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Manganese Exposure and Neurologic Outcomes in Adult Populations

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INTRODUCTION

Manganese (Mn) plays a critical role in many physiologic processes, including protein and energy metabolism, cellular protection from damaging free radicals, bone mineralization, immune function, reproduction, digestion, and metabolic regulation.[1] Although vital in trace amounts, Mn overexposure has been associated with neurodegeneration and neurotoxicity.[2] Chronic exposure to increased levels of Mn in occupational settings has resulted in a condition called manganism. Manganism is characterized by extrapyramidal symptoms, including bradykinesia, dystonia, gait instabilities, and speech impairments.[3] In 1837, Dr

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The authors have nothing to disclose.

John Couper first reported neurologic features associated with Mn exposure when several employees of a Mn processing facility presented with extrapyramidal symptoms. During the twentieth century, research remained focused on occupational exposure to Mn with workplace studies in industries such as welding, mining, and the manufacturing of Mn-containing products. In recent decades, research has become more focused on investigating the impact of chronic low-level exposure to Mn within the general population to understand the subsequent cognitive and neuromotor effects. In 1999, Mergler and colleagues[2] were among the first to investigate the impact of low-level environmental exposure to Mn within a community setting. Subtle neurologic impairments were observed in relation to blood Mn levels. Current research builds on this concept by substantiating that lower-level environmental exposures are associated with subclinical neurologic effects.[4]

Abundant exposure to Mn occurs through diet,[5] with factors such as age, gender, and nutritional status affecting absorption rates, which range from 1% to 5%.[6] Although Mn is naturally present throughout the environment, anthropogenic sources such as industrial air pollution, agricultural fungicides, and gasoline additives contribute to the burden of excess environmental Mn. The inhalation of Mn is concerning because of greater absorption rates, especially within the brain.[5] Homeostatic regulation is efficient at stabilizing levels of ingested Mn; however, airborne Mn may bypass these mechanisms and directly enter the brain by crossing the blood-brain barrier through membrane transporter proteins, transferrin and transferrin receptors,[7] or via the olfactory nerve.[8]

Depending on the route of exposure, Mn absorption occurs via the gastrointestinal tract or lung with subsequent distribution throughout the body.[9] The highest levels of Mn are reported in various organs, including the liver, bone, kidneys, pancreas, adrenal gland, and the pituitary gland within the brain.[10] Typical levels of Mn in blood range from 4 to 15 μg/L.[5] Circulating Mn is typically bound to hemoglobin; thus, the main compartment for Mn is the erythrocytes.[11] The liver plays the primary role in the biological regulation of Mn by conjugating excess Mn to bile for excretion through the intestine.[9] As indicated by the neurologic impairments associated with Mn exposure, the brain is very vulnerable to Mn toxicity. Mn accumulates in the brain with an affinity toward the basal ganglia structures.[12] With a half-life estimated to be around 150 days, Mn has a slow clearance rate from the brain.[13,14] In addition, it is thought that the high energy requirement and longevity of neurons contributes to enhanced neurologic susceptibility to Mn.[9]

This article examines the recent literature investigating the neurologic impact of Mn exposure on adult populations. This article synthesizes study findings to create a better understanding of the current state of research and to provide suggestions for future research directions.

METHODS

This systematic review investigates the effect of Mn exposure on adult neurocognitive and neuromotor function. In 2016, a systematic review assessing Mn exposure and cognition across the lifespan was published.[4] Thus, to incorporate the findings from current research into the discussion regarding adult Mn exposure and neurocognition, the authors searched for studies that were published between January 2016 and November 2019 investigating Mn exposure and neurocognition. We identified studies that met our criteria though PubMed and Medline using the following search terms: (manganese) AND (neurocognition OR cognition OR neuro) AND (adults) AND (occupation OR occupational OR environment OR environ*) ("2016/01/01"[Date – Publication]: "2019/11/01"[Date – Publication]). Previously, a review was published to assess the literature regarding Mn exposure and neuromotor outcomes.[15] Therefore, we searched for studies that evaluated Mn exposure among adults and were published between November 2007 and November 2019. Studies that met our criteria were obtained using both PubMed and Medline and the following search terms: (manganese) AND (neurofunctional OR neuromotor OR motor OR neurobehavioral) AND (adults) AND (welders OR occupational OR occupational OR environ*) ("2007/07/ 01"[Date – Publication]: "2019/11/01"[Date – Publication]).

