Laminar Specific Detection of Amyloid Precursor Protein -Induced Neurodegeneration and Recovery using MEMRI in an Olfactory based Alzheimer's Disease Mouse Model.

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Target audience – Scientists interested in studying animals models of neurodegenerative diseases with MRI.

Purpose – Olfactory dysfunction is an early symptom of Alzheimer's disease (AD). This suggests that olfactory sensory neurons (OSNs) are more sensitive to AD related factors than neurons in other brain parts. A reversible olfactory-based AD model recently established that degeneration of OSNs can be rapidly induced by simply overexpressing amyloid precursor protein (APP) [1]. With this transgenic model, we followed the progression of neuronal pathology and its recovery using MRI. This enables direct tracking of neurodegeneration trough a non-invasive *in vivo* measurement and the ability to correlate with functional assays. Manganese enhanced MRI (MEMRI), provides a unique contrast in the rodent brain. It can detect layers in different areas of the brain, including olfactory bulb (OB), cortex and cerebellum and highlight discrete anatomical features such as glomeruli in the OB. Since OSNs regenerate continuously throughout life and project their axons directly to OB glomeruli, we performed MEMRI in mutant mice to detect both the degeneration and recovery of OSNs with particular focus on the glomerular layer.

Method – For both control and transgenic mice, 100mM $MnCl_2$ isotonic solution was infused i.v. through the tail vein (88mg/kg at a rate of 0.25ml/h). Images were acquired on 11.7T (31cm horizontal bore magnet) using a small surface coil that was placed on the area of the OB, 24h after manganese administration. 3D T_1 weighted images at 50µm isotropic resolution were acquired (TR/TE = 40/4.4 ms, 25° pulse, ns = 2, scan time of 50 min). Overexpression of APP was turned off by feeding 3-4 week old mutant mice with doxycyclin containing food, for either one or three weeks. APP antibody was also used to follow the OSNs recovery, by administrating antibody only to the right nasal of mutant mice for a period of 3 weeks.

Results – Representative MEMRI images of different groups of mice used in the study are shown in Fig. 1. In mutant mice, measurements of the OB volumes showed a ~50% reduction compared to control mice as well as a decrease in manganese enhancement of the glomerular layer. These changes were further supported by looking at the intensity profile across the OB layers, from lateral to medial side (Fig. 1e,f), revealing a much smaller enhancement of the glomerular layer in the mutant mice compared to the control. After APP expression was turned off by feeding 3 week old mutant mice with doxycycline containing chow for a week, images showed a striking increase in the manganese enhancement of the glomerular layer in the OB (Fig. 1c,g), although no significant increase in OB volume was measured. Turning off APP expression for two additional weeks with doxycycline produced farther recovery of the OB, with higher enhancement of the glomerular layer (Fig. 1d,h). The volume of the OB showed a small increase compare to the mutant mice. A MEMRI image of an antibody treated mutant mice is shown in Fig. 2. Following 3 weeks of antibody administration to the right nasal, the right OB shows higher manganese enhancement of the glomerular layer, compare to the left OB (Fig. 2) and to the mutant mice (Fig. 1b). This is further supported when looking at the intensity profile across both OB from the lateral side of the left OB to the right OB (Fig. 2b).

Discussion – This study demonstrates that MEMRI can detect laminar specific anatomical changes associated with both APP-induced neurodegeneration and recovery in the OB. Overexpression of APP in the mutant mice, results in a decrease of OB volume and a reduction in manganese enhancement of the glomerular layer. Turning off APP overexpression with doxycycline, results in an increase in manganese enhancement of the glomerular layer after only 1 week, and a farther recovery in manganese enhancement after 3 weeks. Moreover we have shown that APP antibody has the potential to block olfactory neuronal loss in a similar manner as turning off APP overexpression, which results in an increase in manganese enhancement of the glomerular layer for the treated OB.

Conclusion – MEMRI can be used to assess the ability of different pharmacological reagents to block olfactory neuronal loss and can serve as a unique *in vivo* screening tool to both identify potential therapeutics and test their efficacy.

References – 1. Cheng N. et al, J. Neurosci. 28, 2011.

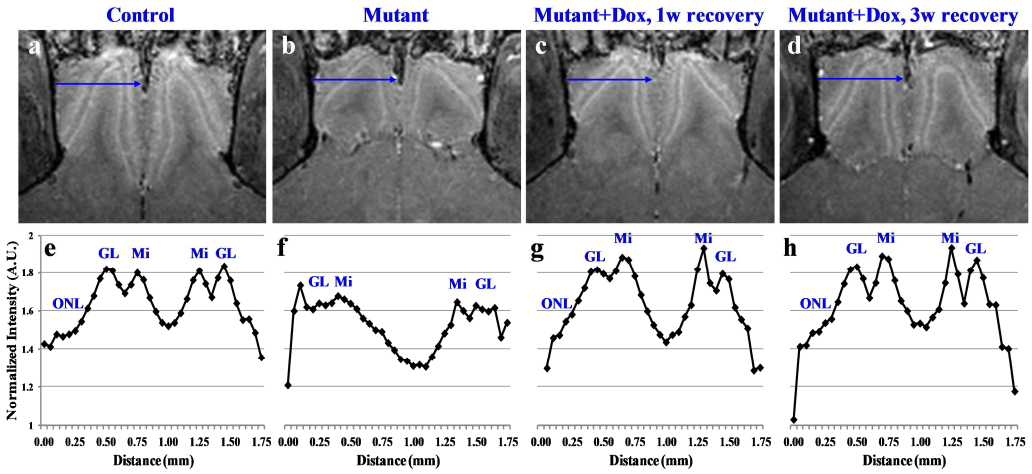

Fig. 1 – T_1-weighted images at 50µm isotropic resolution, taken 24h after IV infusion of 100mM $MnCl_2$ of control (a), mutant (b), mutant after 1 week (c) and 3 weeks (d) of doxycyclin administration, and the corresponding intensity profiles. The intensity profile was taken for each olfactory bulb from lateral to medial side across the OB as shown by the arrows.

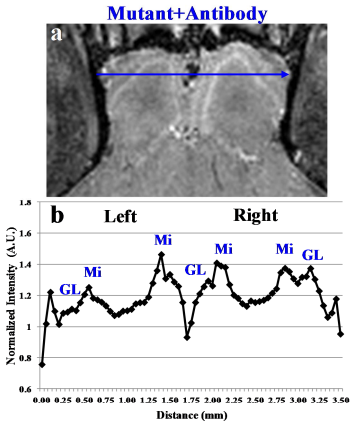

Fig. 2 – T_1-weighted image at 50µm isotropic resolution, taken 24h after IV infusion of 100mM $MnCl_2$ of mutant after 3 weeks of antibody administration to the right nasal (a), and the corresponding intensity profiles. The intensity profile was taken across each olfactory bulb from lateral side of left OB to the right OB as shown by the arrow.