NeuroToxicology 49 (2015) 139–148

Contents lists available at ScienceDirect

NeuroToxicology

Environmental exposure to manganese in air: Associations with cognitive functions

Rosemarie M. Bowler [a,*], Erica S. Kornblith [b], Vihra V. Gocheva [a], Michelle A. Colledge [c], George Bollweg [d], Yangho Kim [e], Cheryl L. Beseler [f], Chris W. Wright [a], Shane W. Adams [a], Danelle T. Lobdell [g]

[a] San Francisco State University, Department of Psychology, 1600 Holloway Ave., San Francisco, CA 94132, USA
[b] California School of Professional Psychology at Alliant International University, 1 Beach St., Suite 100, San Francisco, CA 94133, USA
[c] Agency for Toxic Substances and Disease Registry, Region 5, 77W. Jackson Blvd., MS ATSD-4J, Chicago, IL 60604, USA
[d] U.S. EPA Region 5, 77W. Jackson Blvd., AR 18-J, Chicago, IL 60604, USA
[e] Ulsan University Hospital, University of Ulsan College of Medicine, Department of Occupational and Environmental Medicine, Ulsan 682-060, South Korea
[f] Colorado State University, 1879 Campus Delivery, Fort Collins, CO 80523, USA
[g] U.S. EPA, National Health and Environmental Effects Research Laboratory, MD 58A, Research Triangle Park, NC 27711, USA

ARTICLE INFO

Article history:
Received 7 April 2015
Received in revised form 12 June 2015
Accepted 12 June 2015
Available online 19 June 2015

Keywords:
Manganese
Neuropsychology
Cognitive function
Environmental
Air

ABSTRACT

Manganese (Mn), an essential element, can be neurotoxic in high doses. This cross-sectional study explored the cognitive function of adults residing in two towns (Marietta and East Liverpool, Ohio, USA) identified as having high levels of environmental airborne Mn from industrial sources.

Air-Mn site surface emissions method modeling for total suspended particulate (TSP) ranged from 0.03 to 1.61 $\mu g/m^3$ in Marietta and 0.01–6.32 $\mu g/m^3$ in East Liverpool. A comprehensive screening test battery of cognitive function, including the domains of abstract thinking, attention/concentration, executive function and memory was administered. The mean age of the participants was 56 years ($\pm$10.8 years). Participants were mostly female (59.1) and primarily white (94.6%). Significant relationships ($p < 0.05$) were found between Mn exposure and performance on working and visuospatial memory (e.g., Rey-O Immediate $\beta = -0.19$, Rey-O Delayed $\beta = -0.16$) and verbal skills (e.g., Similarities $\beta = -0.19$).

Using extensive cognitive testing and computer modeling of 10-plus years of measured air monitoring data, this study suggests that long-term environmental exposure to high levels of air-Mn, the exposure metric of this paper, may result in mild deficits of cognitive function in adult populations.

1. Introduction

1.1. Brief overview on manganese and environmental studies

Manganese (Mn) is an essential element for healthy human functioning, especially for bone health and fat and carbohydrate metabolism (Ehrlich, 2013). However, with overexposure, manganese may be neurotoxic to humans.

Manganese is a byproduct of some industrial processes and is released into the air, soil, and water. Environmental studies have most often included rural and suburban populations living close to industries (Bowler et al., 2011; Menezes-Filho et al., 2011; Mergler et al., 1999; Haynes et al., 2010; Lucchini et al., 2014; Viana et al., 2014), and rural populations exposed through contaminated well water (Khan et al., 2012; Wasserman et al., 2006).

The prominent pathophysiological manifestations of Mn inhalation overexposure in humans are encephalopathy and basal ganglia disturbance (Feldman, 1999). This condition clinically resembles Parkinson's Disease (PD), but responds poorly to dopaminergic medications and typically has an earlier onset of cognitive dysfunction than PD (Feldman, 1999).

The recent use of neuroimaging in studying the effects of Mn on the brain has demonstrated increased T_1 signal intensity (Kim et al., 1999, 2007; Kim, 2004; Shin et al., 2007; Chang et al., 2010a,b,c; Criswell et al., 2011). After high exposure to Mn, higher T_1-weighted signal intensities have been observed in the substantia nigra, globus pallidus, caudate nucleus, red nucleus, and the frontal lobes (Long et al., 2014; Chang et al., 2010c). These localized hyperintensities have been associated with mood, motor

* Corresponding author at: 8371 Kent Drive, El Cerrito, CA 94530, USA. Tel.: +1 510 236 5599; fax: +1 510 236 3370.
E-mail address: rbowl@sfsu.edu (R.M. Bowler).

http://dx.doi.org/10.1016/j.neuro.2015.06.004

and tremor disturbances, and also with cognitive deficits (Chang et al., 2010a,b; Long et al., 2014; Kim et al., 1999).

1.2. Published studies of Mn and cognitive effects

1.2.1. Cognitive effects in children using neuropsychological testing

The large majority of studies in the literature that focus on environmental Mn exposure and neuropsychological effects are in children (Wasserman et al., 2006, 2011; Wright et al., 2006; Kim et al., 2009; Riojas-Rodríguez et al., 2010; Bouchard et al., 2011; Menezes-Filho et al., 2011; Khan et al., 2012; Torres-Agustín et al., 2013; He et al., 1994; Lucchini et al., 2012; Haynes et al., 2010, 2012, 2015). These studies have reported decreased verbal, performance, and intellectual ability associated with level of Mn exposure using Mn in hair or blood as a biomarker. Two of these studies investigated the effect of environmental Mn exposure with co-exposure to lead (Pb) (Kim et al., 2009) and arsenic (As) (Wasserman et al., 2011) and found adverse effects on cognitive function from neurotoxicant exposure from air and water. The primary association was with Mn and As, but not Pb. Wright et al. (2006) and Torres-Agustín et al. (2013) reported negative associations between Mn exposure and scores on tests of verbal learning and memory. In a study of children living in a rural village using irrigation and drinking water with highMn content, children from the exposed village had lower scores on tests of attention and concentration, working memory, and visual memory compared to children living in an unexposed village (He et al., 1994). Recently, Haynes et al. (2015) reported associations between hair and blood Mn and both full scale and subscale IQ scores in children from the same Ohio towns as the current study. Because children's brains are developing, they may be more vulnerable than adults (Zoni and Lucchini, 2013).

1.2.2. Few environmental studies for adults using neuropsychological testing

Although Mn effects in exposed workers have been studied frequently with tests of motor function, including tremor, formal neuropsychological testing has been somewhat infrequent. In a sequence of studies of welders, deficits in attention and concentration, memory, visuospatial function, verbal learning, executive and other cognitive functions were reported, and a dose-effect relationship was found between cognitive function and Mn in blood (Bowler et al., 2007; Antunes et al., 2007; Park et al., 2006; Roels et al., 2012). In these occupational Mn exposure studies, where Mn is typically higher than in environmental settings, well-normed standardized tests were also used, including verbal and performance tests (Bowler and Lezak, 2015).

Environmental studies have examined the effects of exposure to Mn in adults by primarily evaluating motor function and tremor symptoms (Kim et al., 2011; Solís-Vivanco et al., 2009; Rodriquez-Agudelo et al., 2006; Baldwin et al., 1999; Beuter et al., 1999; Bowler et al., 1999; Mergler et al., 1999). Most of these studies did not assess cognitive function.

One of the early community studies examining environmental Mn exposures in Quebec (Mergler et al., 1999) used tests of cognitive function. An association between Mn exposure and verbal learning, as well as attention, was reported. Canadian women with higher Mn blood levels had lower scores on a test of visual memory and lower scores on recall of Digit Span forward. For men in the same sample, higher Mn blood levels were associated with poor initial learning and recall of both visual and verbal test scores.

