Increased Thalamic GABA and Decreased Glutamate-Glutamine in Chronic Manganese-exposed Metal Workers and Manganism Patients

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Purpose: Overexposure to manganese (Mn) is known to be neurotoxic and may lead to parkinsonian symptoms, such as bradykinesia and postural tremor[1], referred to as manganism. Yet the underlying mechanism of Mn neurotoxicity is not well understood and early detection is needed. Given the hypokinetic characteristics of the motor deficits, this study aimed to test the hypothesis that in addition to T1-hyperintensities found in the brain due to Mn accumulation, thalamus γ-aminobutyric acid (GABA) is increased and cortical glutamate is decreased in asymptomatic Mn-exposed metal workers and manganism patients.

Methods: 20 Mn-exposed welders, 19 Mn-exposed smelters, 37 age- and gender-matched controls with no history of Mn exposure, and 7 diagnosed manganism patients were recruited from China. Magnetic resonance imaging and spectroscopy (MRI/MRS) scans were performed on a 3T Philips Achieva scanner equipped with an eight-channel head coil. Short-TE ^{1}H spectra (TR/TE=1500ms/30ms) were acquired from a volume of interest (VOI) in the frontal cortex (8 ml), as well as from a second VOI (22.5 ml) that was centered on the thalamus but also contained portions of the adjacent basal ganglia structures (Fig 1). In addition, a GABA-edited proton spectrum was acquired from the thalamus VOI using a MEGA-PRESS J-editing sequence (TR/TE=2000 ms/68 ms with 256 averages)[2-3]. Resulting GABA levels are referred to as GABA+ due to contributions from co-edited macromolecules at 3.0 ppm and homocarnosine. MRS data processing and quantification were performed with LCModel[4], and metabolite concentrations were expressed as a ratio of metabolite to total creatine (tCr). In addition, a series of T1-weighted inversion recovery images were used to calculate T1 values in the globus pallidus of the four groups.

Results: While asymptomatic, both smelters and welders had significantly decreased T1 values in the globus pallidus, indicating Mn accumulation ($p<0.01$, Fig 1). Smelters, welders and manganism patients all showed significantly increased thalamus GABA+/tCr compared to controls ($p<0.01$). Smelters had significantly decreased levels of frontal Glu/tCr and Glu+Gln (expressed as Glx)/tCr (both $p<0.05$), as well as thalamic Glu/tCr and Glx/tCr (both $p<0.01$). Welders only had significantly decreased Glu/tCr and Glx/tCr in the thalamus ($p<0.05$). In addition, manganism patients showed a tendency towards decreased frontal Glu/tCr ($p=0.08$).

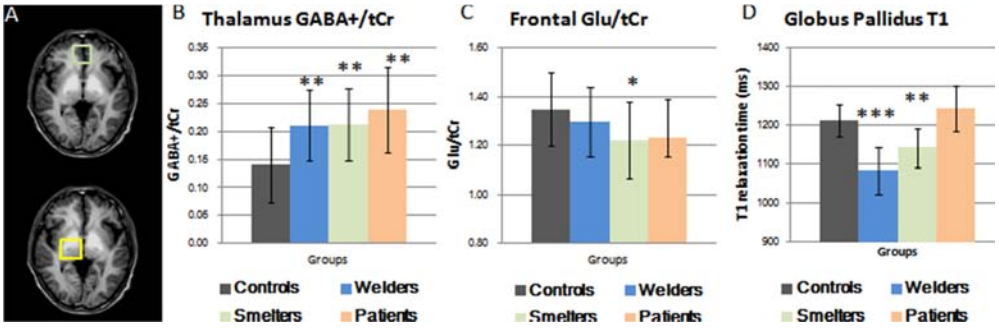

Figure 1: Volumes of interest for thalamus and frontal cortex and means and standard deviations of thalamus GABA+/tCr, frontal Glu/tCr, and globus pallidus T1 in welders, smelters, manganism patients and controls. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Discussion: Our findings of increased thalamic GABA in Mn-exposed workers and manganism patients, as well as decreased Glu and Glx in the frontal cortex of smelters, are consistent with both an earlier study in only 10 smelters [5] and the hypokinetic motor deficits associated with Mn exposure. These metabolic changes may aid in understanding the mechanism of Mn-induced motor and cognitive deficits. Together with the evidence of Mn accumulation in the brain, they also may serve as early markers of Mn neurotoxicity.

References: [1] Guilarte TR. Environ Health Perspect. 2010 Aug;118(8):1071-80; [2] Mescher M et al.1998. NMR Biomed 11(6):266-272; [3] Edden RA, Barker PB. 2007. Magn Reson Med 58(6):1276-1282; [4] Provencher SW. 1993. Magn Reson Med 30(6):672-679. [5] Dydak U et al. Env. Health Persp. 2011;119:219-24. **Acknowledgement**: The authors acknowledge financial support by NIH/NIEHS R21 ES-017498 and National Science Foundation of China Grant #81072320.