factory and university controls, indicating significant co-exposure of non-welding factory workers. For motor function, the t-test analysis further found that UPDRS results of university controls (mean 1.9±1.6) were significantly lower than both the factory control group (mean 5.1 ± 3.9) and welders (mean = 6.8±4.4). No significant difference was found between groups in GABA or Glx within the ACC. However, ACC GSH was found to be reduced both in welders ($p = 0.02$) and factory controls ($p = 0.07$) compared to university controls. Correlation analysis revealed a significant negative relationship between UPDRS and GSH levels across all subjects ($R = -0.4$, $p = 0.0035$), suggesting that decreased GSH in the ACC is associated with worsened motor performance. No significant correlations were found between Mn levels and UPDRS ($R = 0.05$, $p = 0.75$), Mn and GSH ($R = 0.13$, $p = 0.35$), or Fe and GSH ($R = 0.05$, $p = 0.75$). **Conclusions:** Decreased levels of the antioxidant GSH have been validated as a marker of increased oxidative stress[3]. Thus, the results of this study reveal the presence of oxidative stress in Mn exposed subjects, even among factory controls. Air sampling data suggests that these factory control subjects are likely co-exposed to welding fumes due to working within the same large factory hall. Additionally, the reduction in GSH levels correlates with a higher score on the Unified Parkinson's Disease Rating Scale (UPDRS), indicating decreased motor function in subjects with greater exposure to Manganese, in line with results by Racette et al.[4]. The effects of the very small exposure of factory controls are striking, but it must be noted that factory controls and welders share other stress factors like shift work and dust exposures, that may contribute to their differences from university controls. In the next step the relation between ACC metabolism and cognitive function will be investigated. **References:**
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3809 Cerebellar Alterations in Glutathione (GSH) and Motor Variations in Welders Exposed to Manganese

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Background and Purpose: Manganese (Mn) is an essential trace mineral vital for human metabolism, particularly within the central nervous system (CNS), where it functions as a cofactor for various enzymes. However, excessive occupational Mn exposure can lead to neurotoxic effects, resulting in cognitive, psychiatric, and motor impairments resembling Parkinsonian symptoms and, in severe cases, progressing to Manganism. While the cerebellum's role in motor control is well-known, its involvement in Mn toxicity in humans remains underexplored. Previous animal and cell studies, as well as our prior research in welders, indicate that Mn overexposure disrupts GABAergic and glutamatergic transmissions within basal ganglia pathways. Decreased GSH concentrations, an indicator of oxidative stress, are critical for mitigating damage from reactive oxygen species. This study investigates the impact of Mn accumulation on motor and metabolic disruptions in the cerebellum, employing Magnetic Resonance Spectroscopy (MRS) to measure neurotransmitter levels and markers of oxidative stress. **Methods:** We studied 37 steel welders exposed to manganese (Mn) through inhalation of welding fumes (mean air Mn = 200.51 ± 227.1 mg/m^3), alongside two control groups: non-welding factory workers (N = 29, mean air Mn = 7.43 ± 9.49 mg/m^3) and university controls (N = 12, mean air Mn = 0.075 ± 0.06 mg/m^3). Each participant underwent magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) on a 3T Siemens MAGNETOM Prisma to non-invasively quantify brain metabolites and neurotransmitters. Cerebellar glutathione (GSH) and gamma-aminobutyric acid (GABA) levels were measured using HERMES editing (TE/TR = 80 ms/2000 ms; 256 averages). The volume of interest (VOI: 35x25x25 mm^3) was positioned in the right cerebellar lobe, and non-water-suppressed reference spectra were acquired for each sequence.Spectra were aligned, pre-processed with Osprey, and quantified with LCModel using simulated basis sets for sLASER and HERMES, respectively. Metabolite concentrations were water-referenced and CSF-corrected. Outliers were excluded based on LCModel SD% > 50 or poor spectral quality upon visual inspection. Participants completed a battery of motor and cognitive tests, with this abstract focusing specifically on the Unified Parkinson Disease Rating Scale (UPDRS) Part III to assess motor function. UPDRS-III subscores were calculated for rigidity and tremor.Each participant's Cumulative Exposure Index (CEI) was calculated based on recent Mn exposure over the last 3 months, using personal air sampling from a work shift and work history data. Participants were categorized into high (HEX) and low (LEX) exposure groups, with HEX (N = 12) defined as greater than 0.04 mg/m^3/yr and LEX (N = 25) below this level. Differences in metabolite and motor outcomes across groups were assessed using a two-tailed, unequal variance t-test, and associations between cerebellar metabolites and motor scores were examined with the Spearman correlation coefficient (R). **Results:** Cerebellar glutathione (GSH) levels were significantly reduced ($p < 0.001$) in high exposure welders (HEX, mean = 0.81 ± 0.6 mM) compared to low-exposure welders (LEX, mean = 1.49 ± 0.4 mM), with no significant group differences found between LEX, factory controls (FC, mean = 1.49 ± 0.7 mM) and university controls (UC, mean = 1.59 ± 0.6 mM). , Additionally, there was a negative correlation between CEI Mn levels and GSH levels ($R = -0.32$, $p = 0.017$) amongst welders.Cerebellar GABA levels were lowest in UC, slightly higher in FC, peaked in LEX welders (mean = 1.71 ± 0.4 mM), but then decreased again in HEX welders (mean = 1.51 ± 0.5 mM), with a significant difference between HEX and LEX welders ($p<0.01$), while differences to FC and UC groups were not statistically significant after multiple comparison corrections.Motor impairment, as assessed by UPDRS-III scores, displayed an exposure-response trend, with the highest scores (indicating worse performance) observed in HEX (11 ± 4.6), followed by LEX (5.18 ± 3.05), FC (4.93 ± 3.6), and the lowest in UC (1.92 ± 1.6). Significant differences were found between LEX and UC ($p < 0.001$), HEX and UC ($p < 0.001$), and even factory controls (FC) performed significantly worse than university controls (UC) ($p < 0.01$). The rigidity and tremor subscores of UPDRS-III showed a similar exposure-related pattern, with the HEX group scoring the worst among all groups ($p \leq 0.001$). Both LEX and FC groups performed similarly but still showed significantly worse results compared to UC ($p < 0.01$ for rigidity and $p = 0.1$ for tremor severity). For welders, all three motor test scores correlated positively with UPDRS, with correlations as follows: UPDRS ($R = 0.39$, $p = 0.00045$), Rigidity ($R = 0.35$, $p = 0.0018$), and Tremor ($R = 0.23$, $p = 0.042$). **Conclusions:** Cerebellar GSH levels, an indicator of antioxidant capacity, were significantly reduced in high-exposure welders (HEX) compared to other groups, suggesting increased oxidative stress in the cerebellum associated with Mn exposure. The observed negative correlation between Mn levels and GSH further supports this association.This study highlights the neurotoxic impact of occupational Mn exposure on motor function and cerebellar metabolism. The observed correlations between Mn levels and both motor symptoms and metabolic disruptions provide insights into the underlying mechanisms of Mn neurotoxicity. These findings support the need for enhanced protective measures in occupational settings. Interestingly, GABA levels exhibited a non-linear pattern, with the highest levels observed in low-exposure welders (LEX). This increase in GABA among LEX welders may reflect an adaptive, protective response to moderate Mn exposure, potentially helping to regulate calcium levels and prevent oxidative damage. However, at the higher exposure levels seen in HEX welders, this protective system may become overwhelmed, leading to mitochondrial dysfunction, impaired calcium regulation, and ultimately lower GABA levels as the system fails to compensate for the increased oxidative stress.The exposure-response trend in motor impairment, as measured by UPDRS-III scores and its subscores for rigidity and tremor, aligns with previous literature on the dose-response relationship between Mn exposure and motor function. A limitation of this study is the small sample size of the UC group. Future studies will follow welders longitudinally, especially at the beginning of exposure or after cessation, to gain insight into the temporal changes in cerebellar GABA and GSH, their reversibility, and their relation to motor function. **Acknowledgements:** Funded by F31ES035299 (HM), R01ES020529 (UD), R01ES032478 (UD), International Manganese Institute (UD) and NIOSH (CGL).