Santos-Burgoa et al. (2001) conducted a pilot study of Mexican residents in two rural mining communities. Mn content in outdoor and indoor air, river water, well water, food, indoor dust, and blood was assessed. These authors assessed cognitive function and found that low-level cognitive function on the Mini Mental State Examination (MMSE) was associated with higher blood Mn levels. Also working in Mexico, Solis-Vivanco et al. (2009) used Digit Span recall and reported an association between Mn levels and poor performance on these tests, including a negative association between Mn levels in air at a participant's residence and Digit Span recall. Menezes-Filho et al. (2011) conducted a study of mothers and children in Brazil and found that Mn in hair was negatively associated with the scores on Raven's Progressive Matrices, a measure of nonverbal cognitive ability and abstract reasoning (Raven and Court, 1995), among mothers exposed to Mn in the environment from a ferro-manganese alloy plant. Two of these published papers contain analyses of data, collected as part of a larger study in a mining district in Mexico, which may be of concern regarding generalizability given the age, low education level and low socioeconomic status of the participants (Riojas-Rodríguez et al., 2010; Solís-Vivanco et al., 2009).

A recent study by Viana et al. (2014) investigated the neuropsychological effects of environmental Mn exposure from industrial emissions in an adult population from Brazil. They found an association between Mn in hair and fingernail concentrations and tests of visual working memory, as well as tests designed to measure intelligence.

1.3. Objectives

With few reports available from environmental epidemiologic studies of Mn exposed adults, the current study examined Mn exposed adult residents of two Ohio, USA, towns (East Liverpool and Marietta). Both towns have previously been identified as having high levels of air-Mn from industrial sources (ATSDR, 2007, 2009, 2010). The objectives of this study are to (1) evaluate cognitive function and to (2) determine whether Mn exposure through long-term inhalation is associated with cognitive dysfunction.

2. Methods

2.1. Study design and participant selection

A cross-sectional study design was used to examine the potential effects of exposure to air-Mn from industrial sources on the cognitive function of residents of two exposed towns. This approach was made possible by the availability of residents living near a ferromanganese smelter and an open-air Mn storage and packaging facility. In the present study, the data from both exposed towns were combined to achieve greater statistical power.

The recruitment and selection of participants from Marietta are described in detail by Bowler et al. (2012) and Kim et al. (2011). Similar recruitment procedures were followed in East Liverpool. The recruitment zone in Marietta was within 12 miles from the emission source. Due to the larger particle size and reduced dispersion range of the Mn emissions in East Liverpool, the participant recruitment zone in East Liverpool was limited to two air-miles downwind of the emissions site.

Based on power analyses, the goal was to recruit 100 participants from each town. Because Ohio has areas with naturally occurring Mn and iron in groundwater, only households served by public water companies, which are required to reduce Mn and iron levels to national secondary maximum contaminant levels, were eligible for participation (Bowler et al., 2012). For Marietta residents, a random sample of parcels was drawn from December 2008 property tax records within the ZIP code of the pre-defined Mn exposure zone of 0.04 $\mu g/m^3$ or higher. In East Liverpool, a sample of single family units, multifamily units, and trailer addresses located within two air-miles west-northwest of the S.H. Bell Stateline facility was purchased from a commercial vendor (Spectrum Mailing Lists) in 2011. To ensure completeness, the address list was cross-checked with East Liverpool parcel maps and the mapping system and address database of the Columbiana County 9-1-1 Emergency Response. The sampling list of addresses was then processed through Geographic Information Systems (GIS) mapping at the Agency for Toxic Substances and Disease Registry (ATSDR) to ensure that all recruitment addresses were within the boundary of two air-miles of the S.H. Bell Stateline facility. Random recruitment was not feasible for all study participants due to the limited number of residences located in the area of interest in East Liverpool. In Marietta, 1732 letters were mailed to randomly selected addresses as outlined above. Letters were successfully delivered to 1569 residents of which 264 residents were interested and 122 were eligible for participation. In East Liverpool, 1309 letters were mailed, of which 1213 were successfully delivered and 192 residents were interested and 123 were eligible for participation.

The inclusion and exclusion criteria for Marietta and East Liverpool were identical. A minimum of 10 years of residency in each town, age 30–75 years without a major illness or exposure to toxic substances requiring hospitalization, and without a diagnosis of psychiatric (schizophrenia, bipolar disorder, major psychiatric diagnosis, including depression or anxiety) or degenerative (multiple sclerosis, Alzheimer's dementia, Huntington's chorea, PD) disorder was required for participant inclusion. Only residents who never worked at either Mn-emitting facility in the two towns were eligible for participation in the study. Up to two members of a household could participate. Subsequently, the number of eligible residents tested in Marietta was 100 in 76 households and 86 residents in East Liverpool in 72 households. Target recruitment in East Liverpool was 100, but 14 no-shows were due to personal or work scheduling conflicts. Participants were given $50 gift certificates upon completion of the testing.

Approximately one year after data collection took place in each of the communities, participants were sent feedback letters providing their individual test results by domain of function, indicating whether their scores were "within normal limits" or "of concern" in comparison to normative data, which included an age, sex, race/ethnicity and geographically representative sample (Wechsler, 1997). If any of their summary test results were indicated to be "of concern," they were asked to bring the feedback letter to their personal physician for potential further evaluation and/or consultation with the P.I. of the study.

Both the Marietta and East Liverpool study protocols were approved by the IRBs at SFSU, the Ohio Department of Health, and the University of North Carolina at Chapel Hill on behalf of the U.S. EPA.

2.2. Procedures and test battery

Data collection took place in August 2009 (Marietta) and November 2011 (East Liverpool) at a central location in each town. The East Liverpool study took place later because sufficient funding was not available in 2009. As part of the data collection, tests of cognitive functions were included.

All tests were administered by experienced psychometricians with advanced degrees in psychology in accordance with the standardized administration instructions in the respective manuals. The examiners had all completed an NIH course on the protection of human research subjects prior to the recruitment phase of the study. To the extent possible, the testers were the same for each town, and three of the eight neuropsychological testers administered tests in both towns. The order of the administration of the neuropsychological tests was identical for the two towns and the test administration took approximately 2 h. All psychometricians were extensively trained and observed by the P.I. prior to test administration. All test protocols were scored twice to ensure accuracy, and discrepancies in scoring were resolved by the P.I. Double data entry was used to ensure accuracy.

Table 1 lists the cognitive tests administered by domain of function. Raw test scores were standardized to *z*, *T*, or scaled scores using the appropriate normative data. WAIS-III Digit Span, Digit Symbol, and Similarities subtest raw scores were converted to scaled scores using age-stratified normative data (Wechsler, 1997). Stoop Color/Word test *T*-scores were also adjusted for age (Strauss et al., 2006), as were Rey-Osterrieth (Rey-O) Immediate and Delayed Recall *T*-scores (Strauss et al., 2006) and the Auditory Consonant Trigrams (ACT) *z*-scores (Boone et al., 1990). *T*-scores for the Trail Making Test (Lezak et al., 2012; Army Individual Test Battery, 1944) were obtained using the Heaton norms, stratified by age, sex, education, and ethnicity (Heaton et al., 2004). Raw scores from the Animal Naming test (Lezak et al., 2012) were adjusted for age and education and converted to standard scores. For the Memory Module of the Neuropsychological Assessment Battery (NAB) (Stern and White, 2003) age, sex, and education-corrected *T*-scores were obtained for the List Learning, Story Learning, Shape Learning, and Daily Living Memory subtests.

