

Towards building a high resolution atlas of Mn^{2+} deposition in rat brain

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Introduction Mn^{2+} -enhanced MRI has been widely used for neuronal tract tracing and mapping regional brain activation [1]. High resolution MEMRI can be used to reveal fine cytoarchitecture such as cortical laminar structure [2] and single glomeruli in the olfactory bulb [3]. In this study we proposed a protocol to analyze high resolution MEMRI data with a voxel-based approach. The aim is to build a high resolution MEMRI atlas which can be used to reveal fine cytoarchitecture of the brain at the group level, and to identify functionally distinct brain regions which show differential activities in Mn^{2+} uptake/deposition.

Materials and methods *Animal preparation:* Twelve male Wistar rats (260±15 g) received daily intraperitoneal injection of 30 mg/kg $MnCl_2$ for consecutive 5 days. The animals were housed in groups and given ad libitum access to food and water. *MRI experiments:* All rats were imaged on a 7 T/20 cm Bruker Biospec scanner before and 1d after the 5-day Mn^{2+} treatment under 1.5-2% isoflurane anesthesia (in pure O_2). A 72-mm diameter volume coil was used for RF transmission, and a 4-channel phase-array coil for signal detection. High-resolution T_1 -weighted images were acquired with a 3D FLASH sequence with the following parameters: TR 35 ms, TE 5.5 ms, FOV 3 cm×3 cm×3 cm, matrix size 512×384×60 and 1 signal average. The voxel size was 58 μm ×78 μm ×500 μm . *Data analysis:* SPM8 was for image analysis. All images were first manually stripped out of the non-brain tissue pixels and corrected for image intensity ununiformity artifacts. Initial templates of non-manganese-enhanced (NME) images and manganese-enhanced (ME) images were first created by resampling representative datasets, respectively, to an isotropic voxel size of 58 μm ×58 μm ×58 μm . All NME datasets were then co-registered to the initial NME template, followed by generation of an average NME template. Similar procedures were also performed for ME datasets. The average NME template was then co-registered to the average ME template with nonlinear affine transformation, followed by generation of a mixed template. All NME and ME datasets were then co-registered to the mixed template. For each rat, the pixel-wise signal intensity was normalized to the average signal intensity of the whole brain. The NME and ME images were smoothed with a 0.12-mm FWHM Gaussian kernel before being subjected to voxel-wise two-tailed independent samples t-tests.

Results The accuracy of image co-registration is demonstrated in Fig. 1. Figure 2 shows the results of voxel-wise comparison between ME images and NME images. Gray matter showed above-the-whole-brain-average (warm color) deposition of manganese, while white matter and CSF showed under-the-whole-brain-average (cold color) deposition. With the data analysis protocol proposed, cortical laminar structures can be detected at group level (Figs. 2 and 3). Functionally distinct (in terms of Mn^{2+} uptake/deposition) nuclei (i.e., different parts of amygdala) could be delineated (Figs. 2 and 3).

Discussion Manganese distributes in nearly the whole brain after systemic Mn^{2+} administration. The amount of Mn^{2+} deposition in one particular nucleus, however, depends on many factors such as the permeability of local blood-brain-barrier, the baseline neuronal activity, the type of neurotransmission, the number of afferent and efferent projections etc. With the high resolution

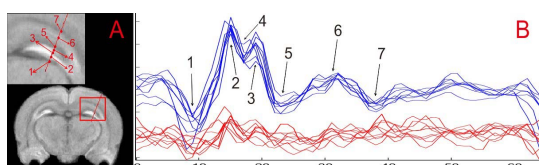


Figure 1. Signal intensity profiles (B) along the line in (A) obtained from individual spatially normalized ME (blue) or NME (red) dataset. In (B), X-axis denotes x-coordinate of the voxels along the line and Y-axis denotes signal intensity.

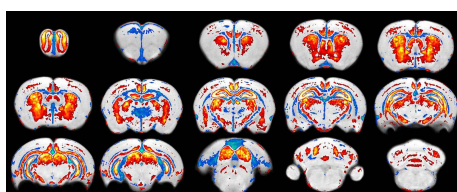


Figure 2. Brain regions showing statistically above-the-whole-brain-average (warm color) and under-the-whole-brain-average (cold color) deposition of Mn^{2+} ($p<0.01$, uncorrected).

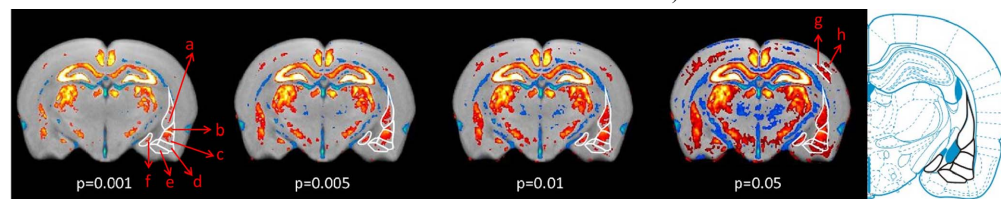


Figure 3. Cortical laminar structures and the fine structures of amygdala can be revealed by changing the statistical power of group comparison. a: striatum, b: lateral amygdaloid nucleus, dorsolateral part, c: lateral amygdaloid nucleus, ventromedial part, d: basolateral amygdaloid nucleus, posterior part, e: basomedial amygdaloid nucleus, posterior part, f: medial amygdaloid nucleus, posterodorsal part, g: internal pyramidal layer, h: external pyramidal layer

MEMRI atlas created in this work, it is possible to delineate nuclei with distinct pattern of uptake/deposition of Mn^{2+} . Such information may shed light on the functional organization of the brain.

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