

Motor and Cognitive Processing Networks show increased Manganese Accumulation in Metal Workers

Chien-Lin Yeh^{1,2}, Elizabeth Zauber³, Sandy Snyder¹, Zaiyang Long^{1,2}, and Ulrike Dydak^{1,2}

¹School of Health Sciences, Purdue University, West Lafayette, Indiana, United States, ²Dept. of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, Indiana, United States, ³Dept. of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, United States

Introduction

Although Manganese (Mn) is essential for brain metabolism, excessive exposure to Mn in occupational settings such as in welding can lead to cognitive and motor deficits [1,2]. Several MRI studies have shown increased Mn accumulation in the basal ganglia of exposed subjects by using intensity changes of T1-weighted images caused by the paramagnetic properties of Mn [3]. Studies on Mn-exposed non-human primates manifested a more widespread accumulation of Mn in white matter and cortex [4], while neurobehavioral exams also revealed a cortical dysfunction, including impaired short-term memory, computational ability and visuospatial learning ability both in Mn-exposed workers [5,6] and non-human primates [7]. However, no systematic and quantitative analysis of Mn accumulation in cortical brain areas has been performed *in vivo* to date. In this study, we used 3D whole-brain T1 mapping as an inverse indicator of Mn deposition in deep brain structures and the cerebral cortex in US welders with typical occupational exposure to Mn.

Methods

Twenty-four welders from a truck-trailer manufacturer (years of welding: 15 ± 8.5 yrs) and nine healthy controls have been analyzed to date. Subjects underwent an MRI exam performed on a 3 T GE Signa MR scanner. The imaging protocol included a 3D high-resolution T1-weighted sequence (FSPGR, TR/TE: 6.26/2.67 ms, resolution: $0.9 \times 0.9 \times 1 \text{ mm}^3$). T1 mapping was achieved using a 3D spoiled gradient echo sequence with two echoes (SPGR, TR/TE: 6.36/1.76 ms, flip angles: $3^\circ, 17^\circ$, resolution: $1 \times 1 \times 2 \text{ mm}^3$). An inversion recovery sequence (IR-SPGR, TI: 250ms) with the same parameters as the T1 map was used to correct the inhomogeneity of the RF field [8]. All images were coregistered and normalized to the Montreal Neurological Institute template (MNI-152 template) in SPM8. T1 maps were calculated using in-house software in Matlab using the approach described in [9]. To compare the control and welder groups, a nonparametric Kruskal-Wallis test was conducted pixel by pixel.

Results and Discussion

A wide-spread accumulation of Mn can be discerned in Figure 1. Outside the basal ganglia, the whole-brain T1 maps show significantly lower T1 values, indicative of higher Mn concentration, in the superior frontal gyrus and inferior parietal gyrus in the welder group (all $p < 0.05$), which is consistent with the neurobiological study of cellular degeneration in the frontal cortex [9]. Mn deposition in the supplementary motor cortex, primary motor cortex and somatosensory cortex points toward an effect of Mn deposition on the motor regulation network. High Mn concentrations ($p < 0.05$) were also found in superior primary visual cortex (V1), secondary visual cortex (V3-V5), superior parietal cortex and inferior temporal lobe, all belonging to visual association areas. An especially significant difference was found in the precuneus ($p < 0.01$), an area engaged in visuospatial function [10]. These findings suggest increased Mn accumulation in the motor regulation and visuospatial network, which may be related to reported impaired neurobehavior as a result of Mn exposure [6]. The statistically higher Mn accumulation in insula ($p < 0.01$), which contributes to hand and eye motor control and cognitive function would equally explain impairment of these domains due to Mn [11].

Conclusion

Our quantitative T1 map reveals significant Mn deposition in the cerebral cortex of welders. Mn accumulation in the frontal cortex, motor cortex, insula and the visuospatial pathway is consistent with the described neuropsychological impairments in non-human primates and welders [5-7], suggesting that the location of Mn accumulation affects the function of the corresponding brain networks.

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Reference: [1] Schneider et al. *Brain Research* 1118:222-31(2006) [2] Guilarte et al. *Environ Health Perspect* 118:1071-80(2010) [3] Zheng et al. *NMR Biomed.* 17:544-53 (2004) [4] Guilarte et al. *Toxicol. Sci.* 94:351-8(2006) [5] Josephs et al. *Neurol.* 64:2033-9(2005) [6] Bowler et al. *Occup Environ Med* 64:167-77(2007) [7] Schneider et al. *Toxicol. Letters* 221:146-51(2013) [8] Deoni et al. *jMRI* 26:1106-11(2007) [9] Sabati et al. *MRI* 31:1752-9(2013) [10] Cavanna et al. *Brain* 129:564-83(2006) [11] Menon et al. *Brain Struct Funct* 214:665-7(2010)

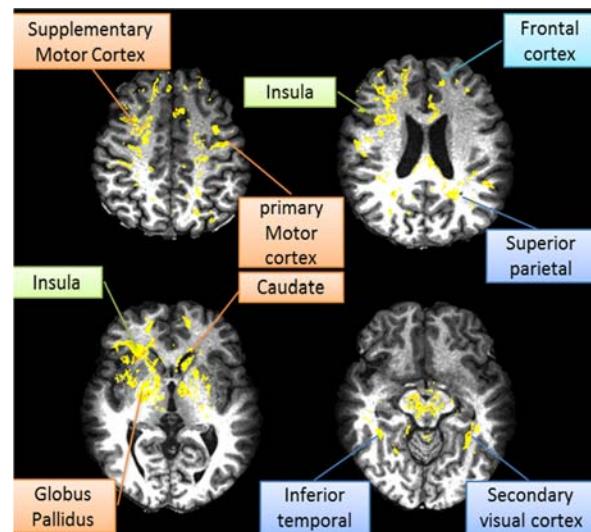


Figure 1: T1-difference maps (significant reduction of T1, $p < 0.05$) overlaid on corresponding T1-weighted images of a welder's brains. Areas showing Mn accumulation include the motor network (orange), the visuospatial network (blue), as well as other cortical regions such as insula (green), and superior frontal cortex (cyan).