DISCUSSION

Exposure Biomarkers

There is a substantial amount of research characterizing Mn exposure through environmental matrices such as water,[16–18] soil,[16,18,19] and air.[16,20–36] Although these markers indicate levels of external exposure, they are not able to specify individual dose concentrations. In epidemiologic studies, personalized biomarkers of exposure strengthen study findings by capturing internal dose measurements and minimizing reporting bias. However, there is no concurrence on which biomarker of Mn exposure is ideal. Table 1 provides an overview of several different biomarkers commonly used in the studies included in this article.

Blood Mn/iron ratio (MIR) was used as the biomarker for exposure in a study conducted in Guizhou, China.[27] The decline in fine motor movement was worsened by Mn exposure, and plasma MIR was inversely associated with fine motor skills. Viana and colleagues[44] in 2014 incorporated saliva measurements in a study of residents in Brazil living near a ferromanganese refinery to assess Mn exposure; however, no significant correlations were detected with saliva. Urine has been used as a Mn biomarker in many studies[16,18,19,28,29]; however, the future use of urine as a biomarker is not recommended. Toenails, fingernails, and hair are more frequently collected and analyzed for Mn content.[21,44–47] A Brazilian community study also collected scalp hair, axillary hair, and fingernail specimens, all of which were positively correlated with neuromotor function. Bone, a novel biomarker of Mn exposure, is an appealing biomarker of exposure because of the long-term storage of Mn. Rolle-McFarland and colleagues[45] in 2019 described associations between bone Mn levels and cognitive deficits, which may stem from underlying hippocampal and striatal impairments. Wells and colleagues[48] in 2018 found similar associations between increased hand bone Mn concentrations and reduced manual dexterity in an occupational cohort.

Many factors influence personal exposure levels, including ingestion or inhalation rates, age,[4] gender,[49] iron (Fe) status,[50] and nutritional status.[6] Although exposure may remain constant, variability in individual accumulation of Mn has also been noted. Mutations in Mn transporter and Fe metabolism genes are associated with variations in Mn accumulation,[51–54] thus predisposing an individual to Mn excess or depletion. An Italian study discovered that there was a higher prevalence of Parkinson disease (PD) in the areas surrounding a ferroalloy smelter.[19] Polymorphisms in ATP13A2 (PARK9), a PD-related gene, had a significant impact on the observed effects among the older participants.

Occupational Findings

With known increased exposure levels, the earliest adverse effects related to Mn exposure were first noted in occupational settings. Since the initial observations, regulatory measures have been established to govern exposure; however, a strong consensus on the proper exposure limits is lacking.[55] Table 2 provides an overview of the occupational studies included in this review. A recent study of welders assessed Mn exposure through reported work history[56] and accumulated exposure to welding fumes.[57] Lower cognitive scores were associated with welding fume exposure. In China, a questionnaire was administered to welders to assess potential Mn exposure through queries such as duration of work and type of workplace.[35] Similarly, increased Mn exposure through welding histories was associated with negative health outcomes.

In a cohort study, welders compared with nonwelder referents had poorer performance on motor tests; however, there were no statistically significant associations indicating poorer test performance related to Mn exposure.[28] Similarly, Mn exposure assessed from personal monitoring was significantly associated with worse stability of handwriting among welders.[30] When measuring Mn dust at a ferromanganese alloy plant, initial and follow-up examinations on exposed workers showed a significant association between poorer motor performance and exposure.[58] In a cohort of welders, Mn cumulative exposure was strongly associated with the progression of limb bradykinesia and limb rigidity.[22] In another study, the duration of Mn exposure and Mn small respirable particulates were strongly associated with motor function.[59]

