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:**1. Dydak U, et al. Environ Health Perspect. 2011;119(2):219-224. 2. Ma R, et al. Neurotoxicology. 2018;64:30-42.3. Zitka O, et al. Oncol Rep. 2012;28(4).4. Racette BA, et al. NeuroToxicology 2012;33:1356-1361.

PS 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/m³), alongside two control groups: non-welding factory workers (N = 29, mean air Mn = 7.43 ± 9.49 mg/m³) and university controls (N = 12, mean air Mn = 0.075 ± 0.06 mg/m³). 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 mm³) 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/m³/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).

PS 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/m³, compared to the controls' mean Mn concentrations of 0.005 µg/m³. 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-

pared to the control cohort, indicating excess Mn accumulation throughout much of the cerebral white matter and deep brain structures. However, the maps acquired two months after PAPR use showed a significant decrease in elevated Mn deposition. Specifically, Mn accumulation was visibly reduced in the bilateral globus pallidus, thalamus, and several white matter tracts, with minimal reduction observed in the brainstem. **Conclusions:** Mn accumulation significantly decreased in welders in several brain regions within just 1-2 months of using a PAPR, with varying reduction rates observed across brain regions. Upon investigating the one welder who did not show much change, it was found that he welds only part-time and wears the PAPR exclusively during welding. However, his workstation is located adjacent to a welding robot, leading to co-exposure even when he is not welding, which may explain the lack of observed changes. Future work will include a one-year follow-up of these four welders and an increase in the sample size. Overall, this study provides the first insight into the spatio-temporal dynamics of brain Mn washout in humans following reduced Mn exposure and highlights the impact of PAPR use. **Acknowledgements:** Funded by F31ES035299 (HM), R01ES020529 (UD), R01ES032478 (UD), International Manganese Institute (UD) and NIOSH (CGL).

3811 Cognitive impairment of welders and non-welding factory workers compared to non-factory controls: Manganese is not the full story

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Background and Purpose: Welders are occupationally exposed to manganese (Mn) via welding fumes. At high levels of exposure to Mn—such as in individuals working in Mn alloy plants, welding in enclosed spaces and living near open-air Mn storage— there are well-documented neurological consequences, including deficits in verbal learning, memory, and fine motor skills. However, most studies to date have compared individuals exposed to Mn to groups which are not well matched demographically (for example, comparing factory workers to university employees). The current study sought to directly investigate how welders exposed to Mn performed on tests of neuropsychological function relative to a well-matched group of factory workers employed at the same factory but who do not weld, as well as to a university control group **Methods:** 34 Welders (3 females; mean age=40.44±11.16) and 24 non-welding factory-worker controls e.g. assembly workers (8 females; mean age=42.96±12.19) were recruited from a nearby truck manufacturer; 10 non-factory worker controls were recruited from the university community (5 females; mean age=43.09±10.36). Cumulative exposure to Mn was modeled using each participant's work history and personal air sampling inside the welding hood over one work shift. Participants completed a comprehensive neuropsychological battery and a life-history questionnaire in conjunction with personalized air sampling in order to estimate their lifetime exposure to Mn. Groups were compared using one-way Analysis of Variance (ANOVA) and controlled for multiple comparisons using Tukey's Honestly Significant Difference (HSD) test. **Results:** There was a significant difference in lifetime exposure to Mn between groups ($F_{2,65}$=5.619, p=0.006, η^2=0.147), and this was driven by welder's significantly greater lifetime exposure to Mn (mean= 1.145 (mg/m³)*yr) relative to factory controls (mean=0.124 (mg/m³)*yr; p=0.015) and to university controls (mean=0.001 (mg/m³)*yr; p=0.035). Participants were age and sex frequency matched between the welder and non-welder factory workers, but the university control group had a significantly higher percentage of females than the other two groups. With regard to neuropsychological functioning, groups exhibited significant differences in performance on a test of processing speed (NIH toolbox pattern comparison: $F_{2,60}$=3.561, p=0.035, η^2=0.106), episodic memory (NIH toolbox picture sequence memory: $F_{2,60}$=15.119, p<0.001, η^2=0.335), nonverbal reasoning (PMAT: $F_{2,65}$=6.607, p=0.002, η^2=0.169), verbal fluency (Animal naming: $F_{2,65}$=4.282, p=0.018, η^2=0.116), verbal acquisition (HVLT total recall: $F_{2,64}$=6.850, p=.002, η^2=0.176), verbal learning (HVLT delayed recall: $F_{2,64}$=3.491, p=0.036, η^2=0.098), fine motor dexterity (Grooved Pegboard dominant hand: F2,61=3.758, p=0.029, η^2=0.110; non-dominant hand: F2,62=5.380, p=0.007, η^2=0.148), and paranoid ideation (BSI: F2,65=3.310, p=0.043, η^2=0.092). These differences were in all cases driven by worse performance or worse symptoms among welders relative to university controls, but there were no observed differences between the welders and the well-matched factory worker control group. **Conclusions:** The welders in this study demonstrated significant deficits in several neuropsychological domains (processing speed, episodic memory, nonverbal reasoning, verbal fluency, verbal acquisition, verbal learning, fine motor dexterity, and symptoms of paranoid ideation) relative to controls recruited from the university community. The non-welding factory-worker controls exhibited no difference in these domains relative to the welders. This suggests the observed deficits in functioning are likely due to factors other than Mn neurotoxicity, such as shift work, exposure to non-Mn particulate matter, socio-economic status, etc. Limitations of this study are the small sample size of the university control group, which was not originally designed to serve as the control group. Furthermore, sex differences will need to be investigated in the future. The results of this study are of particular interest given the extant literature that has largely interpreted neuropsychological differences between welders or other metal workers and controls recruited from white-collar environments as being directly attributable to Mn exposure. **Acknowledgements:** Funded by F31ES035299 (HM), R01ES020529 (UD), R01ES032478 (UD), International Manganese Institute (UD) and NIOSH (CGL).

