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Manganese body burden in children is associated with reduced visual motor and attention skills

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Abstract

Manganese (Mn) is an essential element, however, children with moderate to high Mn exposure can exhibit neurobehavioral impairments. One way Mn appears to affect brain function is through altering dopaminergic systems involved with motor and cognitive control including frontal – striatal brain systems. Based on the risk for motor and attention problems, we evaluated neurobehavioral function in 255 children at risk for Mn exposure due to living in proximity to coal ash storage sites. Proton Induced X-ray Emissions (PIXE) analysis was conducted on finger and toenails samples. Multiple neuropsychological tests were completed with the children. Fifty-five children had Mn concentrations above the limit of detection (LOD) (median concentration = 3.95 ppm). Children with detectable Mn concentrations had reduced visual motor skills ($\beta = -5.62$, CI: −9.11, −2.12, p=0.008) and more problems with sustained attention, based on incorrect responses on a computerized attention test, ($\beta = 0.40$, CI: 0.21, 0.59, $p<0.001$) compared with children who had Mn concentrations below the LOD. Findings suggest that Mn exposure impacts attention and motor control possibly due to neurotoxicity involving basal ganglia and forebrain regions. Visual-motor and attention tests may provide a sensitive measure of Mn neurotoxicity, useful for evaluating the effects of exposure in children and leading to better treatment options.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords

manganese exposure; children's neurobehavioral problems; attention; visual motor skills; children's environmental health; neurotoxicity

1. Introduction

Manganese is an essential trace metal that is required for normal brain development and function (Keen et.al, 1999). Although nutritional Mn deficiency is rare due to its availability in food, mutations in a Mn transporter gene (SCA39A8) have been shown to lead to brain atrophy due to deficient Mn (Park et al., 2015). Of greater concern for brain function, however, is Mn excess which can lead to neurotoxicity. Children with chronic air- and water-borne exposures have been found to have lower scores on intelligence tests (Bouchard et al, 2007; Bouchard et al., 2011; Haynes et al., 2015; Haynes; 2018; Henn et al., 2017; Kim et al., 2009; Menezes-Filho et al., 2011; Wasserman et al., 2006) and reduced academic achievement (Khan et al., 2012). Increased Mn exposure has been shown in some studies to impact fine motor skills (Lucchini et al., 2012) and postural stability (Rugless et al., 2014). Some evidence suggests an association of Mn exposure with ADHD (Shin et al., 2015) and attention problems (Carvalho, et al., 2014). Both internalizing and externalizing behavior problems have also been shown to be related to Mn exposure (Khan et al., 2011). Although evidence for Mn childhood neurotoxicity is noted in a number of studies, results across studies are inconsistent possibly because of differences in exposure measures, age of the child, and outcome measure used (Coetzee et al., 2016).

The neurotoxic effects of Mn on dopaminergic systems in the brain appear to involve brainstem and forebrain interactions. Brain imaging studies in adults with occupational exposure to Mn have found reduced volume of the globus pallidus and cerebellum correlated with cognitive and motor impairments (Chang et al., 2013). Similar findings were seen in a study of the basal ganglia in children (Lao et al., 2017) indicating a potential brain site involved in Mn toxicity (Tuschl et al., 2013). The basal ganglia are involved in cognitive and motor processes in the brain and could account for the symptoms seen in children. Emotional and behavioral differences could also be explained through disruption in frontal striatal circuits involving this dopaminergic pathway (Norman et al, 2016).