To assess the permanency of Mn-associated health outcomes among acutely exposed welders, a follow-up neuromotor examination was done 3.5 years after cessation of confined-space welding.[60] Symptoms including extrapyramidal, olfactory, and mood disturbances did not improve over time and may even have deteriorated, whereas cognitive function seemed to improve for the retired welders. To investigate even longer-term cessation of exposure to Mn, a study recruited welders who had been retired for an average of 18 years.[61] Results were similar among retired welders and referents.[61]

Community Findings

The studies of community exposure to Mn are described in Table 3. A study among people living near a ferromanganese refinery in Ohio and a demographically similar community examined the effects of long-term, low-level environmental Mn exposure on neuromotor function.[33] No association was found between blood Mn levels and Unified Parkinson’s Disease Rating Scale (UPDRS) data or postural sway; however, adjusted models showed significant differences between the exposed and the referents, with heightened impairments observed among the exposed. Similar results were seen using the same study population, where blood Mn and cumulative exposure index did not predict any motor outcomes.[62] Another study conducted in the same region showed a significant association of airborne Mn with several neuromotor outcomes.[25] Increased tremor and motor symptoms, executive dysfunction, and tremor-dominant and non–tremor-dominant symptom clusters were identified in chronically exposed residents.[20]

Older populations are vulnerable to environmental exposures for multiple reasons. First, older adults have the opportunity for chronic exposure, particularly if they reside in a community with a Mn point source. Second, older generations were likely exposed to contaminants at greater levels than are present today because of changes in regulations and advances in control technology. Third, aging is a key risk factor for neurologic decline and the development of neurodegenerative disorders. Studying older populations provides an insight into the potential health issues that may burden future generations if exposure patterns are not altered. An Italian study recruited older adults living near a ferroalloy plant to represent people with lifelong exposure to environmental Mn.[16] The researchers observed a negative correlation between airborne Mn and coordination, with women showing greater motor dysfunction than men. Using the same cohort, Rentschler and colleagues,[19] in 2012 described a negative association between soil Mn and motor coordination, again with women showing greater motor dysfunction.[19]

Although personal biomarkers are generally preferred, some studies justify applying environmental measures to indicate Mn exposure. In a study of environmentally exposed adults,[20,63] Mn exposure was estimated based on the US Environmental Protection Agency's AERMOD (atmospheric dispersion modeling) dispersion models. Researchers aimed to determine whether subtypes of Mn neurotoxicity were similar to those observed in PD.[20] Among those exposed to low levels of Mn, subtle cognitive impairment was observed; however, there was no indication of motor dysfunction. Findings indicate that PD and Mn-induced motor disorders have distinct pathophysiology patterns.

Neuroimaging

MRI is useful as a biomarker of exposure because of its ability to show Mn accumulation in the brain. Because of its paramagnetic properties, Mn is a longitudinal relaxation time (T1) contrast agent, which means that, when water is excited with radiofrequency pulses within the MRI scanner, the manner in which the signal decays is influenced by accumulated Mn. For T1-weighted images, regions of the brain with Mn accumulation show higher signal than other regions. One method to assess Mn accumulation is with the pallidal index (PI). This metric takes the ratio of signal intensity in 2 anatomic locations of a T1-weighted image, usually the globus pallidus and frontal white matter. PI seems to be higher in exposed groups versus controls[64] and shows a dose-response relationship with blood Mn and recent air-exposure Mn,[26,64] as well as workers' cumulative Mn exposure.[65] Shin and Aschner[66] found a significant relationship between PI and motor dysfunction, as measured by pursuit aiming tests and finger tapping, respectively.

Another method for assessing Mn accumulation in the brain is by directly measuring T1. Because Mn accumulation leads to shorter T1 values, the inverse of the T1, R1 ($R1 = 1/T1$), is commonly used. Researchers have found that the relationship between Mn exposure and Mn accumulation in the brain is not straightforward. For 1 cohort of welders, R1 increased after 300 hours of work in the past 90 days, suggestive of a Mn exposure threshold below which there are no significant increases in R1.[36,67] In another cohort of welders, R1 increased significantly only for those exposed to air exposure greater than 0.1 mg/m^3.[68] In addition, R1 was sensitive to changes in Mn exposure and changed proportionately with fluctuating levels of Mn exposure.[69] However, changes in R1 in relation to short-term Mn exposure are influenced by the person's lifetime cumulative exposure,[70] suggesting that lifetime exposure may have a longer-lasting effect on Mn retention in the brain. Some studies associated T1 with impaired cognitive performance. Shorter T1 was related to lower performance on verbal fluency, verbal learning, memory, and preservation tests.[23] Verbal dysfunction, which is not commonly tested, may be an early symptom of Mn exposure. In addition, T1 changes have been detected when there is low Mn exposure and before neurologic changes are clinically evident.[71]