2.3. Exposure estimates of Mn in air

The methodology for developing personal exposure estimates for each study participant is described in detail by Colledge et al. (2015). Briefly, a unit emission rate of 1 g/s was assumed over the surface area of both Mn source facilities and concentrations at participant residences and air monitoring sites were modeled using the U.S. EPA's AERMOD dispersion model in order to compare the two exposed towns. A long-running air monitor was selected as a reference location among three area monitors and ratios of all modeled receptor points to that monitor were computed using air measurements from the reference location. These ratios were multiplied by the actual ambient air-Mn measured at the reference monitoring location to yield receptor-specific long term (>10 year) Mn concentration averages in $\mu g/m^3$ (TSP) for each resident. It should be noted that air measurements were 24-h samples, and the data were averaged to estimate chronic residential exposure estimates. Short-term measurements were not evaluated because residential exposures were assumed to be chronic, and although residents may leave their residence for various reasons (work, school, etc.) we assumed that in general, they spend the majority of their time at home. The air sampling in both towns was performed from 2003 to 2013 and sampling and analytical methods were identical for both exposed towns. Modeled all-year average air-Mn (TSP) exposure in the environment ranged from 0.03 to 1.61 $\mu g/m^3$ in Marietta and 0.01–6.32 $\mu g/m^3$ in East Liverpool, with arithmetic means (AM) of 0.21 $\mu g/m^3$ for Marietta and 0.88 $\mu g/m^3$ for East Liverpool, both of which exceeded the U.S. EPA reference concentration (RfC) of 0.05 $\mu g/m^3$ but only East Liverpool exceeded the more recently derived ATSDR minimal risk level (MRL) value of 0.3 $\mu g/m^3$ (ATSDR, 2012). A recent study by Haynes et al. (2010) in the same area of study, reported a range of "estimated annual average ambient air Mn concentrations" obtained from AERMOD of 0.02–2.61 $\mu g/m^3$. Both East Liverpool and Marietta were identified in the U.S. EPA's School Air Toxics (SAT) initiative as having increased potential for non-cancer health effects from exposure to Mn (U.S. EPA, 2010a,b).

The fingerprinting analysis of Mn in both towns, conducted by the U.S. EPA at the National Enforcement Investigations Center (NEIC), determined that Eramet (Marietta) had an impact radius of at least 10 miles. In East Liverpool, the same analysis determined that the particles of Mn were much larger (35% were $<d_{ae}$ of 10 μm) and would be expected to have more local deposition.

Table 1
Neuropsychological test battery (cognitive).

Domains of function and tests administered	Cognitive function(s) assessed	Type of score
Cognitive flexibility and executive functioning		
Stroop Color/Word	Inhibiting automatic response of reading color words printed in incongruent colors	*T* score[a]
Rey-Osterrieth Copy	Ability to plan and execute an organizational strategy	Raw score
Trails B	Category switching, sequencing, scanning, visuomotor tracking	*T* score[b]
Information processing speed		
Stroop Color *T* score	Speeded naming of color hues	*T* score[a]
Stroop Word *T* score	Speeded word reading	*T* score[a]
Memory [Neuropsychological Assessment Battery (NAB)]		
NAB Memory Index	Overall performance on visual and verbal immediate and delayed memory	Standard score[c]
NAB Daily Living Memory Immediate Recall	Immediate recall of medication instructions and a person's contact information	*T* score[c]
NAB Daily Living Memory Delayed Recall	Delayed recall of medication instructions and a person's contact information	*T* score[c]
Working memory/attention and concentration/learning		
WAIS-III Digit Span	Attention and working memory (see below)	Scaled score[d]
WAIS-III Digit span forward longest	Simple auditory attention, repetition of digits	*z* score[d]
WAIS-III Digit span backward longest	Mental tracking of digits requiring working memory	*z* score[d]
Auditory Consonant Trigrams 3″ *z* score	Measure of frontal lobe function, memory with 3 s distraction	*z* score[e]
Auditory Consonant Trigrams 9″ *z* score	Measure of frontal lobe function, memory with 9 s distraction	*z* score[e]
Auditory Consonant Trigrams 18″ *z* score	Measure of frontal lobe function, memory with 18 s distraction	*z* score[e]
Visuospatial memory		
Rey-Osterrieth Immediate Recall *T* Score	Visuospatial constructional ability and immediate (3 min) recall	*T* score[a]
Rey-Osterrieth Delayed Recall *T* Score	Visuospatial constructional ability and delayed (30 min) recall	*T* score[a]
Visuomotor tracking speed		
Trails A	Visual scanning and visuomotor tracking of sequential numbers	*T* score[b]
WAIS-III Digit Symbol Coding	Fine visual-motor speed and accuracy of non-verbal learning	Scaled score[a]
Verbal skills		
WAIS-III Similarities	Capacity for verbal concept formation, abstract thinking	Scaled score[a]
Animal Naming	Verbal category fluency	Standard score[f]
Effort		
Rey-15 Items Test	Memory problems exaggeration (remembering repetitive items)	Raw score
Victoria Symptom Validity Test (if needed)	Memory problems exaggeration	Raw score

T score: $M = 50$, SD = 10.
Scaled score: $M = 10$, SD = 3.
z score: $M = 0$, SD = 1.
Standard score: $M = 100$, SD = 15.
[a] Age-corrected (Strauss et al., 2006).
[b] Age, gender, education, and ethnicity-corrected (Heaton et al., 2004).
[c] Age, gender, and education-corrected (Stern and White, 2003).
[d] Age-corrected (Wechsler, 1997)
[e] Age-corrected (Boone et al., 1990).
[f] Age and education-corrected (Lezak et al., 2012).

The EPA conducted air-monitoring in both East Liverpool and Marietta and the ATSDR analyzed the data for heavy metals in addition to Mn, including Pb, Cd and identified Mn as the only metal exceeding background levels and health based guidelines (ATSDR, 2009, 2010). Furthermore, average blood concentrations of Pb, Hg and Cd in this study population were also within the ranges observed in the general population of the U.S. (Kim et al., 2015).

2.4. Statistical analyses

Descriptive statistics were obtained for all variables. Means and standard deviations are presented for each town and for the combined sample for continuous demographic, exposure, and test score variables. Independent sample *t*-tests were used to compare the two towns on continuous variables. For categorical variables, the frequencies for each level of the categorical variables and *p*-values from the Fisher's exact test were reported. Adjustments for multiple comparisons were made within the domain of function using the Benjamini–Hochberg False Discovery Rate (Benjamini and Hochberg, 1995). Tables 3 and 4 present the adjusted *p*-values. All analyses were conducted with estimates of exposure calculated with the *site surface emissions method modeling*, which was calibrated with TSP air-Mn measurements. The calculation of respirable particles over the ten-year period was assumed to be a constant percentage of the TSP over time, which was determined by filter analyses in both towns. The associations between test scores and modeled air-Mn were assessed using nonparametric Spearman's rho correlation coefficients. Nonparametric measures of association were used due to the non-normal distribution of the modeled air-Mn exposure variable, as determined by visual inspection of the histogram and evaluation of skewness and kurtosis statistics.