Children can be exposed to manganese through drinking water, air pollution, or by living near ferromanganese refineries or metal recycling facilities. Another potential source of Mn exposure to children is living near coal ash storage sites that contain byproducts from coal-burning power plants, including fly ash. Fly ash, is mainly comprised of iron, aluminum, silicon, oxygen, and calcium. However, trace levels of heavy metals such as chromium, mercury, and Mn are found within the fly ash particles. (Bednar et al., 2013, Bhangare et al., 2011, Popovic et al., 2001, Zierold & Odoh, 2020). Fly ash particles can range in size including small particles that can enter the bloodstream and cross the blood brain barrier. We identified detectable levels of Mn in toenails and fingernails of children aged 6–14 years living in proximity to coal ash storage sites. The levels detected are above levels appearing to be neurotoxic based on previous studies using toenails as biomarkers of

exposure (Ntihabose et al., 2018, Rodrigues et al., 2018). The overall purpose of this study was to assess the implications of Mn levels (body burden) in children as related to child motor and attention problems. Based on evidence of neurobehavioral differences related to Mn exposure involving dopaminergic systems (Beaudin et al., 2013), we hypothesized that children with Mn body burden will display impair motor skills and attention.

2. Materials and Methods

2.1 Participants

Children, aged 6 to 14 years and living within ten miles of coal ash storage sites in Jefferson County, Kentucky, were recruited for the study through flyers mailed to parents or by foot recruiting in neighborhoods (Odoh et al., 2019; Zierold et al., 2020). Following the invitation to participate, parents contacted the study investigators and appointments were arranged to enroll children and a parent who met the inclusion criteria that included living in the study area for at least 2 years. Exclusion criteria included history of traumatic brain injury, a genetic disorder impacting development, lack of proficiency in English, or an inability to complete neurobehavioral testing. A total of 255 participants were enrolled in the study (Table 1). Participants were tested in their home following informed consent. The study was approved by the University of Louisville Institutional Review Board (IRB#14.1069).

2.2 Manganese Analysis

Mn body burden was assessed through analysis of the children's toenails and fingernails. Goulle et al. (2009) reported that concentrations of manganese in toenails and fingernails as determined from ICP-MS did not differ. Were et al. (2009) reported that differences in metal(loid) concentrations between fingernails and toenails were minimal compared to urban/rural concentration differences. Participants collected nails over several weeks until 150 mg were obtained. After complete collection, samples were triple cleaned with acetone and deionized water and sent to a laboratory for Proton Induced X-ray Emission Spectroscopy (PIXE). The procedure is capable of simultaneously identifying levels of 72 inorganic elements making it useful for studies of children with potential multiple exposures and where concentrations are unknown. (Odoh et.al. 2019).

2.3 Neurobehavioral Measures.

To assess children's neuropsychological function, a trained clinical psychologist conducted a series of six tests. Two tests were completed at a table with the child, while four additional tests were completed using the Behavior Assessment Research System. All tests were conducted in the participant's home.

1. Beery VMI. Participants were first administered the Beery-Buktenica Developmental Test of Visual Motor Integration (VMI) (Beery and Beery, 2004). The VMI presents children with geometric forms that are copied and scored based on standards for correct design reproduction. A total raw score is obtained that is converted to a standard score (mean=100, SD=15) based on age norms derived from a standardization sample. The test is widely used as a measure of

visual motor copying skills. Each child's standard score from the VMI was used as an outcome measure.

2. Purdue Pegboard. Following completion of the VMI, participants were administered the Purdue Pegboard using standard procedures for testing of the dominant, non-dominant, and bimanual hand performance (Tiffin and Asher, 1948). For this task, children place pegs in holes as rapidly as possible with a raw score obtained based on the number of pegs placed in 30 seconds providing a measure of fine motor speed and dexterity. The total pegs placed with the dominant and non-dominant hand were used for subsequent analyses

Behavior Assessment Research System (BARS).—The BARS is a computerized assessment of memory, sustained attention, processing speed, visual memory, and associative learning. Stimuli are presented on a laptop connected to a 9-button response keypad used for response measurement for all of the tests. BARS tests were selected based on previous research on use of the test to identify environmental exposures (Rohlman et al., 2001; Rohlman et al., 2003; Sears et al., 2020).

3. The BARS Finger Tapping (FT) test measures finger tapping speed for the dominant and nondominant hand. The child is told to place the palm of the hand on the 9-button keypad and press a key as rapidly as possible for 30 seconds. A tap score is obtained for each hand that is summed to obtain a total tapping raw score.