MRI technology can also be used to measure neurochemicals in vivo with magnetic resonance spectroscopy (MRS). MRS can measure many chemicals in the millimolar range, including gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Because of its high abundance in the basal ganglia, GABA has been targeted as a potential biomarker for motor dysfunction with Mn exposure. Consequently, thalamic GABA levels have been found to be higher in workers in smelters[29,72] and welders,[31,70] where it also correlated with Mn exposure as measured at 12-month and -month intervals. In a study of welders by Ma and colleagues[31] (2018), highly exposed welders had higher thalamic GABA levels as well as higher UPDRS3 scores compared with less exposed welders and controls. Although thalamic GABA also correlated with R1 in the substantia nigra and frontal cortex, thalamic GABA did not correlate with UPDRS3 scores. Thalamic GABA changes proportionately with increasing or decreasing Mn exposure in the workplace; however, UPDRS3 scores seem to remain static.[70]

To measure cognitive processes during tasks, functional MRI (fMRI) is a useful biomarker of effect. fMRI is based on the principle that the brain uses more energy in regions of the brain that are used during particular tasks, which results in measurable increased blood flow (seen as blood oxygen level–dependent contrast) in regions of increased cognitive use. To test the effect of Mn on memory, Chang and colleagues[32] (2010) used a commonly used paradigm, the *N*-back task, where participants are asked to remember pertinent items from *N* trials previously presented. Chang and colleagues[32] used a 2-back task and found welders have increased brain activity in working memory networks compared with controls. Using the Wisconsin Card-sorting Task (WCST), Seo and colleagues[73] (2016) found that welders had lower activation compared with controls in the areas of the brain related to executive function, such as the prefrontal cortex, under conditions of higher cognitive demand. However, although air Mn exposure was measured in both of these studies, there was large variability within each cohort and air Mn exposure was not taken into account in any of the reported analyses.

In addition, brain structure can be assessed using diffusion tensor imaging (DTI) and voxel-based morphometry (VBM). DTI measures the integrity of white matter by determining how free water can diffuse within a given location. The greater water diffusion is restricted within fibers, the higher its fractional anisotropy (FA), and vice versa. Higher FA corresponds with increased fiber organization. In general, FA has been found to be lower in the corpus collosum,[34] frontal white matter,[34] and basal ganglia[36,74] in welders. Specifically, lower FA was found in the basal ganglia of welders with 30 years or more of experience welding,[36] suggesting that long-term exposure to Mn might have a degradational effect on neuronal integrity beyond normal aging. Lower FA was also related to fine motor dysfunction, as measured by synergy indices.[74]

Using VBM, Chang and colleagues[75] (2013) found decreased brain volume in the globus pallidus and cerebellar regions in welders, which correlated with cognitive performance and grooved-pegboard performance. However, this is the only study to have been performed with significant results in morphometry, which is confounded because of the difficulty in segmenting the basal ganglia because of high signal intensity caused by Mn exposure.