The relationships between modeled air-Mn and performance on the tests of cognitive functions were analyzed using hierarchical multiple regression analyses. Prior to conducting the analyses, diagnostic tests were conducted to assess whether the data met the assumptions for valid measurement in regression, including normality, linearity, and homoscedasticity (Cohen et al., 2003; Tabachnick and Fidell, 2006). Examination of regression standardized residuals, p-p plots of standardized residuals, plots of observed versus predicted values, and residuals versus predicted values revealed no violations of assumptions that would suggest alternative analyses. Demographic variables, including level of education and town of residence, were entered in step one of the model to control for the effect of these variables on test performance. Controlling for "town" effectively and parsimoniously controls for any differences between them (e.g., age, income, ethnicity, years of residence) and allows for the effects of exposure on neuropsychological outcomes to be isolated. No sex differences were observed on neuropsychological tests, with the exception of women scoring higher on Digit-Symbol Coding, which was adjusted in the regression model in Table 4. Therefore, sex was not included as a covariate. The education variable was derived by dichotomizing participants' responses to the question of highest completed degree into the two categories of "High school or less" and "More than high school." Although all but one of the tests in this battery use age-adjusted test scores, not all were adjusted for education (Table 1) and thus, education was used as a covariate in models where the tests were not already adjusted for education. The modeled air-Mn exposure variable was log transformed due to a positively skewed distribution and entered in step two. Squared semi-partial correlations were computed to elucidate the unique contribution of each variable to predicting variance in performance on each cognitive test. SPSS version 22 was used for all analyses (IBM Corp., 2013) and results were considered significant at the 0.05 level.

3. Results

3.1. Description of the exposed residents

Table 2 contains demographic characteristics of the two towns. Overall, both towns were predominantly white (94.6%). There was a larger proportion of East Liverpool residents with a high school education or less (48.8%) than in Marietta (28%). East Liverpool residents also resided more years in their respective town (mean years: East Liverpool 47.0 ± 16.4 and Marietta 36.1 ± 15.8), and had lower household income compared to Marietta. The two towns had similar proportions of disabled participants and all disabilities had non-neurodegenerative causes (e.g. orthopedic). Participants' reported alcohol consumption was computed in grams of alcohol/week using questions from the diet questionnaire enquiring about type of alcoholic beverage, quantity and frequency of consumption. Although Marietta participants consumed more alcohol than East Liverpool participants (31.7 g/week vs. 9.28 g/week, $p = 0.002$), the amounts of consumed alcohol are notably low and correspond to two glasses of wine/week in Marietta and less than one glass of wine/week in East Liverpool (CDC, 2014) (data not shown). Log blood lead levels were not associated with cognitive test scores (data not shown).

Statistical distributions of community exposure were as follows: Marietta [TSP: 0.21 $\mu g/m^3$ (AM), range 0.03–1.61 $\mu g/m^3$, PM_{10}: 0.18 $\mu g/m^3$ (AM), range 0.03–1.33 $\mu g/m^3$; $PM_{2.5}$: 0.05 $\mu g/m^3$ (AM), range 0.007–0.34 $\mu g/m^3$]; East Liverpool [TSP: 0.88 $\mu g/m^3$ (AM), range: 0.01–6.32 $\mu g/m^3$, PM_{10}: 0.31 $\mu g/m^3$ (AM), range 0.005–2.21 $\mu g/m^3$; $PM_{2.5}$: 0.03 $\mu g/m^3$ (AM), range 0.001–0.23 $\mu g/m^3$]. Although the modeled air-Mn levels in East Liverpool were generally higher than in Marietta, different particle sizes in the two towns suggest that the Marietta residents have a higher exposure to respirable Mn (PM_{10}).

3.2. Bivariate analysis of associations between modeled air-Mn and performance on tests of cognitive functions

Descriptive statistics of scores on tests of cognitive functions by town of residence and for the combined sample are shown in Table 3. No significant differences by town appeared for any of the neuropsychological test variables using independent sample

Table 2
Demographic Information for Marietta, East Liverpool, and Combined.

Continuous characteristic	East Liverpool			Marietta			Combined towns			Town comparison
	n	Mean ± SD	Median	*n*	Mean ± SD	Median	*n*	Mean ± SD	Median	*p*-value
Age	86	56.0 ± 11.9	57.0	100	54.4 ± 9.9	55.5	186	55.2 ± 10.9	56.0	0.323
BMI	83	27.4 ± 5.6	27.0	92	28.9 ± 6.4	27.8	175	28.1 ± 6.1	27.2	0.099
Years of residence	86	47.0 ± 16.4	50.0	100	36.1 ± 15.8	37.0	186	41.1 ± 16.9	42.0	**<0.001**
Air manganese, $\mu g/m^3$	86	0.9 ± 1.2	0.3	100	0.2 ± 0.2	0.2	186	0.5 ± 0.9	0.2	**<0.0001**
Categorical characteristic	*n*	%		*n*	%		*n*	%		Town comparison *p*-value
Education										**0.002**
High school or less	42	49.4		28	28.0		70	37.8		
More than high school	43	50.6		72	72.0		115	62.2		
Annual household income										0.254
$0–$29,999	31	40.3		26	28.3		57	33.7		
$30,000–$69,999	26	33.8		36	39.1		62	36.7		
≥$70,000	20	26.0		30	32.6		50	29.6		
Sex										0.216
Male	31	36.0		45	45.0		76	40.9		
Female	55	64.0		55	55.0		110	59.1		
Race										0.510
Caucasian	82	95.3		94	94.0		176	94.6		
African-American	3	3.5		2	2.0		5	2.7		
Asian	0	0		2	2.0		2	1.1		
Native American	1	1.2		2	2.0		3	1.6		
Employment status										
Employed full-time	36	42.4		52	52.0		88	47.6		0.190
Unemployed	9	10.6		9	9.0		18	9.7		0.716
Full-time student	3	3.5		0	0		3	1.6		0.058
Retired	19	22.4		21	21.0		40	21.6		0.824
Employed part-time	10	11.1		7	7.0		17	9.2		0.264
Homemaker	16	18.8		10	10.0		26	14.1		0.085
Part-time student	1	1.2		1	1.0		2	1.1		0.908
Disabled	8	9.4		6	6.0		14	7.6		0.382

Bold = $p < 0.05$.

Table 3
Neuropsychological test score means, standard deviations, and non-parametric correlations with modeled air-Mn.