4. The BARS Continuous Performance Test (CPT) is a measure of attention, response inhibition, and processing speed. The CPT requires the child to press a key for a target stimulus presented on the computer screen and ignore a nontarget stimulus. The time to press a button following presentation of a target circle and the accuracy in discriminating target and nontarget stimuli are recorded. Response latency provides a measure of processing speed based on the time to respond to a target in milliseconds. Omission and commission errors occur with a missed button press to a target or a key press response to a nontarget, respectively. The variable d'prime is calculated based on the ability to discriminate targets from nontargets using signal detection theory (Rohlman et al., 2001). For testing, 300 trials were administered with 20% being targets requiring a button press. Stimuli were presented for 0.05 seconds with 1 second between trials. CPT outcome measures in this study were response latency, omission errors (misses), commission errors (false alarms), and d'prime.

5. The BARS Selective Attention Test (SAT) requires the child to press a key with either the right or left hand depending on the location of a dot on the computer screen. Correct responses are recorded as a proportion correct variable while wrong count indicates an incorrect key press to the stimulus. Omit count indicates a lack of response to a target stimulus. Processing speed is measured in milliseconds and indicates the response latency for a correct key press. The SAT included 30 trials with equal presentations to each side and 80% being targets requiring a button press reflecting which box contained the dot.

The interstimulus interval was titrated from 0.1 to 5 msec based on response accuracy. The response latency, proportion correct, wrong count, and omit count were used for subsequent analyses.

6. The BARS Serial Reaction Test (SRT) involves presentation of a target on the computer screen cueing the child to press a key as quickly as possible. For this task, response time was recorded in milliseconds to assess processing speed. A total of 50 trials were administered with a variable interstimulus interval averaging 3 seconds with a minimum of one second.

2.4 Statistical Analyses

The concentration of Mn in parts per million (ppm) was determined for each participant. A total of 201 participants were below the PIXE limit of detection (LOD) (Median = 1.65 ppm, Q1, Q3 = 1.37, 1.89). Since a level of Mn body burden was not available for each participant, the Mn level was categorized into below (Mn Below LOD group) or above LOD (Mn Detected group) for each participant. The Wilcoxon or chi-square test was used to compare participant's self-identified age, sex, race, and maternal education of children with Mn below and above LOD. We used generalized linear model regression to assess the relationship of Mn with each of the neurobehavioral measures. We identified covariates using directed acyclic graphs (DAGs) and adjusted models for participant's self-identified race, age, sex, mother's education, and smoking in the home. (Supplemental Figure 1). Negative binomial regression was used to examine the association between Mn and count outcomes (CPT False Alarms, CPT Misses, SAT Wrong Count, and SAT Omit Count respectively). Some outcomes were transformed to better fit distributions, as indicated by the Box-Cox transformation. The SRT average correct latency was modeled with its reciprocal. SAT Percent Correct was transformed into SAT Total Errors for negative binomial regression modelling; the error count is the sum of SAT Wrong Count and SAT Omit Count. Quantile regression was used to model CPT d'prime and SAT Average Latency, as they did not fit normal distributions after transformations. The p-values from the models were adjusted based on the false discovery rate (FDR) due to control for multiple comparisons (Benjamini & Hochberg, 1995). An FDR adjected p-value ≤0.05 was considered statistically significant (Supplementary Table 1).

3. Results

3.1 Description of Study Population

A total of 54 children had Mn concentrations above the LOD, while 201 had levels below the LOD. The 54 subjects with detected Mn had a median level of 3.95 ppm (Q1, Q3 = 3.40, 5.50). Differences in demographics between the groups are shown in Table 1. Children with detected Mn body burden were more likely to be younger ($p<0.001$) and white ($p=0.03$) compared with children who had Mn below the LOD. There were no differences in sex or maternal education between Mn groups.

