In vivo manganese-enhanced MRI of amyloid pathology in a mouse model of AD

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Introduction: Senile plaques - extracellular deposits of aggregated forms of the β-amyloid peptide, are one of the defining neuropathological hallmarks of Alzheimer's Disease (AD). Due to their small size, *in vivo* imaging of plaques is challenging, yet methods to detect plaques non-invasively are highly desirable to provide translatable biomarkers of AD and the efficacy of potential therapeutics. Using MEMRI (manganese enhanced MRI), in which signal enhancement is provided by T1/T2 reducing Manganese II Chloride ($MnCl_2$), we succeeded in detecting plaque like hypointense foci in a well-characterized transgenic model of AD, the '5xFAD' mouse[1], which develops amyloid plaque-like deposits, in addition to other AD-related pathologies, from as early as 2 months of age.

Methods: Mice (TG, 5xFAD, 6-7 months old), or age-matched wild type (WT) controls were administered 0.15mmol/kg $MnCl_2$ in four daily subcutaneous injections (cumulative dose 0.6mmol/kg). One day after the final dose of $MnCl_2$, the mice were imaged *in vivo* in a Bruker BioSpec 94/20. For all mice, images were acquired using a 3D multiple gradient echo sequence: TE = 5, 12, 19, 26 ms; TR = 250 ms; FA = 50°; BW = 40 kHz; matrix = 200×150×20; FOV = 12×9×4.8 mm; 4 averages, lasting 60 minutes. Following MRI, the mice were transcardially perfused with 4% paraformaldehyde, and their brains processed with Congo red histological staining which labels amyloid in plaques.

Results: In the longer echo images, hypointense spots were visible predominately in the hippocampi of 5xFAD mice (Fig 1). Similar spots were not present in the wildtype littermate controls. The location of the spots coincided with the Congo red-positive structures in the histological sections (Fig 2).

Discussion: Previous attempts to image AD plaques relied on complex MR protocols, cardiac & respiratory gating, long scan times and/or *ex vivo* imaging, none of which are readily applied to longitudinal studies for monitoring disease progression and therapeutic interventions. Using MEMRI and 3D multi gradient echo sequence at 9.4T, we present a simple and a relatively fast & non-invasive method of plaque detection. Interestingly, the majority of plaque-like spots were detected in the hippocampi despite there being histological evidence of cortical and thalamic plaques as well. This raises the possibility that certain features make the hippocampal plaques more readily visible by MRI; this is a subject of our ongoing histological and biochemical examinations.

Conclusion: The ability to detect plaque-like pathology *in vivo* confirms that MEMRI could serve as a potential biomarker of AD-related changes, raising the possibility of utilising MEMRI as a non-invasive assay for longitudinal therapeutic interventions in animal models of AD.

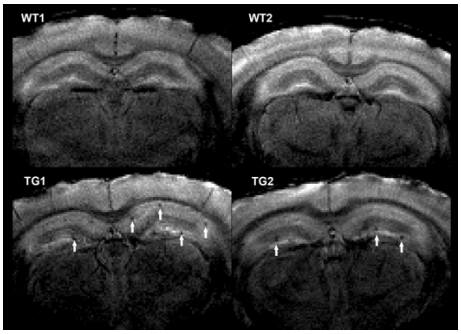

Fig 1. Representative images of four mouse brains (2xWT, top, and 2xTG, bottom) at the level of the hippocampus. Plaque like hypointense spots (white arrows) appear in the hippocampi of all TG mice.

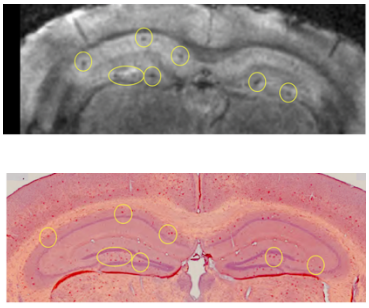

Fig 2. Co-registration of Congo red positive plaques in *ex vivo* histology (bottom) with the hypointense spots in *in vivo* MRI of the same TG mouse (top).

[1]Oakley *et al. J. Neurosci.* **26,** 10129 (2006)