GABA level correlates with occupational manganese exposure and motor tests in smelters

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Introduction: Overexposure to manganese (Mn) can lead to parkinson-type motor symptoms, for which no treatment exists to date [1]. Elevated gamma-aminobutyric acid (GABA) has been reported in the basal ganglia/thalamus area of asymptomatic, occupationally exposed smelters [2]. Since elevated GABA levels in basal ganglia are known to be involved in movement disorders [3] and recently also have been reported in Parkinson Disease [4], we hypothesize that GABA may serve as a presymptomatic biomarker of the neurotoxic effects of manganese exposure. The present, ongoing study is thus designed to explore the relationship between occupational Mn exposure, changes in brain GABA levels measured by magnetic resonance spectroscopy (MRS), and motor deficits indicated by the Purdue Pegboard test.

Materials and Methods: To date nine male Mn-exposed smelters and ten matched controls were recruited from a Mn-Fe alloy factory in China. MRS scans were performed on a 3T Philips Achieva whole-body clinical scanner (Philips Healthcare, Best, the Netherlands), equipped with an eight-channel head coil. GABA-edited spectra as well as short-echo-time (TE) ^{1}H spectra (TR/TE=1500ms/30ms) were acquired from a volume of interest (VOI) in the posterior cingulate cortex (PCC) (26.2 ml) and a VOI centered on thalamus (22.5 ml), but also containing portions of the globus pallidus, putamen and other basal ganglia structures ("GABA VOI") (Fig 1). MEGA-PRESS J-editing [5,6] was used for GABA detection (TR/TE=2000 ms/68 ms, 256 averages). The result is 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 [7], using basis sets generated from density matrix simulations, and using total creatine (tCr) as internal reference. Each subject also completed the Purdue Pegboard test (Lafayette Instrument, Indiana, USA) to assess manual dexterity and steadiness.

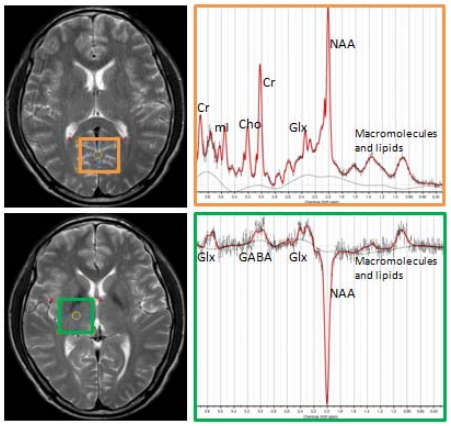

Figure 1: Volumes of interest for two brain regions and representative spectra with LCModel fitting for each region: posterior cingulate cortex (PCC) with a corresponding short-TE spectrum and the "GABA VOI" with a MEGA-PRESS difference spectrum.

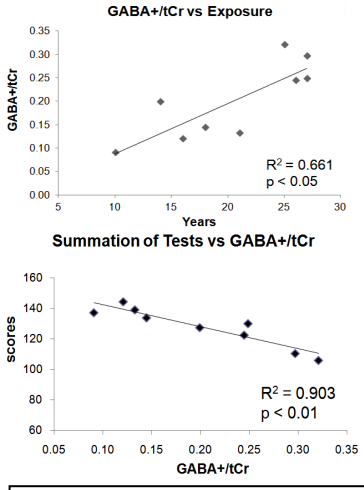

Figure 2: Correlation plots of GABA+/tCr in the thalamus versus years of Mn exposure and with the summation of all Purdue Pegboard test scores for the Mn-exposed smelters.

Results: Multiple regression analysis revealed (1) a significant correlation between the increase in GABA+/tCr level and the duration of exposure (R^2 = 0.661, $p < 0.05$)(Fig 2) and (2) significant inverse correlations between GABA+/tCr level and all Purdue pegboard test scores. At the group level a non-significant increase of 17% ($p = 0.37$) in GABA+/tCr level was detected in smelters compared to controls.

Discussion: Our results revealed a significant correlation between motor deficits and increasing thalamic GABA+ level, suggesting that altered GABA+ status may underlie the mechanism of motor deficits in smelters. GABA+ may function as a biomarker of Mn-induced toxic effects, in particular of motor deficits.

References: [1] Guilarte TR. 2010. Environ Health Perspect 118(8):1071-80; [2] Dydak U et al. 2011. Environ Health Perspect 119(2):219-24; [3] Galvan A, Wichmann T. 2007. Prog Brain Res 160:287-312; [4] Emir U, Tuite PJ, Oz G. 2012. Plos One 7(1); [5]Mescher M et al. 1998. NMR Biomed 11(6):266-272; [6] Edden RA, Barker PB. 2007. Magn Reson Med 58(6):1276-1282; [7] Provencher SW. 1993. Magn Reson Med 30(6):672-679; **Acknowledgement**: The authors acknowledge financial support by NIH/NIEHS R21 ES-017498**;**