Manganese Induced Changes In Thalamic GABA Levels Influence Cognitive and Motor Performance

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Purpose: Chronic occupational exposure to Manganese (Mn) may lead to cognitive and motor disorders, progressing to symptoms similar to Parkinson disease[1,2]. Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter, has been reported to be elevated in the thalamus of Mn-exposed workers[3]. Since GABA and the associated functioning of fronto-striatal loops have strong modulatory effects on cognitive processes including action control,[4] we investigated the connection between thalamic GABA levels measured by magnetic resonance spectroscopy (MRS) and cognitive and motor function in typical US metal workers.

Methods: 26 welders and 11 controls were recruited from a US truck trailer manufacturer. MRI/MRS data were acquired on a 3T GE Signa scanner equipped with an 8 channel head coil. The GABA volume of interest (VOI) was centered on the thalamic region (25×30×25mm^3) (Fig. 1). GABA spectra were acquired using the MEGA-PRESS sequence[5] (TR=2000ms, TE=68ms, 256 averages) and quantified using LCModel V6.3-1B[6], with a basis set generated by density matrix simulation and GABA coupling constants from Kaiser et al[7]. Response time (RT) as measured in Simon[8] and Flanker[9] tasks, which has been observed to be impaired in Parkinson patients[10], was used to represent aspects comprising attention, response inhibition and processing of spatial information. These tasks are based on manipulations of spatial stimulus-response (S-R) compatibility to measure different aspects of action control and have been conducted on 11 welders and 11 controls. Comprehensive motor performance was examined by Part III (motor part) of the Unified Parkinson's Disease Rating Scale (UPDRS-III)[11] administrated by a neurologist. Higher UPDRS scores indicate greater motor disabilities, with values up to 15 belonging in the normal range. Statistical analysis of the data was performed using SAS 9.3. Group differences characterized by student t-tests and Spearman partial correlations controlled for age were examined.

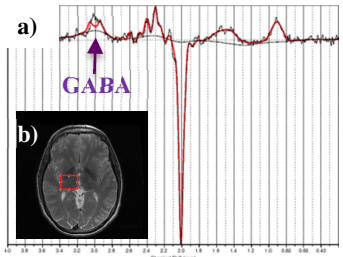

Figure 1. a) GABA edited spectrum fitted with LCModel b) Axial view of GABA VOI

Results: Similar to a study conducted in China[3], thalamic GABA levels were significantly elevated for welders compared to controls (0.30± 0.12 vs. 0.22 ± 0.07, p<0.05). Significant correlations between GABA/tCr levels, UPDRS-III scores and all RTs were found in the welder group (Fig. 2). Spearman partial correlation coefficients R and p-values are shown in Table 1. No correlations were found in controls. The mean total UPDRS-III score of welders was only slightly higher than that of controls (7.04±5.4 vs. 4.64±2.29, p=0.17). RTs in all trials in the two cognitive tests were generally longer in welders than in controls, but the differences were not significant.

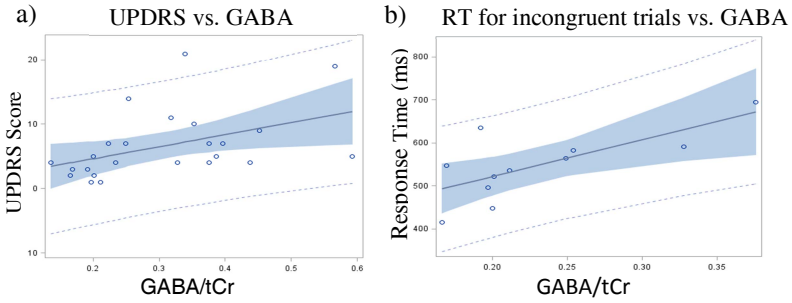

Figure 2. a) Correlations between UPDRS and GABA/tCr. b) Response time (RT) for incongruent trials in Simon task versus GABA/tCr.

Table 1. Spearman partial correlations controlled for age for GABA with UPDRS and cognitive tests

	R	p-value
UPDRS	0.560	0.01
RT Correct (*Flanker*)	0.702	0.02
Simon task:		
RT Parallel Hands	0.709	0.02
RT Crossed Hands	0.726	0.02
RT Congruent	0.798	0.01
RT Incongruent	0.697	0.02

Congruent / Incongruent trials refer to the trials with the stimulus and responding hand on the same / different side(s)

Conclusion: The elevation of thalamic GABA levels may be a marker of neurotoxic effects due to Mn exposure. In particular, the positive correlation between thalamic GABA levels and motor UPDRS score suggests an effect of Mn on the motor system, while the correlation between behavioral measures of action control and inhibition and GABA may indicate an effect of Mn on cognition in exposed subjects. While these results are preliminary, they suggest that thalamic GABA levels may serve as early biomarker for motor and cognitive changes in welders. Since high Mn exposure can cause permanent neurological disorders resembling Parkinson's disease, early detection of Mn neurotoxicity may have significant occupational health implications.

Acknowledgement: The authors acknowledge financial support by NIEHS R01 ES020529**.**

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