3.2 Mn Group Differences

Table 2 displays mean scores and standard deviation for neurobehavioral measures by manganese group. Median, quartiles, minimum and maximum are also provided.

Table 3 displays the estimates of Mn group from generalized linear models adjusted for age, self-identified race, sex, mother's education, and smoking in the household. The type of distribution is specified in Table 3. Children with Mn above the LOD had lower Beery VMI scores compared with children who had values below the LOD, indicating reduced visual motor skills ($p=0.008$). In adjusted models, children with Mn above the LOD also had a higher number of CPT omission errors (CPT Misses, $p=0.03$) and poorer signal detection (CPT d'prime, $p=0.05$), indicating reduced sustained attention, compared with children who had Mn below the LOD. Similar weaknesses were seen among children with Mn values above the LOD on the SAT with increased errors noted in Total Incorrect ($p<0.001$), Omit Count ($p=0.004$), and Wrong Count ($p=0.01$). Table 4 provides rate ratios for the results of the binomial models. All but CPT-False Alarms had significant rate ratios. In particular, children with Mn above the LOD had approximately 1.50 times (95% CI: 1.24, 1.81) the rate of SAT Total Incorrect responses compared with children who had values below the LOD.

No group differences were seen in fine motor speed and dexterity as noted by pegboard and finger tapping tasks. There were also no differences in processing speed on the CPT, SAT, or SRT. Mn body burden did not appear to impact fine motor or processing speed at this level of exposure.

4. Discussion

This study compared neurobehavioral performance in children aged 6 to 14 years based on Mn body burden using tests sensitive to attention and motor control likely to be altered in dopaminergic systems affected by Mn. Our results indicated that, at higher levels of Mn in nails, there is no effect on fine motor speed and dexterity. However, more complex visual motor skills were impaired. Another area of deficit was in sustained attention as measured by omission errors on continuous performance and selective attention tests. Response latency did not differ between groups indicating that processing speed was not affected by Mn.

Findings of impaired visual motor skills are consistent with a previous study looking at Mn exposure assessed through hair samples (Hernandez-Bonilla et al., 2016). Effects on visual motor skills may involve widespread regions of the brain. The visual motor copying task relies on cortical and basal ganglia connections in addition to cerebellar and brainstem areas (Sripada et al., 2015). The lack of effect on fine motor speed and dexterity suggests that primary motor pathways were not impacted at this level of exposure, however, with a more complex task requiring visual motor integration, modest levels of Mn can disrupt visual motor skills, likely through effects on basal ganglia and cortical areas involved in integrating visual input with motor output. While high levels of Mn body burden can produce significant motor impairment, neurotoxic effects of lower levels of exposure may be detected in tasks assessing more complex visual motor skills. Tasks such as the Beery

VMI may provide a more sensitive measure of neurotoxicity related to moderate levels of Mn overexposure.

Differences in attention control related to Mn exposure have been observed in children with Mn exposure using hair as a biomarker (Oulhote et al., 2015) and in animal models (Beaudin et al., 2017). Attention control is thought to involve frontal-striatal brain pathways (Norman et al., 2016) that are altered by Mn neurotoxicity (Lin et al., 2020). The use of attention to assess neurotoxic effects has the advantage of potentially being more sensitive to moderate effects of Mn overexposure compared to other measures that have been used such as IQ from intelligence tests.