3812 Increased expression of Slc30a10 in dopaminergic or glutamatergic neurons protects against manganese-induced motor deficits in mice

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Background and Purpose: Manganese (Mn) is an essential micronutrient, but in excess, it is neurotoxic. Under conditions of over-exposure, Mn builds up in the basal ganglia of the brain and induces motor deficits. SLC30A10 is a specific Mn efflux transporter that is required for Mn excretion at the whole-organism level and regulates brain Mn levels under physiological conditions. We previously showed that loss of SLC30A10 in the brain leads to elevated Mn levels in the basal ganglia, lifelong motor deficits, and impaired evoked dopamine release. Previous studies also revealed that selective loss of SLC30A10 in dopaminergic or glutamatergic, but not GABAergic, neurons leads to early-life motor deficits. These findings show that the activity of SLC30A10 in dopaminergic or glutamatergic neurons is required to protect against Mn toxicity and suggest that Mn targets dopaminergic and glutamatergic, but not GABAergic, neurons of the basal ganglia. **Methods:** To determine the neuronal targets of Mn, we have developed dopaminergic-, GABAergic-, or glutamatergic-specific Slc30a10 knockin mice. These mouse models allow us to selectively increase Slc30a10 expression in dopaminergic, GABAergic, or glutamatergic neurons, with the expectation that Mn levels in the targeted neurons will be attenuated after Mn exposure. Knockin mice and control littermates received Mn or vehicle treatment from birth and were run through various behavioral assays at early-life time-points. **Results:** Results have shown that both GABAergic-specific Slc30a10 knockin mice and control littermates develop early-life Mn-induced motor deficits. Importantly, both dopaminergic-specific and glutamatergic-specific Slc30a10 knockin mice are protected from early-life Mn-induced motor deficits after exposure compared to control littermates. **Conclusions:** These findings corroborate the hypothesis that Mn targets dopaminergic and glutamatergic neurons of the basal ganglia to induce motor disease in early-life.

3813 Loss of Function of Manganese Efflux Transporter SLC30A10 in Dopaminergic or Glutamatergic Neurons Induces Early-life Motor Dysfunction

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Background and Purpose: Manganese (Mn) is a trace metal that is fundamental for various physiological processes and must be maintained within an optimal window. Exposure to excess Mn is neurotoxic, leading to accumulation in the basal ganglia of the brain and inducing an incurable disease known as Mn-induced neurotoxicity. Recent work has shown increased susceptibility of early life individuals (newborns, infants, and adolescents) to environmental sources of exposure, i.e., contaminated water sources, with around 2.6 million people in the United States exposed to groundwater sources with elevated Mn levels above current EPA health guidelines (0.3 mg/L). Further, early life exposure to Mn leads to lasting impairments in fine and gross motor function, postural balance, and cognitive deficits. Despite this, current understanding of the mechanism and cellular target of this disease is lacking. **Methods:** To address this, we generated cell-specific knockouts for SLC30A10, the critical Mn efflux transporter, to selectively alter Mn levels in the main neuronal populations found in the basal ganglia: dopaminergic, GABAergic, or glutamatergic neurons. **Results:** Validation studies show decreased expression of *Slc30a10* mRNA and, in tested strains, increased Mn levels in targeted basal ganglia nuclei of neuron-specific *Slc30a10* knockouts when compared to littermate controls. At PND 28, dopaminergic-, but not GABAergic-, specific *Slc30a10* knockouts display sensorimotor deficits in the form of missteps on the beam balance test. At PND 56, dopaminergic- or glutamatergic-specific, but not GABAergic-specific, *Slc30a10* knockouts display deficits in locomotion using the open field test. Despite the neuromotor phenotype, *in vivo* microdialysis and no-net-flux microdialysis, sampling from the dorsal striatum, revealed that baseline and stimulated extracellular dopamine concentrations of dopaminergic-specific *Slc30a10* knockouts were comparable to controls. **Conclusions:** Thus, (1) expression of *Slc30a10* in dopaminergic or glutamatergic neuronsis required to protect against Mn-induced motor dysfunction; (2) Mn likely targets dopaminergic and glutamatergic neurons to induce neurological disease and (3) the role of dopamine homeostasis in the disease biology remains unclear.

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