

Occupational Manganese Exposure Levels Correlate with Brain GABA Levels

Ulrike Dydak^{1,2}, Eric J Ward³, Ruoyun Ma¹, Sandy Snyder¹, Elizabeth Zauber⁴, James B Murdoch⁵, Zaiyang Long¹, and Frank Rosenthal¹

¹School of Health Sciences, Purdue University, West Lafayette, IN, United States, ²Dept. of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, United States, ³School of Health Sciences, Purdue University, West Lafayette, IN, United States, ⁴Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, United States, ⁵Toshiba Medical Research Institute USA, Mayfield Village, OH, United States

Purpose: While the metal manganese (Mn) is essential for brain function as a trace element, high exposure to Mn is known to be neurotoxic and may lead to cognitive and motor dysfunction^[1]. Occupational exposure limits have recently been reduced to 0.02 mg/m³ (ACGIH TLV value, USA), but compliance with such low levels of exposure is particularly challenging for the welding profession. To better assess biological and toxic effects in low-exposure settings, a neuroimaging study is being conducted on a cohort of typically exposed welders in the US. Based on findings of elevated thalamic γ -aminobutyric acid (GABA) levels in highly exposed smelters in China^[2], this study explores the relationship between brain GABA levels and individual exposure levels.

Methods: To date 24 male welders from a US truck trailer manufacturer (13 from the “south plant” and 11 from the “north plant”) and 11 male controls from the same factory but not exposed to Mn fumes have been included in the analysis. Personal air sampling was conducted during working shifts. A detailed work history as well as dietary information was assessed to properly model individual cumulative exposure to Mn. The exposure model included modifying factors such as ventilation and use of personal protective equipment as described in [3]. Each subject underwent an MRI and MRS scan (3 T GE Signa scanner, 8-channel head coil). GABA spectra were acquired using the MEGA-PRESS sequence^[4,5] (TR/TE = 2000ms / 68ms, 256 averages) from a volume centered on the thalamus (25×30×25mm³) and quantified using LCModel V6.3-1B^[6] with a basis set generated by density matrix simulation^[2]. GABA levels are reported as ratios to total creatine (tCr) to minimize partial volume effects. Statistical analysis was performed using two-sided student t-tests for group differences and Spearman partial correlations controlled for age using SAS 9.3.

Results: Cumulative exposure values were significantly higher for south plant welders than for north plant welders, driven by different operations in the south vs. the north plant and the respective percentage of welding time during the work shift (Fig. 1a). Several cumulative exposure time windows (past month, past 3 months, past year, lifetime) were assessed for each subject. Cumulative exposure over the past 3 months correlated the strongest with thalamic GABA/tCr levels ($R = 0.64$, $p=0.001$) (Fig. 1c). The lower exposure level of the north plant welders did not lead to changes in GABA/tCr, whereas the 2-fold higher exposure in the south plant led to a significant increase of GABA/tCr (Fig. 1b).

Discussion and Conclusion: Our findings confirm that Mn exposure in an occupational setting affects brain GABA levels. Moreover, the data indicates that GABA seems to be a biomarker of *recent* exposure (past 3 months), rather than lifelong cumulative Mn exposure. Following this cohort of workers over the next few years with continued exposure assessments, neuroimaging and neuropsychological testing will further elucidate the connection between Mn exposure and brain GABA levels, and demonstrate how brain GABA levels affect cognitive and motor skills.

References: [1] Guilarte TR. Environ Health Perspect. 2010 Aug;118(8):1071-80; [2] Dydak U et al. Env. Health Persp. 2011; 119: 219-24; [3] Hobson A et al. Annals of occupational hygiene 2011; 55(1), 113-125. [4] Mescher M et al. 1998. NMR Biomed 11(6):266-272; [5] Edden RA, Barker PB. 2007. Magn Reson Med 58(6):1276-1282; [6] Provencher SW. 1993. Magn Reson Med 30(6):672-679. **Acknowledgement:** The authors acknowledge financial support by NIEHS R01 ES020529 and CDC/NIOSH T03 OH008615.

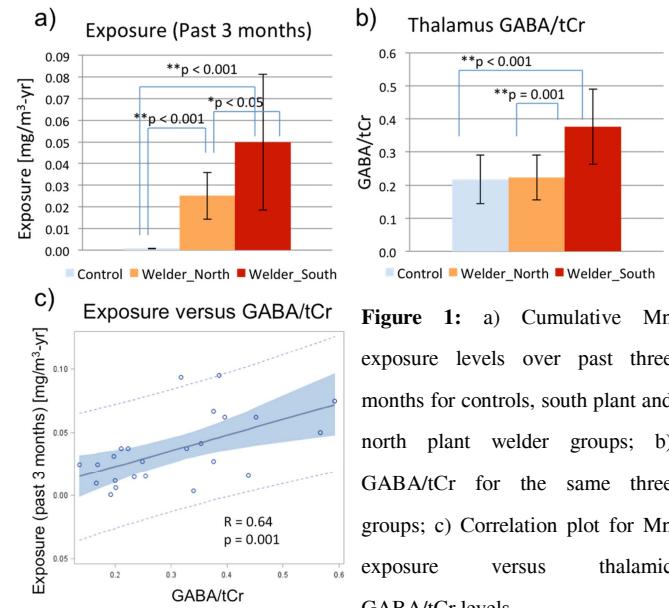


Figure 1: a) Cumulative Mn exposure levels over past three months for controls, south plant and north plant welder groups; b) GABA/tCr for the same three groups; c) Correlation plot for Mn exposure versus thalamic GABA/tCr levels.