Limitations of this study include the large number of subjects below the level of detection limiting the ability to analyze effects of lower levels of Mn body burden that have been shown to have an adverse effect in a study of infants and children (Vollet et al., 2016). Furthermore, exposure to other neurotoxic metals found in fly ash particles may be correlated with Mn and also contribute to the neurobehavioral outcomes. However, there are a variety of Mn exposure sources, and we did not find strong correlations between Mn concentrations and several other neurotoxic metals (copper, chromium, nickel, zinc) that are found in coal ash. We were unable to determine the effect of two well-studied neurotoxins, lead and arsenic, as these metal(loid)s were not detected in the children's nails. Although PIXE is a good analytical method for unknown elements and unknown concentrations, the limits of detection are higher than other analytical methods (Zierold et al., 2021). This study occurred among children living near coal ash storage sites, but the burden of manganese in the nails may reflect other sources, such as manganese in drinking water or additional air exposures that were not accounted for. Additionally, the effects of Mn exposure likely differ by age, and the effects of chronic exposure may increase neurotoxic effects compared with acute exposures. Also, since this study is cross-sectional, it is difficult to determine effects related to timing of exposure. An additional limitation is the difficulty in comparing findings across studies of Mn exposure due to differences in outcome measures and biomarkers used for estimating neurotoxic effects. Despite the range of findings in the current literature (Vollet et al., 2016) the current study aligns with observations from an animal model of Mn exposure showing effects of Mn body burden on dopaminergic systems involving attention and motor control. The neurobehavioral observations and plausible model for studying Mn neurotoxicity make the results of this study relevant for understanding neurotoxicity and for developing potential treatments (Beaudin et al., 2017).

5. Conclusions

In this study, children with increased Mn body burden displayed reduced visual motor skills and problems with attention. The findings of this study correspond to observed neurotoxic effects of Mn in dopaminergic systems involving the basal ganglia and frontal lobe regions underlying motor control and cognition. Modest impairments in attention and visual motor control as seen in this study could have adverse effects on learning and behavior especially in children with other risk factors for neurodevelopmental problems. Greater attention to environmental Mn exposures appears warranted based on results of this and other studies and a larger concern about the potential for long-term neurocognitive effects with lifelong

exposures. Future research may benefit from a focus on neuropsychological measures sensitive to neurotoxic effects in the dopaminergic system to produce consistency in studies and enhance the potential for developing treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Manganese (Mn) was identified in children living near coal-fired power plants.
- Neuropsychological function was assessed with fine motor and attention tests.
- Body burden of Mn was measured by Proton-Induced X-ray Emissions analysis.
- Children with detectable Mn in nail samples had reduced visual motor skills.
- Children with Mn in nail samples had more problems with sustained attention.

Table 1.

Characteristics of Mn groups[a]

Demographics	Mn Below LOD (n = 201)	Mn Detected (n=54)	p-value
Age in Years (SD)	11.18 (2.42)	9.59 (2.48)	<0.001
Sex (%)			0.99
Female	97 (48.3%)	26 (48.2%)	
Male	104 (51.7%)	28 (51.9%)	
Race (%)			0.03
White	139 (69.9%)	44 (84.6%)	
Another Race	60 (30.2%)	8 (15.4%)	
Median Mn ppm (Q1, Q3)	N/A	3.95 (3.40, 5.50)	N/A
Education (%)			0.72
High School or Less	42 (21.7%)	11 (22.5%)	
Some College	68 (35.1%)	17 (34.7%)	
College	56 (28.9%)	11 (22.5%)	
Grad School	28 (14.4%)	10 (20.4%)	

[a]Age analyzed via Wilcoxon test. Sex and race analyzed via chi-square contingency tables.

Table 2.

Neurobehavioral outcome measures by Mn group.

