Manganese Accumulations in Brain and Toenails reflect Different Time Periods of Exposure

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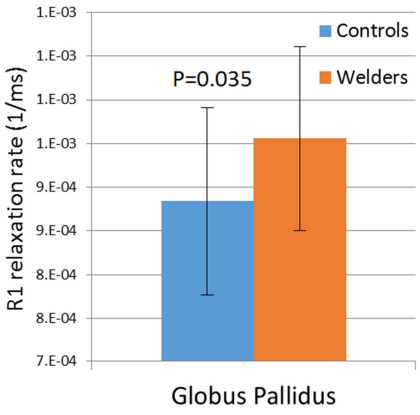
Target Audience: Neuroscientists and clinicians with interest in environmental causes of parkinsonism and neurotoxicity.

Purpose: It is well established that high exposure to manganese (Mn) causes motor impairments closely resembling Parkinson's disease[1]. Excess Mn accumulation in the brain furthermore induces deficits in fronto-executive function and causes emotional disturbances[2]. Due to the paramagnetic property of Mn, R1 relaxation rate mapping in MRI is used to indicate *in vivo* Mn accumulation in the brain of exposed subjects[3]. In this study, we investigated the relationship between Mn deposition in the brain as given by the R1 relaxation rate, with Mn accumulation in toenails, a reliable biomarker of Mn exposure that correlates with Mn exposure at 6-12 months prior to nail clipping[4] in welders occupationally exposed to Mn.

Method: MRI scans using a 3T GE Signa scanner were conducted on 31 welders and 19 non-exposed controls recruited from a U.S. truck-trailer manufacturer. Toenails were clipped at the time of the MRI exam and metal content was measured by ICP-MS. Individual Mn exposure was estimated with a model combining work histories and personal air sampling. Acquired MR images included a 3D high-resolution T1-weighted sequence (FSPGR, TR/TE: 6.26/2.67 ms, resolution: 0.9x0.9x1 mm^3) and R1 mapping using a 3D spoiled gradient echo sequence with two echoes (SPGR, TR/TE: 6.36/1.76 ms, flip angles: 3°, 17°, resolution: 1x1x2 mm^3). The R1 relaxation rate was calculated as described in Sabati et al[5]. To obtain regional R1 relaxation rates, 6 brain regions (including inferior frontal cortex, motor cortex, putamen, thalamus, hippocampus, and globus pallidus) were extracted by automatic parcellation by SPM (Wellcome Trust, UCL). The mean R1 values of these regions were then correlated with toenail Mn as well as Mn exposure integrated over different time periods by using an age-corrected Spearman correlation.

Results: A significant ($p<0.05$) increase in R1 relaxation rate in welders compared to controls was found in the inferior frontal cortex, the motor cortex, and the structures in the basal ganglia. Toenail Mn was also significantly increased in welders ($p<0.001$). In welders, a correlation between Mn exposure in the past 3 months and R1 relaxation rate in welders was found in the inferior frontal cortex ($r=0.53$, $p=0.006$) (figure 2) and in the motor cortex ($r=0.44$, $p=0.02$). Toenail Mn significantly correlates with exposure 7-12 months ago ($p<0.0001$), but not with exposure in the past 3 months. No correlation was found between toenail Mn and R1.



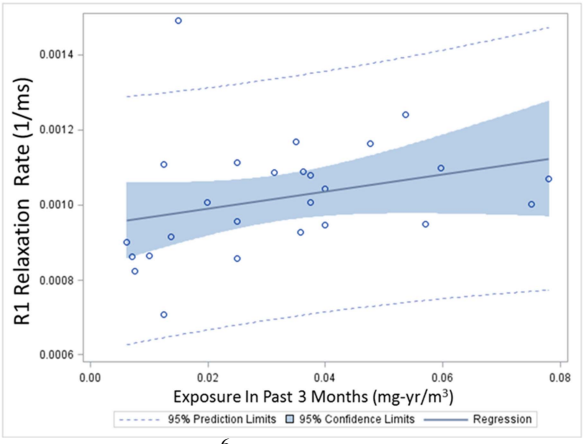


Figure1(left). The increased R1 relaxation rate in the globus pallidus of welders compared to controls ($p=0.035$) indicates increased Mn accumulation in this area. **Figure2**(right). R1 relaxation rate at the inferior frontal cortex is correlated with Mn exposure during past three months (Spearmen correlation, $R=0.53$, $p=0.0064$).

Discussion: Significant Mn accumulation in the basal ganglia, frontal cortex and motor cortex concur with early symptoms of Mn neurotoxicity such as reduced response speed, compulsive behavior, and irritability[6]. While both the Mn burden in brain and toe nails is clearly increased in welders, the lack of correlation between the two can be explained by the fact that the R1 rate best reflects exposure over the past three months, agreeing with a wash-out time of brain Mn of ~6 months[7], while toenails reflect exposure 6-12 months ago due to the growth rate of the nails.

Conclusion: These results show that while R1 in certain brain regions and toenail Mn may both serve as biomarkers of exposure to Mn, they reflect different time periods of exposure.

Reference: 1.Klos et al.(2006) E.J.Neurol.13:1139-41. 2.Schneider et al.(2006) Brain Research 1118:222-31. 3. Yeh et al. (2014) 22nd Annual Meeting of ISMRM. P.2831. 4. Sriram, et al. (2012) toxicology, 291:73-82. 5. Sabati et al. (2013) MRI 31:1752-9 6.Mergler and Baldwin at el.(1997) Envir Res.,73:92-100. 7. Nelson et al. (1993) British Industrial Med.50:510-513.