In Vivo Tracking of Axonal Disruption and Recovery in the Rat Olfactory System by MnCl2 Enhanced MR Statistical Maps

D. J. Cross[1,2], Y. Anzai[1], K. R. Maravilla[1], T. J. Morrow[2,3], J. A. Flexman[4], S. Miyoshi[4], S. Minoshima[1,4]

[1]Radiology, University of Washington, Seattle, WA, United States, [2]Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI, United States, [3]Neurology, Ann Arbor VA Hospital, Ann Arbor, MI, United States, [4]Bioengineering, University of Washington, Seattle, WA, United States

PURPOSE:

To map statistically the normal functional connections of the rat olfactory system in vivo using MRI and manganese as a transport-mediated transsynaptic tracer with parametric brain mapping techniques. To apply this technique to investigate and quantify initial disruption and recovery of transport following stereotactic radiofrequency (RF) lesion of the lateral olfactory tract (LOT).

MATERIALS AND METHODS:

Six young male rats were scanned under isoflurane on a 1.5T MR scanner using a custom rat brain volume coil. 3D-SPGR (TE=6.8 ms; TR=15 ms; flip angle 45 degrees; 4 NEX) imaging was performed at pre-injection, and 6, 12, 24, 36, and 48, 72 hours (6 rats) and 5.5, 7.5, 10.5, and 13.5 days (3 rats) post injection of 10 microliter manganese chloride ($MnCl_2$) into the right nasal cavity. Image sets at different time points from the same rat were coregistered precisely to the same orientation and registered to the stereotactic atlas[1] using fully automated algorithms (NEUROSTAT software[2]). Global intensity and drift across scans was normalized using a stochastic algorithm insensitive to local intensity change. Pre and post injection scans (each time point) were subtracted in a pair-wise manner and compared statistically across subjects on a pixel-by-pixel basis. T-statistics were converted to Z maps and superimposed on to a template anatomical image for display. Z score threshold of 4.0 ($p < 0.05$ adjusted for multiple comparisons) was estimated to indicate pixels with a significant transport of tracer. ROI analysis using regions identified as statistical peaks. To apply this technique to investigation of brain injury and repair, 5 new rats were RF lesioned stereotactically in the LOT and underwent 3 separate scanning sessions. The first session (scans at pre-injection, 24, 48, 72 hours post injection) was prior to lesioning. The other 2 series of scans were obtained at 1 week and 4 weeks post surgery. Injections, imaging parameters, and data analysis were identical to the first study.

RESULTS:

Peak analysis showed that most of the significant changes in cortical (non-bulb) intensity were confined to the lateral olfactory tract (LOT 70% Z=15.4) at the early time points. From 24hrs post injection and beyond, other structures accumulated enough manganese to have consistent percent change in enhancement across subjects, resulting in cortical peaks outside the tract and in more posterior regions of the brain (tubercle 36% Z=10.1; anterior commissure 30% Z=6.4; ventral pallidum 26% Z=5.0; piriform cortex 28% Z=6.1; amygdaloid piriform transitional area 15% Z=5.0) (Fig 1). In the lesion study, ipsilateral transport at 1 week post-lesion LOT anterior to the site of lesion showed no change (pre-lesion 60±22%; 1 week post lesion 56±18%), however posterior LOT had significant reduction in transport (pre 41±20%; 1 week 22±10%, $p<0.05$). After 4 weeks post-lesion, recovery of Mn transport in ipsilateral LOT posterior to lesion site was seen (pre 41±20%; 4 weeks 36±21%). Additional significant increase in contralateral LOT was seen at 4 weeks (pre 6±9%; 4 weeks 25±15%, $p<0.01$) associated with greater transport through the anterior commissure (Fig. 2).

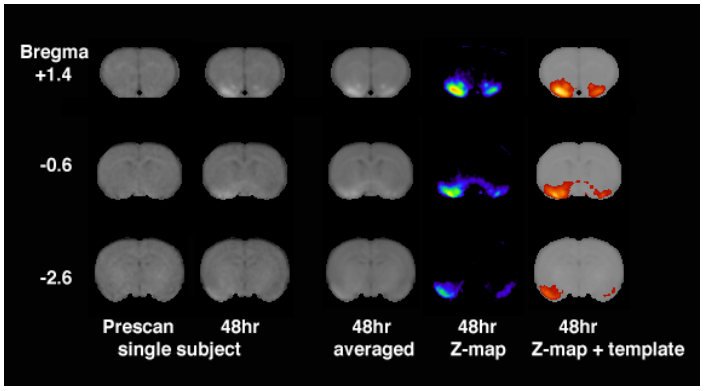

Figure 1. Group averaged (n = 6) versus single subject improves signal to noise ratios. Z-maps further delineate statistically areas of manganese enhancement in stereotactic coordinates.

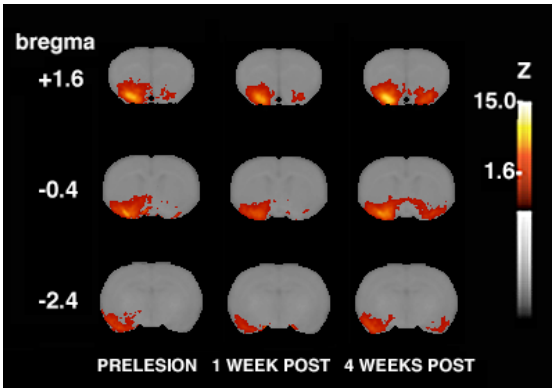

Figure 2. Pre-lesion map (1st column) and 1-week post-lesion map (2nd column) show reduced transport in regions posterior to lesion location (middle and bottom rows). Recovery of transport at 4 weeks is seen posterior to lesion, plus significantly increased contralateral transport (3rd column) (n = 5, scans of 48hrs post- compared to pre-injection)

SUMMARY AND CONCLUSIONS:

Mn uptake and transport into rat olfactory system can be consistently quantified using statistical brain mapping techniques. RF lesioning interrupted Mn transport through rat olfactory tract at 1 week post surgery. However, recovery of manganese transport to regions posterior to lesion site as well as significant contralateral transport indicating possible plastic change to the alternative contralateral pathway through commissural fibers were demonstrated at 4 weeks post surgery. These findings suggest two differential modes of reorganization of neuronal connectivity after damage to the brain that can be demonstrated in vivo.

REFERENCES: 1. Paxinos G and Watson C. The rat brain in stereotaxic coordinates. New York Acad Press, 1998; 2. University of Michigan and University of Washington.