	East Liverpool		Marietta		Combined		Correlation with modeled air-Mn: Spearman's rho (*p*-value)		
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	East Liverpool	Marietta	Combined
Cognitive flexibility and executive functioning									
Stroop Color-Word T	46.88 ± 8.6	47.0	48.32 ± 10.0	49.0	47.67 ± 9.4	43.0	−0.15 (0.17)	−0.17 (0.10)	−0.16 (0.06)[†]
Rey-O Copy Raw score	27.52 ± 6.1	29.0	29.92 ± 4.9	31.0	28.82 ± 5.6	30.0	−0.12 (0.29)	−0.05 (0.60)	−0.15 (0.06)[†]
Trails B *T*-score	49.46 ± 9.9	50.5	52.62 ± 10.7	53.0	51.18 ± 10.4	52.0	−0.06 (0.57)	−0.004 (0.97)	−0.11 (0.13)
Information processing speed									
Stroop Word *T*-score	43.44 ± 7.1	43.0	46.67 ± 7.4	46.5	45.20 ± 7.4	45.0	−0.05 (0.67)	−0.03 (0.81)	−0.12 (0.11)
Stroop Color *T*-score	42.91 ± 9.0	41.0	43.75 ± 7.9	43.5	43.23 ± 8.3	43.0	0.05 (0.68)	−0.07 (0.48)	−0.03 (0.71)
Memory									
NAB Memory Index	98.22 ± 14.9	97.0	100.81 ± 15.8	99.5	99.62 ± 15.4	99.0	−0.05 (0.65)	−0.84 (0.41)	−0.10 (0.19)
NAB DLM immediate T	50.93 ± 10.5	50.0	54.92 ± 11.1	57.0	53.09 ± 11.0	53.0	−0.13 (0.24)	0.02 (0.83)	−0.15 (0.06)[†]
NAB DLM delayed T	48.61 ± 10.5	50.0	51.20 ± 9.8	55.0	50.01 ± 10.2	51.0	−0.12 (0.26)	−0.11 (0.29)	−0.17 (0.06)[†]
Working memory/attention & concentration/learning									
WAIS Digit Span SS	9.37 ± 2.6	9.0	10.61 ± 2.8	10.5	10.04 ± 2.7	9.0	−0.13 (0.24)	−0.04 (0.70)	−0.19 (0.07)[†]
Digits forward *z*-score	−0.15 ± 0.9	−0.2	0.23 ± 0.9	0.3	0.05 ± 0.9	−0.1	−0.09 (0.41)	0.037 (0.72)	−0.11 (0.16)
Digits backward *z*-score	−0.09 ± 1.0	−0.3	0.08 ± 0.9	0.1	0.01 ± 0.9	−0.3	−0.14 (0.19)	−0.011 (0.28)	−0.16 (0.09)[†]
ACT 3′ delay *z*-score	−0.38 ± 1.5	−0.3	−0.17 ± 1.1	0.2	−0.27 ± 1.3	0.1	0.03 (0.80)	−0.18 (0.08)	−0.07 (0.34)
ACT 9′ delay *z*-score	−1.03 ± 1.3	−0.9	−0.52 ± 1.3	−0.4	−0.76 ± 1.3	−0.7	−0.02 (0.89)	−0.06 (0.56)	−0.13 (0.12)
ACT 18′ delay *z*-score	−0.84 ± 1.3	−0.9	−0.34 ± 1.1	−0.5	−0.57 ± 1.2	−0.5	−0.11 (0.31)	−0.03 (0.74)	−0.13 (0.13)
ACT mean of 3′, 9′, 18′ *z*	−0.75 ± 1.2	−0.6	−0.35 ± 1.0	−0.3	−0.53 ± 1.1	−0.4	−0.05 (0.67)	−0.11 (0.26)	−0.15 (0.09)[†]
Visuospatial memory									
Rey-O Immediate T	39.79 ± 12.5	39.0	42.60 ± 13.5	43.0	41.31 ± 13.1	40.0	−0.22 (0.05)	−0.16 (0.11)	**−0.21 (0.005)**
Rey-O Delayed T	38.01 ± 12.1	37.0	41.48 ± 12.7	42.5	39.89 ± 12.5	40.0	−0.17 (0.13)	−0.22 (0.03)	**−0.20 (0.005)**
Visuomotor tracking speed									
Trails A *T*-score	49.12 ± 9.8	50.0	47.14 ± 11.0	47.0	48.56 ± 9.6	48.0	−0.01 (0.93)	−0.004 (0.97)	0.01 (0.88)
WAIS Digit Symbol	10.28 ± 2.8	10.0	10.98 ± 3.3	11.0	10.66 ± 3.1	11.0	−0.18 (0.94)	−0.02 (0.89)	−0.12 (0.22)
Coding SS									
Verbal skills									
WAIS Similarities SS	9.58 ± 2.8	9.0	10.80 ± 3.1	11.0	10.24 ± 3.0	10.0	−0.24 (0.03)	−0.18 (0.08)	**−0.30 (0.002)**
Animal Naming SS	106.72 ± 18.5	103.0	110.01 ± 17.2	109.0	108.50 ± 17.8	107.0	−0.08 (0.49)	−0.25 (0.01)	**−0.19 (0.01)**

Note: DLM Immediate *T* = Daily Living Memory Immediate Recall *T* Score, DLM delayed T = Daily Living Memory Delayed Recall *T* Score, SS = Scaled Score. Benjamini–Hochberg corrected false discovery rate probabilities: $p < 0.05$ in bold.
[†] Approaching significance ($p < 0.10$).

t-tests. Using a conservative cutoff of two standard deviations below the normative mean, as used in clinical evaluations (Bowler and Lezak, 2015), in the feedback letters to participants, only one Marietta participant had scores "of concern" on tests of attention (none in East Liverpool). All participants scored "within normal" on delayed visual memory. Delayed verbal memory was indicated as "of concern" for three participants from East Liverpool but none from Marietta. Cognitive flexibility was "of concern" for one Marietta and two East Liverpool participants.

Spearman's rho analyses were used to evaluate associations between neuropsychological test scores and air-Mn (Table 3). Significant inverse relationships occurred between modeled air-Mn concentrations and test performance for cognitive measures of visuospatial memory (Rey-O Immediate and Delayed) and verbal skills (WAIS Similarities and Animal Naming). Relationships approached significance between modeled air-Mn and performance for tests of cognitive flexibility, executive function, immediate and delayed visual memory, working memory, attention/concentration and learning. Of the 21 examined relationships, 18 meet and exceed the threshold for a small effect as shown in Table 3 (Cohen, 1992). These significant associations indicate that higher modeled air-Mn is associated with lower performance on tasks in the above-mentioned cognitive domains among residents of East Liverpool and Marietta.

3.3. Hierarchical multiple regression analyses

Hierarchical multiple regression analyses predicting performance on measures of cognitive functioning associated with modeled air-Mn levels and controlling for education and town of residence found significant relationships in several cognitive domains (Table 4). Higher modeled air-Mn concentrations predicted lower test scores on measures of visuospatial memory (Rey-O Immediate and Delayed), immediate daily living memory (NAB DLM Immediate), and verbal reasoning (WAIS Similarities). Predictive relationships approached significance for higher modeled air-Mn concentrations and lower test scores on measures of cognitive flexibility and executive function. Of the 21 examined relationships, 11 meet and exceed the threshold for a small effect (Cohen, 1992).

4. Discussion and conclusion

4.1. Study findings in relation to Mn exposure and brain mechanisms

Few previous studies have examined cognitive function in adults environmentally exposed to Mn. Even fewer environmental studies have included a clinically sensitive, brief, and comprehensive cognitive test battery. Although higher than in other U.S. areas, the relatively low levels of Mn, common in environmental exposures, resulted in significant associations between models derived from measured Mn levels in air and cognitive test scores. Significant associations between Mn exposure and cognitive function were obtained in the domains of visuospatial memory and verbal skills. Tests of cognitive flexibility and executive function approach significance at $p < 0.10$.

These functions require abstract thinking, attention, concentration, executive function, and memory, which have also been negatively associated with high Mn exposures in a large body of occupational literature (Bowler et al., 2007; Yuan et al., 2006; Sadek et al., 2003; Roels et al., 1987; Ellingsen et al., 2008; Bast-Pettersen et al., 2004; Bowler et al., 2003). Mn has previously been shown to impact the basal ganglia (Kim et al., 1999), a collection of subcortical brain structures responsible for purposeful movement.

Table 4
Multiple regression analyses predicting performance on cognitive tests controlling for education and town of residence.

