Brain Regions showing Manganese Accumulation in the Human versus the Rat Brain

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Introduction

While manganese (Mn) is commonly used as a contrast agent for MRI in animal studies, high exposure to Mn is known to be neurotoxic. Extensive environmental and/or occupational exposure to Mn, as seen for example in welding or smelting, can lead to Parkinson's-like movement disorders. In this study we studied the spatial distribution of Mn accumulation in the exposed human brain and compared it to the typical rodent model used in studies of neurotoxicity of chronic Mn exposure. While rodent MEMRI studies show most prominent T1 shortening indicative of Mn accumulation in the hippocampus, olfactory bulb and gray matter in the cerebellum [1], human data predominantly shows Mn accumulation in the globus pallidus [2,3] (Figure 1). In this work, we used a high-resolution 3D whole-brain T1-weigthed sequence to study all the human brain structures showing T1 shortening due to Mn exposure in a cohort of smelters and welders, and compared this data to non-exposed controls as well as to a rat model of chronic Mn exposure.

Typically in Mn neurotoxicity studies, the pallidal index (PI), a signal intensity ratio between globus pallidus and frontal white matter is used as semi-quantitative measure of the Mn accumulation [4]. Therefore, this study further compares the sensitivity of the pallidal index measure to the T1 relaxation time obtained via a series of inversion recovery images with varying inversion times in a volume of interest within the globus pallidus in the exposed subjects.

Materials and Methods

Nine smelters, eight welders and ten controls were recruited from two Mn-Fe alloy manufactures in China. Mean air Mn levels were 0.23 mg/m^3 for the smelters, 0.025 mg/m^3 for the welders and <0.005 mg/m^3 for controls. None of the subjects showed neurological or motor disorder symptoms. The mean duration of exposure was 19 ± 7 years (range 10 – 26 years) for the smelters and 6.6 ± 3 years (range 3-12years) for the welders.

All human MRI scans were performed on a 3T Philips Achieva whole body system using a 12-channel head coil. A 3D T1-weighted gradient echo sequence (TE/TR = 4.6ms/9.7ms, voxel size=1x1x1.25 mm^3, 120 slices) was used to obtain high-resolution images from the whole brain. Abnormal T1 hyperintensities in the 3D images were evaluated by a radiologist. In addition, a series of T1-weighted inversion recovery images (single coronal slice through globus pallidus, slice thickness 5mm, TR/TE = 4000/15ms, IR = 3000, 1221, 534, 100ms) was used to determine the T1 relaxation time in a region of interest (ROI) in the globus pallidus. The PI was calculated based on (a) the signal ratio between a ROI within the globus pallidus (GP) and white matter in the frontal cortex (PIwm) and (b) the signal ratio between the same ROI in the GP and a ROI in the neck muscle (PImu).

For the animal model of chronic Mn exposure, male Sprague-Dayley rats (220g) received ip injections of $MnCl^2$ (6 mg Mn/kg bodyweight, 5 d/wk) for 6 weeks. MRI images were aquired after 6 weeks on a 9.4T Varian Horizontal Bore MRI Scanner using a T1-weighted sequence (TR/TE = 500/ 10 ms, 4 averages, pixel size 0.2 x 0.2 x 0.8 mm^3, ~5 min scan time).

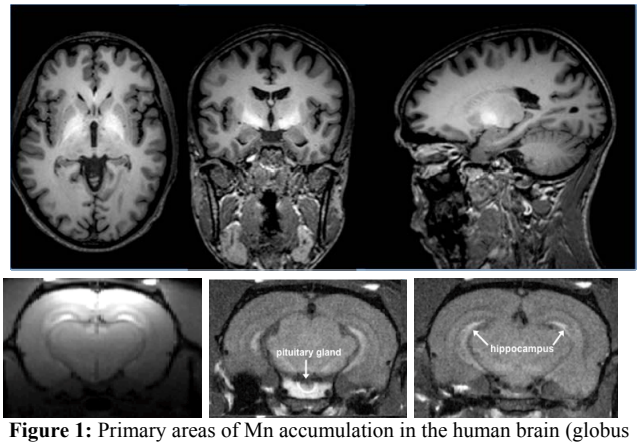

Figure 1: Primary areas of Mn accumulation in the human brain (globus pallidus) and the rat brain (hippocampus, pituitary gland) in chronic Mn exposure.

