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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