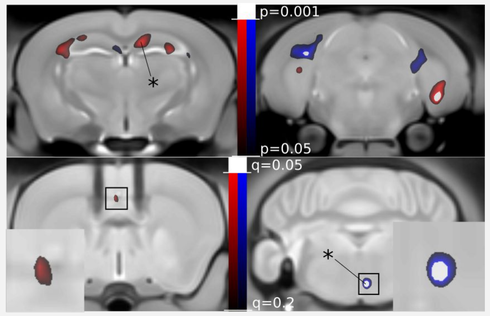

Figure 3. Parametric maps of adult mice receiving stimulation compared to sham controls. Maps are thresholded at p<0.05 for hypothesised, memory circuit effects (top row) and at a 20% false discovery rate for whole brain comparisons (bottom row). Red indicates relatively larger areas in stimulated mice and blue indicates relatively smaller areas. Asterisks indicate voxels chosen for display (fig. 4).

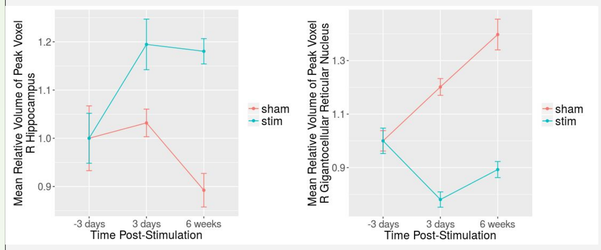

Figure 4. Relative volume trajectories of selected peak voxels from the right hippocampus and right gigantocellular reticular nucleus in stimulated vs sham control mice.

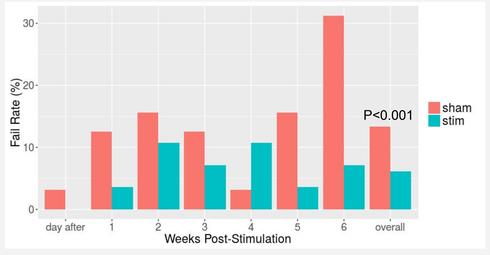

Figure 5. Stimulated adult 3Tg mice fail to find the platform significantly less than controls as tested by a longitudinal Morris Water Maze.

Results-Young Mice

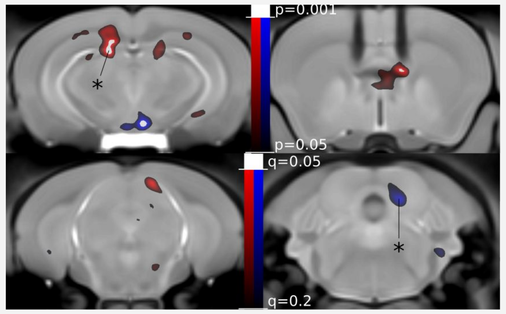

Figure 6. Parametric maps of young mice receiving stimulation compared to sham controls. Maps are thresholded at p<0.05 for hypothesised, memory circuit effects (top row) and at a 20% false discovery rate for whole brain comparisons (bottom row). Red indicates relatively larger areas in stimulated mice and blue indicates relatively smaller areas. Asterisks indicate voxels chosen for display (fig. 7).

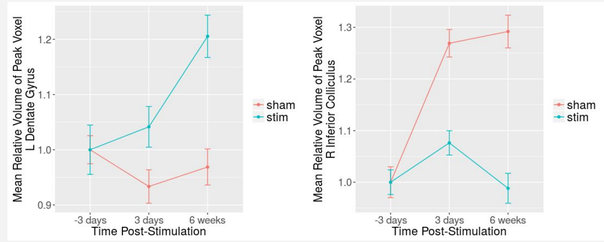

Figure 7. Relative volume trajectories of selected peak voxels from the left hippocampus (dentate gyrus) and right inferior colliculus in stimulated vs sham control mice.

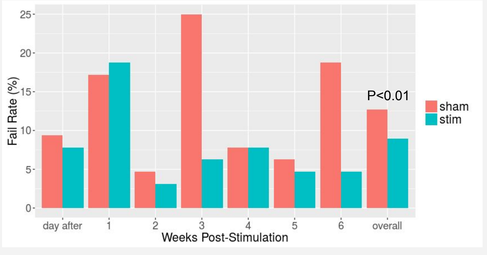

Figure 8. Stimulated young 3Tg mice fail to find the platform significantly less than controls as tested by a longitudinal Morris Water Maze.

Methods-Imaging

- 1.5% isoflurane anesthesia
- 7T magnet, 3D-FLASH scan, 100 µm isotropic voxels, matrix of 180x160x90
- TR = 20 ms, TE = 4.5 ms, FA = 20°
- $MnCl_2$ enhanced, fat suppressed
- Analysis with deformation-based morphometry (fig. 9)
- Linear mixed effects model: treatment*timepoint + sex + subject intercept

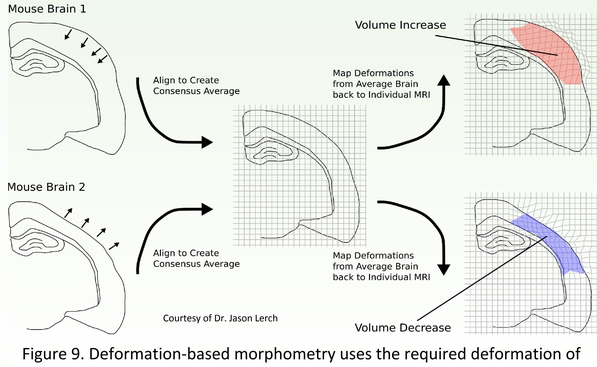

Figure 9. Deformation-based morphometry uses the required deformation of individual images to an average to estimate local volumes in those images.

Methods-Stimulation

- Monopolar, carbon fibre electrodes
- 2 electrodes implanted bilaterally +/- 0.75 mm at bregma, depth of 3.75 mm, perpendicular to skull plane
- Targeting body of fornix and fimbria
- Awake, unrestrained mice for 1 hour
- Monophasic, 100 Hz, 100 µA, ~3 V, pulse width of 100 µs
- Left side negative, right side return (positive)

Figure 3. 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 every week
- Learning assessed by failure count and reduction of latency
- Long term memory assessed by time spent in proximity of previous week's platform location on 1st trial (pseudo probe trial)

Discussion

- Stimulation of the fornix induces remodelling in and outside memory circuit structures
- Remodelling effects depend on the age of the mouse
- Structural changes persist at least 6 weeks later
- Mice receiving stimulation make less errors in water maze, suggesting improved memory and/or cognitive flexibility
- DBS is an exciting potential treatment for AD
- Future work will include investigation of different stimulation regimens

Acknowledgements and Contact Info

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