Measure	Group			
	Below Mn LOD		Mn Detected	
	Mean (Std)	Median (Q1,Q3) [Min, Max]	Mean (Std)	Median (Q1,Q3) [Min, Max]
Beery VMI Standard Score	97.11 (11.30)	97 (90, 105) [61, 122]	92.22 (12.65)	96.5 (86, 100) [46, 110]
Pegboard Non-Dominant Raw Score	12.10 (1.87)	12(11, 13) [5, 17]	11.37 (1.93)	12 (10, 12) [7, 15]
Pegboard Dominant Hand Raw Score	13.15 (1.73)	13 (12, 14) [8, 17]	12.44 (1.98)	12 (11, 14) [7, 16]
FT - Total Taps	214.60 (32.70)	214.5 (189, 238) [131, 317]	198.63 (29.21)	198 (180, 217) [132, 263]
CPT – d'prime	3.79 (0.91)	3.91 (3.18, 4.49) [0.95, 5.24]	3.27 (1.05)	3.38 (2.78, 3.91) [0.92, 5.24]
CPT - Hit Latency (sec)	0.442 (0.073)	0.433 (0.385, 0.483) [0.315, .0671]	0.495 (0.075)	0.480 (0.438, 0.533) [0.374, 0.732]
CPT - False Alarms	3.61 (4.92)	2 (0, 4) [0, 33]	5.31 (6.52)	3 (2, 6) [0, 33]
CPT – Misses	7.30 (8.48)	4 (1, 11) [0, 44]	11.61 (12.41)	7 (4, 14) [0, 52]
SAT - Wrong Count	2.03 (1.52)	2 (1, 3) [0, 7]	3.00 (1.96)	3 (2, 4) [0, 8]
SAT - Omit Count	1.22 (1.59)	1 (0, 2) [0, 10]	2.24 (2.17)	2 (1, 3) [0, 10]
SAT - Average Correct Latency (sec)	0.369 (0.085)	0.349 (0.317, 0.413) [0.228, 0.695]	0.394 (0.092)	0.392 (0.317, 0.455) [0.240, 0.635]
SAT – Total Incorrect	3.24 (2.35)	3 (1, 5) [0, 12]	5.24 (2.83)	5 (4, 7) [0, 11]
SRT - Average Correct Latency (sec)	0.392 (0.084)	0.377 (0.333, 0.431) [0.273, 0.718]	0.452 (0.117)	0.412 (0.379, 0.515) [0.313, 1.031]

Table 3.

Mn group effect on fine motor and cognitive control adjusted for self-identified race, age, sex, mother's education, and smoking in household.[a]

Outcome Measure	Regression	Estimate	Standard Error	95% Confidence Limit	FDR Adjusted p-value
Beery VMI Standard Score	Linear	−5.62	1.78	(−9.11, −2.12)	0.008
Pegboard Non-Dominant Hand Raw Score	Robust Linear	−0.20	0.25	(−0.69, 0.29)	0.55
Pegboard Dominant Hand Raw Score	Robust Linear	−0.36	0.28	(−0.92, 0.20)	0.30
FT - Total Taps	Robust Linear	−1.48	3.29	(−7.95, 5.00)	0.77
CPT – d'prime	Robust Linear	−0.37	0.16	(−0.70, −0.05)	0.05
CPT - Hit Latency (sec)	Linear	0.016	0.008	(−0.000, 0.033)	0.09
CPT - False Alarms	Negative Binomial	0.06	0.16	(−0.27, 0.39)	0.79
CPT – Misses	Negative Binomial	0.45	0.18	(0.11, 0.81)	0.03
SAT - Wrong Count	Negative Binomial	0.29	0.10	(0.09, 0.49)	0.01
SAT - Omit Count	Negative Binomial	0.58	0.17	(0.24, 0.92)	0.004
SAT - Average Correct Latency (sec)	Robust Linear	−0.003	0.012	(−0.027, 0.021)	0.80
SAT – Total Incorrect	Negative Binomial	0.40	0.10	(0.21, 0.59)	<0.001
SRT - Average Correct Latency (sec)	Robust Linear	−0.11	0.06	(−0.23, 0.00)	0.11

[a]See directed acyclic graph shown as supplemental figure 1.

Table 4.

Rate ratios from negative binomial distributions

Outcome Measure	Estimate	Rate Ratio	95% CL	Adjusted p-value
CPT - False Alarms	0.06	1.06	0.76, 1.47	0.79
CPT - Misses	0.45	1.57	1.12, 2.24	0.03
SAT - Wrong Count	0.29	1.34	1.09, 1.64	0.02
SAT - Omit Count	0.58	1.78	1.27, 2.52	0.004
SAT - Total Incorrect	0.40	1.50	1.24, 1.81	<0.001