A neuroimaging study of the effects of early versus late anti-inflammatory treatment in the TgF344-AD rat model of Alzheimer's disease

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Introduction:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no effective treatments or known biomarkers for definitive diagnosis, substantiating the need for early detection and early intervention. Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS) provide a window into the brain by offering robust, non-invasive assays of brain structure and biochemistry that can be performed longitudinally.[1,2] One potential application for MR techniques is preclinical assessment of therapeutic efficacy in animal models of AD.[3] Some evidence suggests that chronic administration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) may mitigate disease progression, but only when administered during pre-symptomatic stages of the disease.[4] Therefore, we aim to assess longitudinal changes in brain volume, neurochemistry, cognitive function, and histopathology in the TgF344-AD[5] rat model of AD during early versus late treatment with Naproxen, a common NSAID.

Methods:

Naproxen: Rats in the treatment group orally received Naproxen (615 ppm) formulated into their chow, starting one week after weaning until 10-months, or from 10-months until 19 months, for the early and late treatment groups, respectively. **^{1}H MRS acquisition and analysis:** Localized MRS data were acquired on a 7 Tesla Bruker Biospec 70/30 Scanner from a 31 μL voxel (2.5x3.5x3.5) mm in the dorsal hippocampus. FASTMAP was used for shimming (water linewidth 11.0 ± 1.3 Hz) prior to PRESS MRS acquisition (TR/TE=3000/11 ms). Pre-processing was performed using the FID-A toolkit;[6] MRS spectra were analysed in LCModel with metabolites referenced to total creatine.[7] **Barnes Maze:** Rats were given a maximum of three minutes to use spatial cues surrounding the maze to find an escape box, located under one of 20 identical holes around the perimeter of the maze.[8]

Results:

MRS measurements at 4- and 10-months of age show TgF344-AD (Tg) rats have elevated myo-Inositol levels, which are mitigated by early treatment (ET) with Naproxen. Glutamine and Taurine also show treatment effects. Cognitive assessment via the Barnes Maze suggests that only wildtype (WT) rats display intact location recall at 10-months of age, indicated by a significantly higher than chance amount of time (45 seconds) spent investigating holes in the target quadrant, whereas Tg rats are impaired.

Discussion:

Proton MRS enables quantitative measurement of the concentrations of up to 20 different metabolites in the brain, many of which are established biomarkers of known pathological traits, and may therefore be used to monitor therapeutic efficacy. The early increase in Taurine in Naproxen-treated rats may have a neuroprotective role, while later treatment effects in Myo-Inositol and Glutamine may suggest Naproxen treatment primarily affects glial cells. No functional outcome (improved cognition) of treatment is seen at 4- or 10-months, as assessed by the Barnes Maze test of spatial learning and memory.

Conclusion:

Preliminary results suggest MRS can be used to monitor treatment response in an AD rat model. Future analyses will determine if metabolite levels predict cognitive impairment.

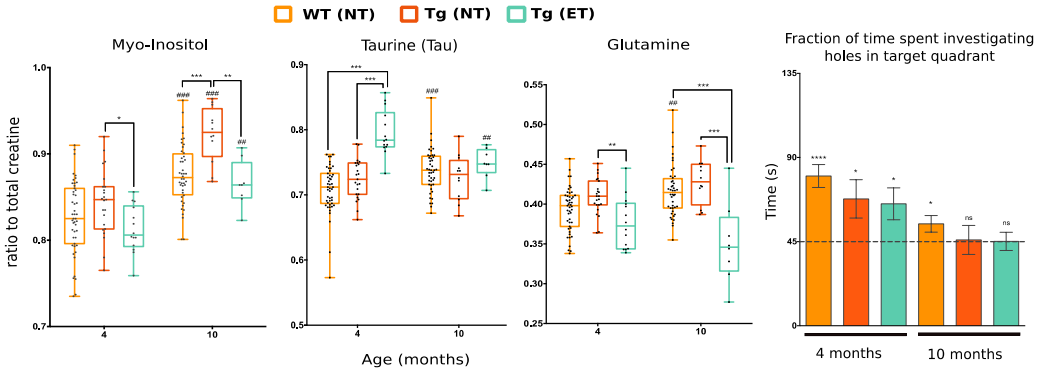

Figure 1: Early Naproxen treatment results in altered neurochemical profile but not improved cognition in TgF344-AD rats. *p>0.05, **p<0.01, ***p<0.001. # denotes significant comparisons between 10- and 4-months.

References: **[1]**Lau, J.C. *NeuroImage* (2008) **[2]**Marjanska, M. *Proc Natl Acad Sci USA* (2015) **[3]**C. Jack. *The Neuroscientist* (2007) **[4]**McGeer, P. *Neurobiol Aging* (2002) **[5]**Cohen, R. *Neurobiol Disease.* (2013) **[6]**Simpson, R. *Magn Reson Med* (2015) **[7]** Provencher SW, NMR Biomed 2001; 14:260-264 **[8]**Attar, A. *PLOS ONE* (2013.