	Modeled air-Mn			sr^2 Control variables	
	β	sr^2	p	Education	Town
Cognitive flexibility and executive functioning					
Stroop Color-Word *T*-score	−0.148	0.02	0.09†	0.006	0.0002
Rey-O Copy Raw score[a]	−0.142	0.018	0.09†	0.015†	0.013†
Trails B *T*-score	−0.095	0.008	0.221	Adjusted for	0.013
Information processing speed					
Stroop Word *T*-score	−0.030	0.001	0.926	0.009	**0.031**
Stroop Color *T*-score	−0.007	0.00005	0.926	0.0004	0.003
Memory					
NAB Memory Index	−0.083	0.006	0.283	Adjusted for	0.003
NAB Immediate *T*-score	−0.108	0.01	0.240	Adjusted for	**0.02**
NAB DLM Delayed *T*-score	−0.114	0.012	0.240	Adjusted for	0.008
Working memory/attention & concentration/learning					
WAIS Digit Span SS	−0.118	0.012	0.389	**0.058**	0.016†
Digits forward *z*-score	−0.009	0.0001	0.908	**0.042**	**0.027**
Digits backward *z*-score	−0.155	0.022	0.280	**0.046**	0.001
ACT 3′ delay *z*-score	0.020	0.0004	0.908	**0.093**	0.0003
ACT 9′ delay *z*-score	−0.006	0.00003	0.908	**0.071**	0.015†
ACT 18′ delay *z*-score	−0.079	0.006	0.681	**0.049**	0.015†
ACT mean of 3′, 9′, 18′ *z*-scores	−0.024	0.001	0.908	**0.100**	0.011
Visuospatial memory					
Rey-O Immediate *T*-score	−0.187	0.028	**0.035**	**0.032**	0.0001
Rey-O Delayed *T*-score	−0.159	0.023	**0.035**	**0.041**	0.002
Visuomotor tracking speed					
Trails A *T*-score	−0.029	0.001	0.706	Adjusted for	0.004
WAIS Digit Symbol Coding SS[b]	−0.107	0.011	0.151	0.013	0.002
Verbal skills					
WAIS Similarities SS	−0.191	0.033	**0.012**	**0.135**	0.003
Animal Naming SS	−0.126	0.014	0.104	Adjusted for	0.003

[a] Age included as a covariate.
[b] Sex included as a covariate.
sr^2 = squared semi-partial correlation, DLM Immediate T = Daily Living Memory Immediate Recall T Score, DLM delay T = Daily Living Memory Delayed Recall T Score, SS = Scaled Score; Benjamini–Hochberg corrected false discovery rate probabilities: $p < 0.05$ in bold.
† Approaching significance ($p < 0.10$).

The basal ganglia are involved in the governance of inhibitory and disinhibitory processes at a cellular and behavioral level throughout the body via pathways connecting them to the frontal lobes (Lezak et al., 2012). Through Mn overexposure, the neurotransmitter dopamine may be disrupted within the substantia nigra, and the pathways (including the dorsolateral pathway), which connect the basal ganglia and frontal lobes, may be damaged. These pathways are responsible in part for the coordination of higher-level cognitive functions including cognitive flexibility, response inhibition, and planning (Miller and Cummings, 2007). Little is known about the pathophysiology of visual and verbal memory changes associated with Mn exposure, although this type of dysfunction has been described in previous environmental research (Mergler et al., 1999). Recent imaging research has shown that in addition to the basal ganglia, Mn affects areas of the cerebral cortex, especially the frontal cortex (Guilarte, 2013). The frontal cortex is associated with the strategic encoding, organization, and retrieval of verbal and visual memories (Brewer et al., 1998; Stuss, 2007). Therefore, dysfunction of the brain areas typically impacted by Mn could account for the pattern of results seen in the current study.

4.2. Other environmental research studies of Mn exposed adults

Previous studies examining cognitive function in adults environmentally exposed to elevated levels of air-Mn showed relationships of Mn not only to psychomotor efficiency and tremor, but to lower scores on verbal learning and memory (Mergler et al., 1999; Viana et al., 2014), attention and concentration (Mergler et al., 1999; Solís-Vivanco et al., 2009), nonverbal cognitive ability (Menezes-Filho et al., 2011), and visual working memory (Viana et al., 2014). This research has been conducted in Canadian (Mergler et al., 1999) and Mexican (Menezes-Filho et al., 2011; Solís-Vivanco et al., 2009) adult populations. The Mexican group, however, had a very low mean years of education (4.6 years). Since years of education are associated with cognitive ability (Heaton et al., 2004), it is difficult to extrapolate from those findings the potential impact of Mn exposure on a more educated group of adults, who have more residual cognitive reserve, even after Mn exposure.

4.3. Strengths

Strengths of this study include the use of stringent selection criteria, clinically trained test administrators, and advanced modeling of Mn exposure. Cognitive function was examined in 186 Mn exposed adult residents of East Liverpool and Marietta, Ohio, USA, which are located near environmental sources that produce high levels of airborne Mn (ATSDR, 2012). To achieve sufficient power to detect an effect, participants from both exposed towns were combined into one exposed sample.

Residents of the two exposed towns had a stable and long residential history with ongoing Mn exposure in air. The mean years of residence was 37 years in Marietta and 47 years in East Liverpool.

Selection criteria included exclusion of participants with any prior or present occupational chemical exposures to Mn or other neurotoxic agents in their workplace, major illnesses, and alcohol and drug abuse or dependence affecting cognitive function.

The approach to measuring airborne Mn exposure used state-of-the-art air monitoring to create and model exposure estimates. The model assumes a unit emission rate over the surface area of both source facilities; the estimation of offsite concentrations at receptor residences and at air monitoring sites uses the U.S. EPA's

AERMOD dispersion model. This model permits the creation of ratios of all modeled receptor points with a long running air monitor as the referent location, using a total of 10 years of air sampling data from 2003 to 2013. Air-Mn sampling data collected over many years has not been used in previous studies of environmentally Mn exposed adults. This approach permitted developing the relatively precise AERMOD dispersion model in the analysis of cognitive function of the exposed residents.

4.4. Limitations

One limitation of this study is the absence of personal sampling of each participant's individual Mn exposure. However, mean blood Mn levels were within the average range of the general population (CDC, 2005; Kim et al., 2015). Analyses of Mn in diet, from the residents' health questionnaire, indicated no significant differences between the two towns in the amount of Mn consumed in foods. Total Mn in diet was not correlated with Mn in blood ($\rho = 0.023$, $p = 0.753$) for the combined sample.

As stated above, the different particle size fractions of Mn in both towns necessitated choosing the difference in recruitment distance for each town. The distances from the exposure sources were based on a computed estimate of the distance the airborne Mn would disperse (Marietta 12 air-miles; East Liverpool 2 air-miles). Differing Mn release characteristics in both towns and air dispersion modeling uncertainties affect Mn inhalation exposure estimates.

The same test administration methodology was used in both 2009 (Marietta) and 2011 (East Liverpool) and the P.I. followed the same interviewing procedure with participants. Due to lack of funding in 2009, it was not possible to study both towns at the same time. Additional funds for East Liverpool were provided to conduct the study in the same way in 2011. No significant regional political and economic events occurred during the intervening time. Potentially confounding factors (i.e., diet, behavior, etc.) are not expected to be influenced by dates of data collection. Random recruitment was not feasible for all study participants due to the limited number of residences located in the area of interest in East Liverpool. This limitation was at least partially mitigated by the strict inclusion/exclusion criteria. The possibility for a self-selection bias was successfully minimized by these criteria, as shown by the fact that the samples from both Marietta and East Liverpool are representative of the U.S. Census data for the two respective towns (data not shown).

4.5. Suggestions for future research

The findings of this study indicate that with appropriate methodology, sensitive clinical tests and well trained clinical examiners, cognitive tests appear useful in detecting the impact of low-level, chronic environmental Mn exposure on brain function. A study using personal Mn air sampling including a small group of residents with additional biomarkers or additional clinical tests such as MRIs, could help to validate the AERMOD model used.

Although power analyses indicated our sample size was sufficient in order to detect the presence of an effect, a larger sample size in different towns with Mn environmental exposure is recommended; this would support and strengthen the findings of this study.

4.6. Conclusion

The identified associations between cognitive function and AERMOD Mn exposure may prove to be important findings. The results suggest that even in non-occupational environmental exposures, Mn exposure appears to be associated with lower performance on neuropsychological tests measuring a variety of cognitive functions. The findings support an association of air-Mn exposure with lowered brain function, consistent with the areas known to be susceptible to damage from Mn.