Manganese and Neurodegenerative Diseases

Evidence suggests that, because of accumulation in the brain, neurotoxic metals may play a role in neurodegenerative diseases.[76] Exposure to toxic levels of Mn results in manganism, a neurodegenerative condition, and is implicated in the etiopathogenesis of several prevalent neurodegenerative diseases, including PD and Alzheimer disease (AD).[77] Because of numerous links between Mn and PD-like symptoms, Mn exposure may be involved with PD development; however, inconsistent results have been reported.[78] A meta-analysis was conducted in 2018 and results suggest that increased Mn concentrations may be a potential risk factor for PD.[79] Multiple assessments may be used to observe the prevalence of parkinsonian symptoms, such as the UPDRS, pegboard tasks, and various motor tasks.[22,36,56] Lee and colleagues[36] observed significantly lower stability in welders compared with controls; however, UPDRS scores were similar. There was an association between cumulative Mn exposure and UPDRS scores in a cohort of US welders.[22] Findings suggest that there are associations between neurodegenerative patterns in Mn toxicity and parkinsonian features along with further potential associations with movement disorder symptoms.[20] Mn seems to accelerate the transmission of misfolded alpha-synuclein, a protein that, when misfolded, clumps and becomes toxic to neurons and has thus been linked to PD.[80] However, contrary to PD, Mn-induced movement disorders likely result from the reduced ability to release dopamine.[78,81,82]

Because of the age distribution among workers, many occupationally based studies do not include senior participants. However, when investigating cognitive decline, older adults may be among the most vulnerable populations to consider when studying the neurotoxic impacts of Mn exposure. More than 35 million people worldwide have dementia and the incidence rate is expected to increase over the next few decades.[83] Dementia is a condition that encompasses significant impairments in memory, thinking abilities, social skills, and behavior.[83] AD, the most common form of dementia, has suggestive causal links with preceding Mn exposure. Pinto and colleagues[18] examined a group of older participants living in close proximity to Estarreja Chemical Complex (ECC), a source of environmental contamination in Portugal. The investigators described an association between mild and moderate dementia and high concentrations of several metals, including Mn. Previous research has proposed that Mn may be a contributing factor in the pathogenesis of AD by disrupting amyloid-β (Aβ) peptide degradation.[84] In a sample of Portuguese residents, Pinto and colleagues[18] observed associations between high concentrations of Mn measured in water and moderate levels of dementia. In mouse models, the intraperitoneal injection of a Mn chelator was effective at reducing Mn levels within the brain, decreasing Aβ peptides, and restoring cognitive function,[84] thereby providing a potential avenue to explore with regard to human intervention. However, opposing observations have been made as well. A meta-analysis conducted by Du and colleagues[85] described low serum Mn levels among people with mild cognitive impairment and AD. Further investigation into the potential relationship between Mn and AD is of great public health and socioeconomic interest.

Summary

Overall, the research included in this review contributes novel and valuable information to the existing literature and provides directions for future research. Innovative biomarkers, including those from advanced neuroimaging, were incorporated into many studies to assess both Mn exposure and neurologic outcomes. Studies examining the effects of occupational exposures to Mn continue to show adverse neurologic outcomes. With participants from communities located near Mn point sources, usually industrial facilities, studies in these populations show variability in the observed effects, which reflects the complexities of Mn exposure measurement, individual absorption, and impairment assessment. Unique populations, specifically those incorporating older adults, were used to study the impact of lifelong Mn exposure and provide insight into what the future may hold for younger exposed populations.

Limitations

The literature is saturated with studies investigating occupational Mn exposure, and, as a result, studies involving women are lacking. Although gender influences the development and progression of AD[86] and PD,[87] hormonal uniqueness is hypothesized to affect the pharmacokinetics of Mn as well.[49] Therefore, gender-based selection bias limits the ability to generalize from many studies. Regarding occupational research, there is possible bias from the healthy worker effect because sicker workers may no longer be actively employed.[58] Inaccurate work history and the lack of a reliable biomarker may contribute to recall bias and exposure misclassification among participants.[22,24,26,30,32,33] In addition, sample size constraints pose a challenge to many epidemiologic studies.[27,30,44–46,60,73,74,88] It is known that coexposures may influence the neurotoxicity of Mn; therefore, possible confounding may be present because of failure to consider concomitant exposures such as tobacco smoke[89] and lead.[90] In addition, because of the cross-sectional nature of many of the reviewed studies, temporality is not feasible to definitively establish and future studies would benefit from using a longitudinal design.