Results

In agreement with literature T1 hyperintensities in the human brain typical of Mn accumulation were most prevalent in the globus pallidus – contrary to the rat brain, where the hippocampus is the area showing highest T1 hyperintensities following chronic Mn exposure (Figure 1). In the human brain, further areas of high Mn accumulation are the subthalamic nucleus, pineal stalk and cerebral peduncle (including frontopontine and cerebrospinal fibers of the corticospinal tract and the substantia nigra) (Figure 2). In cases of high Mn accumulation additional signal changes in red nucleus, pituitary gland and olfactory bulb were found. Both smelters and welders had significantly reduced T1 relaxation times in the GP compared to controls ($p = 0.007$ and $p < 0.0001$, respectively), and a significant difference was also found between welders and smelters ($p=0.0006$). More interestingly, the T1 relaxation values were reduced as a function of years of exposure in the welders ($R=0.935$, $p<0.01$), but did not correlate in the group of smelters, which had much longer duration of exposure on average.

For the pallidal indices, only PImu found a significant difference between the smelters and the control group ($p<0.05$), whereas PIwm did not ($p=0.2$). In the welders both PI's could detect a highly significant group difference ($p<0.005$). Equally, both PI's found a group difference between welders and smelters (PIwm: $p < 0.0001$, PImu: $p = 0.016$).

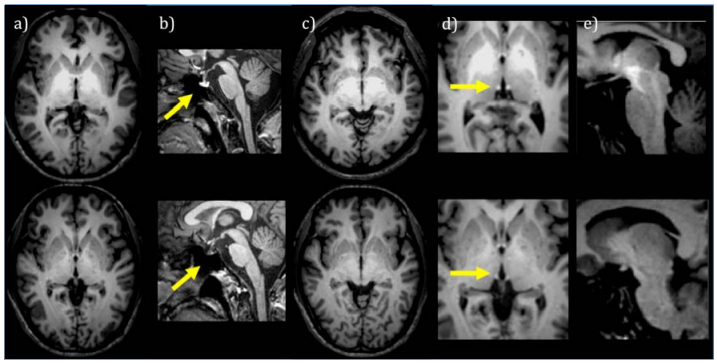

Figure 2: Differences in T1 shortening indicative of Mn accumulation are shown for Mn exposed smelters (top row) versus non-exposed controls (bottom row) for the following brain areas: a) globus pallidus and part of the thalamus, b) pituitary gland, c) subthalamic nucleus, d) pineal stalk, e) medial cerebral peduncle.

Discussion

Several brain areas beside the globus pallidus may accumulate Mn due to occupational exposure. The fact that only PImu but not PIwm could distinguish between the smelting and control group is a further indication that Mn accumulates throughout the brain, including in frontal white matter, as suggested previously [5]. While several brain areas found to prominently accumulate Mn in rodents, such as the pituitary gland, are also found to accumulate Mn in the human brain, there are severe differences in the distribution of Mn throughout the brain between humans and rodents. For example hippocampus is not found to show high T1 signal in humans. These differences need to be taken into account when evaluating the adequacy of animal models to study effects of chronic Mn exposure.

References:

[1] Lee J.H. et al., Magn Reson Med 53:6400648(2005); [2] Nelson et al., Br J Ind Med 50:510-513(1993); [3] Jiang et al., Neurotoxicology 28:126-135(2007); [4] Krieger et al., Lancet 346:270-274(1995); [5] Guilarte et al., J Neurochem 105:1948-1959 (2008)

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