Funding

The research described here has been funded wholly (or in part) by the U.S. Environmental Protection Agency through cooperative agreement number 83416001 to San Francisco State University (Marietta study) and EPA Contracts EP-11-D-000424 and EP-13-D-000146 (East Liverpool study).

Disclaimer

The views expressed in this manuscript are those of the authors and do not necessarily reflect the views or policies of the EPA or ATSDR.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgements

Special thanks are given to Dr. Harry Roels for his extensive input and assistance with planning and carrying out this study. Also acknowledged for valuable support to this study are: Ohio Department of Health, Bureau of Environmental Health (Greg Stein, Robert Frey); East Liverpool City Health District Health Commissioner, Jelayne Dray; East Liverpool City Council and the mayor of East Liverpool, Mr. James P. Swoger; Dr. Alan Ducatman for his medical input into the health questionnaire and medical consultations; Marietta City Health Department Health Commissioner Michael Brockett; Kathleen Meckstroth, Health Commissioner of Washington County Health Department. Also thanked are the doctoral students assisting in testing and test scoring: Ms. Beth Stutzman, Ms. Jessica Warren, Dr. Katherine Wilson, Dr. Linda Mora, Mr. Matthew Berristianos, Dr. Matthew Harris, and Mr. Ralph Rasalan. Most of all, we thank the study participants for their invaluable contribution to the knowledge gained from this investigation.

References

Antunes, M.B., Bowler, R.M., Doty, R.L., 2007. San Francisco/Oakland Bay Bridge welder study: olfactory function. Neurology 69, 1278–1284.

Army Individual Test Battery, 1944. Manual of Directions and Scoring. War Department, Adjutant General's Office, Washington, DC.

ATSDR, 2007. Health Consultation: Washington County Air Quality. ATSDR, Marietta, Washington County, OH. Available: http://www.atsdr.cdc.gov/HAC/pha/marietta3/ATSDRHealthConsultation2007.pdf. (accessed 30.08.10).

ATSDR, 2009. Health Consultation: Marietta Area Air Investigation. ATSDR, Marietta, OH. Available: http://www.atsdr.cdc.gov/HAC/pha/marietta3/ATSDRMariettaHealthConsultationIII2009Final.pdf (accessed 30.08.10).

ATSDR, 2010. Health Consultation: East Liverpool Air Quality. Available: http://www.atsdr.cdc.gov/HAC/pha/EastLiverpoolHC/EastLiverpoolHealthConsultation11210.pdf (accessed 05.05.11).

ATSDR, 2012. Toxicological Profile for Manganese. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Baldwin, M., Mergeler, D., Larribe, F., et al., 1999. Bioindicator and exposure data for a population based study of manganese. Neurotoxicology 20, 343–353.