REFERENCES

1. Aschner M Manganese: brain transport and emerging research needs. Environ Health Perspect 2000;108(Suppl 3):429–32. [PubMed: 10852840]
2. Mergler D, Baldwin M, Belanger S, et al. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. Neurotoxicology 1999; 20(2–3):327–42. [PubMed: 10385894]
3. Rodier J Manganese poisoning in Moroccan miners. Br J Ind Med 1955;12(1): 21–35. [PubMed: 14351643]

4. Vollet K, Haynes EN, Dietrich KN. Manganese exposure and cognition across the lifespan: contemporary review and argument for biphasic dose-response health effects. Curr Environ Health Rep 2016;3(4):392–404. [PubMed: 27722879]
5. Agency for Toxic Substances and Disease Registry. Toxicological profile for manganese 2019. Available at: https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id5102&tid523. Accessed July 29, 2019.
6. Aschner JL, Aschner M. Nutritional aspects of manganese homeostasis. Mol Aspects Med 2005;26(4–5):353–62. [PubMed: 16099026]
7. Peres TV, Schettinger MR, Chen P, et al. Manganese-induced neurotoxicity: a review of its behavioral consequences and neuroprotective strategies. BMC Pharmacol Toxicol 2016;17(1):57. [PubMed: 27814772]
8. Crossgrove J, Zheng W. Manganese toxicity upon overexposure. NMR Biomed 2004;17(8):544–53. [PubMed: 15617053]
9. Chen P, Bornhorst J, Aschner M. Manganese metabolism in humans. Front Biosci (Landmark Ed) 2018;23:1655–79. [PubMed: 29293455]
10. O’Neal SL, Zheng W. Manganese Toxicity Upon Overexposure: a Decade in Review. Curr Environ Health Rep 2015;2(3):315–28. [PubMed: 26231508]
11. Montes S, Riojas-Rodriguez H, Sabido-Pedraza E, et al. Biomarkers of manganese exposure in a population living close to a mine and mineral processing plant in Mexico. Environ Res 2008;106(1):89–95. [PubMed: 17915211]
12. Bouabid S, Tinakoua A, Lakhdar-Ghazal N, et al. Manganese neurotoxicity: behavioral disorders associated with dysfunctions in the basal ganglia and neurochemical transmission. J Neurochem 2016;136(4):677–91. [PubMed: 26608821]
13. Takeda A Manganese action in brain function. Brain Res Brain Res Rev 2003; 41(1):79–87. [PubMed: 12505649]
14. Leggett RW. A biokinetic model for manganese. Sci Total Environ 2011;409(20): 4179–86. [PubMed: 21802707]
15. Zoni S, Albini E, Lucchini R. Neuropsychological testing for the assessment of manganese neurotoxicity: a review and a proposal. Am J Ind Med 2007;50(11): 812–30. [PubMed: 17918193]
16. Lucchini RG, Guazzetti S, Zoni S, et al. Neurofunctional dopaminergic impairment in elderly after lifetime exposure to manganese. Neurotoxicology 2014;45: 309–17. [PubMed: 24881811]
17. Lucchini RG, Aschner M, Landrigan PJ, et al. Neurotoxicity of manganese: Indications for future research and public health intervention from the Manganese 2016 conference. Neurotoxicology 2018;64:1–4. [PubMed: 29429640]
18. Cabral Pinto MMS, Marinho-Reis AP, Almeida A, et al. Human predisposition to cognitive impairment and its relation with environmental exposure to potentially toxic elements. Environ Geochem Health 2018;40(5):1767–84. [PubMed: 28281140]
19. Rentschler G, Covolo L, Haddad AA, et al. ATP13A2 (PARK9) polymorphisms influence the neurotoxic effects of manganese. Neurotoxicology 2012;33(4): 697–702. [PubMed: 22285144]
20. Kornblith ES, Casey SL, Lobdell DT, et al. Environmental exposure to manganese in air: Tremor, motor and cognitive symptom profiles. Neurotoxicology 2018;64: 152–8. [PubMed: 28965701]
21. Hassani H, Golbabaei F, Shirkhanloo H, et al. Relations of biomarkers of manganese exposure and neuropsychological effects among welders and ferroalloy smelters. Ind Health 2016;54(1):79–86. [PubMed: 26423330]
22. Racette BA, Searles Nielsen S, Criswell SR, et al. Dose-dependent progression of parkinsonism in manganese-exposed welders. Neurology 2017;88(4):344–51. [PubMed: 28031394]
23. Bowler RM, Yeh CL, Adams SW, et al. Association of MRI T1 relaxation time with neuropsychological test performance in manganese- exposed welders. Neurotoxicology 2018;64:19–29. [PubMed: 28587807]
24. Chang Y, Kim Y, Woo ST, et al. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. Neurotoxicology 2009;30(4):555–63. [PubMed: 19376157]
25. Bowler RM, Beseler CL, Gocheva VV, et al. Environmental exposure to manganese in air: Associations with tremor and motor function. Sci Total Environ 2016;541:646–54. [PubMed: 26437342]