3810 Imaging of Mn washout in the individual welder brain after wearing powered air-purifying respirators (PAPRs)

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Background and Purpose: Chronic exposure to welding fumes increases manganese (Mn) deposition in the brain, leading to adverse neurobehavioral health effects. Since the signs of metal-induced toxicity are neurological, understanding the spatio-temporal dynamics of accumulated Mn in the human brain is essential. To date, no data exist on the spatial distribution of Mn accumulation in the individual brains of welders, nor has the washout of Mn been measured in the human brain following cessation of exposure. Due to Mn's paramagnetic properties, magnetic resonance imaging (MRI) is the only imaging modality capable of non-invasive, in-vivo assessment of Mn accumulation. Specifically, the longitudinal relaxation time (T1) decreases with increased Mn deposition in the brain. While hyperintensities in T1-weighted MRI images are typically visible only in cases of severe exposure, this study developed a whole-brain Mn-mapping approach to detect subtle but significant increases in Mn deposition in individual welders compared to a normative map from non-welding factory controls. This method enables the first investigation of the spatio-temporal dynamics of brain Mn deposition in response to changes in occupational exposure. In this pilot study, changes in brain Mn accumulation were monitored before and after welders began using powered air-purifying respirators (PAPRs), which significantly reduce exposure to airborne metal particle levels. **Methods:** As part of a larger imaging study on welders, four welders who had recently started using a PAPR and 31 non-welding factory controls were recruited from a U.S. truck manufacturer. All participants provided written informed consent to participate in the study. Personal air sampling was conducted over one work shift to measure respirable Mn concentrations in each subject's breathing zone. MRI scans were performed once for controls and twice for welders — one prior to and the other 1-2 months after initiating PAPR use. Whole-brain T1 relaxometry maps were acquired using a 3T Siemens Prisma MRI. A normative T1 atlas was created by modeling the relaxation time variability within the control cohort using a linear regression model that accounted for the impact of age at each voxel position. Individual z-score maps were then calculated against this atlas to quantify deviations specific to each subject. A threshold of z-scores < -6 and a minimum cluster size of 100 voxels was applied to reduce false positives. The total number of voxels exceeding the threshold was determined, and whole-brain z-score maps, indicating individual Mn deposition, were visualized to assess brain changes before and after PAPR use among welders. **Results:** Respirable Mn concentrations in welders' breathing zones, sampled outside of PAPRs, ranged from 63-321 µg/m^3, compared to the controls' mean Mn concentrations of 0.005 µg/m^3. The total number of thresholded voxels, indicating above-average Mn deposition, decreased by over 60% in 3 of the 4 welders after using the PAPR, with no significant changes observed in one welder. For the 3 welders with significant changes, z-score maps acquired before PAPR use showed widespread significant z-scores of reduced T1 values com-

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