Bast-Pettersen, R., Ellingsen, D.G., Hetland, S.M., et al., 2004. Neuropsychological function in manganese alloy plant workers. Int. Arch. Occup. Environ. Health 77, 277–287.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. 57, 289–300.
Beuter, A., Edwards, R., deGelffroy, A., et al., 1999. Quantification of neuromotor function for detection of the effects of manganese. Neurotoxicology 20, 355–366.
Boone, K.B., Miller, B.L., Lesser, I.M., et al., 1990. Performance on frontal lobe tests in healthy, older individuals. Dev. Neuropsychol. 6 (3), 215–223.
Bouchard, M., Sauvé, S., Barbeau, B., et al., 2011. Intellectual impairment in school-age children exposed to manganese from drinking water. Environ. Health Perspect. 119, 138–431.
Bowler, R.M., Gocheva, V., Harris, M., et al., 2011. Prospective study on neurotoxic effects in manganese-exposed bridge construction welders. Neurotoxicology 32, 596–605.
Bowler, R.M., Gysens, S., Diamond, E., et al., 2003. Neuropsychological sequelae of exposure to welding fumes in a group of occupationally exposed men. Int. J. Hyg. Environ. Health 206, 517–529.
Bowler, R.M., Harris, M., Gocheva, V., et al., 2012. Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure. Int. J. Hyg. Environ. Health 215, 393–405.
Bowler, R.M., Lezak, M.D., 2015. Neuropsychological evaluation and exposure to neurotoxicants. In: Lotti, M., Bleecker Ml, (Eds.), Occupational Neurology. Elsevier, Amsterdam.
Bowler, R.M., Mergler, D., Sassine, M.P., et al., 1999. Neuropsychiatric effects of manganese on mood. Neurotoxicology 20, 367–378.
Bowler, R.M., Roels, H.A., Nakagawa, S., et al., 2007. Dose-effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. Occup. Environ. Med. 64, 167–177.
Brewer, J.B., Zhao, Z., Desmond, J.E., et al., 1998. Making memories: brain activity that predicts how well visual experience will be remembered. Science 281, 1185–1187.
CDC (Centers for Disease Control and Prevention), 2005. National Health and Nutrition Examination Survey 2003–2004. Available: http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/lab03_04.htm (accessed 10.06.10).
CDC, Centers for Disease Control and Prevention, 2014. Fact Sheets – Alcohol Use and Your Health. U.S. Department of Health and Human Services, 2015, Atlanta, GA.
Chang, Y., Lee, J.J., Seo, J.H., et al., 2010a. Altered working memory process in the manganese-exposed brain. Neuroimage 53, 1279–1285.
Chang, Y., Song, H.J., Lee, J.J., et al., 2010b. Neuroplastic changes within the brains of manganese-exposed welders: recruiting additional neural resources for successful motor performance. Occup. Environ. Med. 67, 809–815.
Chang, Y., Woo, S.T., Kim, Y., et al., 2010c. Pallidial index measured with three-dimensional T1-weighted gradient echo sequence is a good predictor of manganese exposure in welders. J. Magn. Reson. Imaging 31, 1020–1026.
Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155–159.
Cohen, J., Cohen, P., West, S.G., et al., 2003. Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Lawrence Erlbaum Associates, Mahwah, NJ.
Colledge, M.A., Julian, J.R., Gocheva, V.V., et al., 2015. Characterization of air manganese exposure estimates for residents in two Ohio towns. J. Air Waste Manag. Assoc. (in press).
Criswell, S.R., Perlmutter, J.S., Videen, T.O., et al., 2011. Reduced uptake of [^{18}F]FDOPA PET in asymptomatic welders with occupational manganese exposure. Neurology 76, 1296–1301.
Ehrlich, S.D., 2013. Manganese. University of Maryland Medical Center, 2015, Baltimore, MD.
Ellingsen, D.G., Konstantinov, R., Bast-Pettersen, R., et al., 2008. A neurobehavioral study of current and former welders exposed to manganese. Neurotoxicology 29, 48–59.
Feldman, R.G., 1999. Manganese. Occupational and Environmental Neurotoxicology Lippincott-Raven Press, New York.
Guilarte, T.R., 2013. Manganese neurotoxicity: new perspectives from behavioral, neuroimaging, and neuropathological studies in humans and non-human primates. Front. Aging Neurosci. 5, 23.
Haynes, E.N., Heckel, P., Ryan, P., et al., 2010. Environmental manganese exposure in residents living near a ferromanganese refinery in Southeast Ohio: a pilot study. Neurotoxicology 31, 468–474.
Haynes, E.N., Ryan, P., Chen, A., et al., 2012. Assessment of personal exposure to manganese in children living near a ferromanganese refinery. Sci. Total Environ. 427–428, 19–25.
Haynes, E.N., Sucharew, H., Kuhnell, P., et al., 2015. Manganese exposure and neurocognitive outcomes in rural school-age children: the communities actively researching exposure study (Ohio USA). Environ. Health Perspect..
He, P., Liu, D.H., Zhang, G.Q., 1994. Effects of high-level-manganese sewage irrigation on children's neurobehavior. Zhonghua Yu Fang Yi Xue Za Zhi 28, 216–218.
Heaton, R.K., Miller, S.W., Taylor, M.J., et al., 2004. Revised Comprehensive Norms for an Expanded Halstead–Reitan Battery: Demographically Adjusted Norms for African American and Caucasian Adults. Psychological Assessment Resources, Lutz, FL, USA.
IBM Corp., 2013. IBM SPSS Statistics for Windows, Version 22.0 IBM Corp., Armonk, NY.
Khan, K., Wasserman, G., Liu, X., et al., 2012. Manganese exposure from drinking water and children's academic achievement. Neurotoxicology 33, 91–97.
Kim, E.A., Cheong, H.K., Choi, D.S., et al., 2007. Effect of occupational manganese exposure on the central nervous system of welders: ^{1}H magnetic resonance spectroscopy and MRI findings. Neurotoxicology 28, 276–283.
Kim, Y., 2004. High signal intensities on T1-weighted MRI as a biomarker of exposure to manganese. Ind. Health 42, 111–115.
Kim, Y., Bowler, R., Abdelouahab, N., et al., 2011. Motor function in adults of an Ohio community with environmental manganese exposure. Neurotoxicology 32, 606–614.
Kim, Y., Kim, B.N., Hong, Y.C., et al., 2009. Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. Neurotoxicology 30, 564–571.
Kim, Y., Kim, K.S., Yang, J.S., et al., 1999. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. Neurotoxicology 20, 901–907.
Kim, Y., Lobdell, D., Wright, C.W., et al., 2015. Blood metal concentrations of manganese. lead, and cadmium in relation to serum ferritin levels in ohio residents. Biol. Trace Elem. Res. 165, 1–9.
Lezak, M.D., Howieson, D.B., Bigler, E.D., et al., 2012. Neuropsychological Assessment. Oxford University Press, New York, NY.
Long, Z., Jiang, Y.-M., Li, X.-R., et al., 2014. Vulnerability of welders to manganese exposure – a neuroimaging study. Neurotoxicology 45, 285–292.
Lucchini, R.G., Guazzetti, S., Zoni, S., et al., 2012. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. Neurotoxicology 33, 687–696.
Lucchini, R.G., Guezzetti, S., Zoni, S., et al., 2014. Neurofunctional dopaminergic impairment in elderly after lifetime exposure to manganese. Neurotoxicology 45, 309–317.
Menezes-Filho, J.A., Novaes, C.O., Moreira, J.C., et al., 2011. Elevated manganese and cognitive performance in school-aged children and their mothers. Environ. Res. 111, 156–163.
Mergler, D., Baldwin, M., Bélanger, S., et al., 1999. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. Neurotoxicology 20, 327–342.
Miller, B.L., Cummings, J.L., 2007. The Human Frontal Lobes. The Guilford Press, New York, NY.
Park, R.M., Bowler, R.M., Eggerth, D.E., et al., 2006. Issues in neurological risk assessment for occupational exposures: the Bay Bridge welders. Neurotoxicology 27, 373–384.
Raven, J., Court, J.H., 1995. Manual for Raven's Progressive Matrices and Vocabulary Scales. Section 7: Research and References: Summaries of Normative, Reliability, and Validity Studies and References to All Sections Harcourt Assessment, San Antonio, TX.
Riojas-Rodríguez, H., Solís-Vivanco, R., Schilmann, A., et al., 2010. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. Environ. Health Perspect. 118, 1465–1470.
Rodriquez-Agudelo, Y., Riojas-Rodriguez, H., Rios, C., et al., 2006. Motor alterations associated with exposure to manganese in the environment in Mexico. Sci. Total Environ. 368, 542–556.
Roels, H., Lauwerys, R., Buchet, J., et al., 1987. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am. J. Ind. Med. 11, 307–327.
Roels, H.A., Bowler, R.M., Kim, Y., et al., 2012. Manganese exposure and cognitive deficits: a growing concern for manganese neurotoxicity. Neurotoxicology 33, 872–880.
Sadek, A.H., Ronald, R., Shulz, P.E., 2003. Parkinsonism due to manganism in a welder. Int. J. Toxicol. 22, 393–401.
Santos-Burgoa, C., Rios, C., Mercardo, L.A., et al., 2001. Exposure to manganese: health effects on the general population, a pilot study in central Mexico. Environ. Res. 85, 90–104.
Shin, Y.C., Kim, E., Cheong, H.K., et al., 2007. High signal intensity on magnetic resonance imaging as a predictor of neurobehavioral performance of workers exposed to manganese. Neurotoxicology 28, 257–262.
Solís-Vivanco, R., Rodríguez-Agudelo, Y., Riojas-Rodríguez, H., et al., 2009. Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese. Environ. Toxicol. Pharmacol. 28, 172–178.
Solís-Vivanco, R., Rodríguez-Agudelo, Y., Riojas-Rodríguez, H., et al., 2009. Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese. Environ. Toxicol. Pharmacol. 28, 172–178.
Stern, R.A., White, T., 2003. Neuropsychological Assessment Battery: Administration, Scoring and Interpretation Manual. Psychological Assessment Resources, Inc., Lutz, FL.
Strauss, E., Sherman, E., Spreen, O., 2006. A Compendium of Neuropsychological Test: Administration, Norms and Commentary. Oxford University Press, New York.
Stuss, D.T., 2007. New approaches to prefrontal lobe testing. Hum. Frontal Lobes: Funct. Disord. 2, 292–305.
Tabachnick, B., Fidell, L.S., 2006. Using Multivariate Statistics. Allyn & Bacon, Inc., Needham Heights, MA.
Torres-Agustín, R., Rodríguez-Agudelo, Y., Schilmann, A., et al., 2013. Effect of environmental manganese exposure on verbal learning and memory in Mexican children. Environ. Res. 121, 39–44.

U.S. EPA, 2010a. SAT Initiative: East Elementary School. U.S. Environmental Protection Agency, East Liverpool, OH. Available: http://www.epa.gov/schoolair/pdfs/EastTechReport.pdf (accessed 13.11.10).

U.S. EPA, 2010b. SAT Initiative: The Ohio Valley Education Center (Marietta, OH), Warren Elementary School (Marietta, OH), and Neale Elementary School (Vienna, WV). U.S. Environmental Protection Agency. Available: http://epa.gov/schoolair/pdfs/MariettaTechReport.pdf (accessed 16.03.11).

Viana, G.F., de Carvalho, C.F., Nunes, L.S., et al., 2014. Noninvasive biomarkers of manganese exposure and neuropsychological effects in environmentally exposed adults in Brazil. Toxicol. Lett. 231, 169–178.

Wasserman, G., Liu, X., Parvez, F., et al., 2011. Arsenic and manganese exposure and children's intellectual function. Neurotoxicology 32, 450–457.

Wasserman, G.A., Liu, X., Parvez, F., et al., 2006. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ. Health Perspect. 114, 124–129.

Wechsler, D., 1997. WAIS-III & WMS-III Technical Manual. The Psychological Corporation, San Antonio, TX.

Wright, R.O., Amarasiriwardena, C., Woolf, A.D., et al., 2006. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. Neurotoxicology 27, 210–216.

Yuan, H., He, S., He, M., et al., 2006. A comprehensive study on neurobehavior, neurotransmitters and lymphocyte subsets alteration of Chinese manganese welding workers. Life Sci. 78, 1324–1328.

Zoni, S., Lucchini, R.G., 2013. Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings. Curr. Opin. Pediatr. 25, 255–260.