Reduced Manganese Enhancement and Flow in the Olfactory Pathway in Mice with Experimental Neuropsychiatric Lupus Demonstrated by Manganese Enhanced MRI

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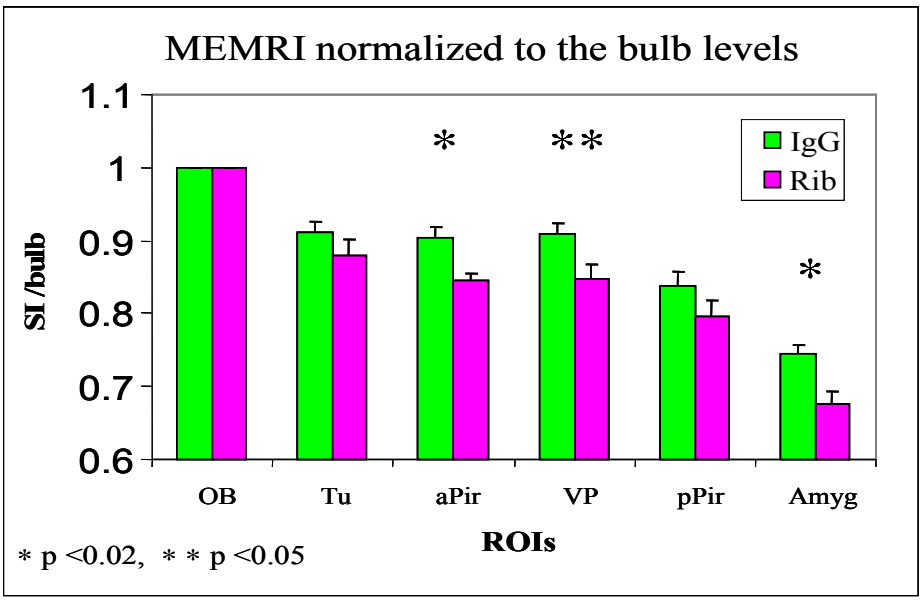
Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease affecting multiple organ systems, including the skin, joints, kidneys, and nervous system. NPSLE is a common neuropsychiatric manifestation in patients with SLE, including cognitive impairment, depression and psychosis, and significant source of morbidity and mortality. Elevated levels of specific auto-antibodies against ribosomal phosphoprotein antibodies (anti-ribosomal-P) are associated with NPSLE (1). Mice with experimental NPSLE, induced by anti-ribosomal-P antibodies, develop depression-like behavior and a diminished sense of smell. In addition, the anti-ribosomal-P antibodies specifically stained neurons in the limbic system and the olfactory cortex (2).
Manganese Enhanced MRI (MEMRI) allows *in-vivo* mapping of functional neuronal connections in the brain, including the olfactory tract (3, 4).
Aims: To characterize neuronal manifestations of experimental NPSLE along the olfactory/limbic cortex by comparing mice treated with anti-ribosomal-P antibodies to a control group using MEMRI.
Methods: Twenty mice were intra-cerebro-ventricular (ICV) injected to the right hemisphere: 10 with human anti-ribosomal-P antibodies (Rib) from a patient with NPSLE and 10 with human IgG antibodies (control). Depression was addressed by forced swimming test (FST), and smell function was evaluated by smelling different concentrations of menthol. MEMRI was used to investigate the abnormalities of the olfactory system in these mice. Brain MRI scans were performed before and 40 hours after intranasal $MnCl_2$ (4µl 500 mM) administration. MRI measurements were performed using 3T HDx GE system, mice volume coil and 3D IR SPGR T_1w sequence. The acquisition included a coronal slab, 52 images, FOV 4cm, 128x128 matrix, SW 0.3 mm, resolution: 300 µm. Mn^{+2} enhancements were measured in a series of ROIs defined according to Paxinos mice brain atlas through the olfactory tract, including the amygdala.
Results: Passive transfer of anti-ribosomal-P to mice resulted in a depression-like behavior accompanied with a significant deficit in olfactory function. MEMRI demonstrated impaired olfactory neuronal function expressed as significant reduction in manganese enhancement and flow throughout the olfactory pathway compared to control mice, as demonstrated in fig 1.
Conclusions: Impaired olfactory neuronal function in mice with experimental NPSLE depression mediated by passive transfer of human-anti-ribosomal-P was demonstrated by MEMRI. Our results propose that autoimmune-CNS conditions, such as NPSLE, may influence olfactory function.

Fig. 1: MRI signal intensities normalized to the bulb in ROIs along the olfactory tract



OB-olfactory bulb, Tu- tubercle, aPir-anterior Piriform, VP- ventral palidum, pPir- posterior Piriform, Amyg- Amygdala.

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