26. Shin YC, Kim E, Cheong HK, et al. High signal intensity on magnetic resonance imaging as a predictor of neurobehavioral performance of workers exposed to manganese. Neurotoxicology 2007;28(2):257–62. [PubMed: 16647136]
27. Cowan DM, Fan Q, Zou Y, et al. Manganese exposure among smelting workers: blood manganese-iron ratio as a novel tool for manganese exposure assessment. Biomarkers 2009;14(1):3–16.
28. Ellingsen DG, Kusraeva Z, Bast-Pettersen R, et al. The interaction between manganese exposure and alcohol on neurobehavioral outcomes in welders. Neurotoxicol Teratol 2014;41:8–15. [PubMed: 24263125]
29. Long Z, Li XR, Xu J, et al. Thalamic GABA predicts fine motor performance in manganese-exposed smelter workers. PLoS One 2014;9(2):e88220. [PubMed: 24505436]
30. Laohaudomchok W, Lin X, Herrick RF, et al. Neuropsychological effects of low-level manganese exposure in welders. Neurotoxicology 2011;32(2):171–9. [PubMed: 21192973]
31. Ma RE, Ward EJ, Yeh CL, et al. Thalamic GABA levels and occupational manganese neurotoxicity: Association with exposure levels and brain MRI. Neurotoxicology 2018;64:30–42. [PubMed: 28873337]
32. Chang Y, Lee JJ, Seo JH, et al. Altered working memory process in the manganese-exposed brain. Neuroimage 2010;53(4):1279–85. [PubMed: 20620213]
33. Kim Y, Bowler RM, Abdelouahab N, et al. Motor function in adults of an Ohio community with environmental manganese exposure. Neurotoxicology 2011;32(5): 606–14. [PubMed: 21840336]
34. Kim Y, Jeong KS, Song HJ, et al. Altered white matter microstructural integrity revealed by voxel-wise analysis of diffusion tensor imaging in welders with manganese exposure. Neurotoxicology 2011;32(1):100–9. [PubMed: 21111757]
35. Zhang H, Xu C, Wang H, et al. Health effects of manganese exposures for welders in Qingdao City, China. Int J Occup Med Environ Health 2017;30(2): 241–7. [PubMed: 28366954]
36. Lee EY, Flynn MR, Lewis MM, et al. Welding-related brain and functional changes in welders with chronic and low-level exposure. Neurotoxicology 2018;64:50–9. [PubMed: 28648949]
37. Laohaudomchok W, Lin X, Herrick RF, et al. Toenail, blood, and urine as biomarkers of manganese exposure. J Occup Environ Med 2011;53(5):506–10. [PubMed: 21494156]
38. Zheng W, Fu SX, Dydak U, et al. Biomarkers of manganese intoxication. Neurotoxicology 2011;32(1):1–8. [PubMed: 20946915]
39. Wang D, Du X, Zheng WJTl. Alteration of saliva and serum concentrations of manganese, copper, zinc, cadmium and lead among career welders. Toxicol Lett 2008;176(1):40–7. [PubMed: 18054180]
40. Coetzee DJ, McGovern PM, Rao R, et al. Measuring the impact of manganese exposure on children’s neurodevelopment: advances and research gaps in biomarker-based approaches. Environ Health 2016;15(1):91. [PubMed: 27576472]
41. Sriram K, Lin GX, Jefferson AM, et al. Manganese accumulation in nail clippings as a biomarker of welding fume exposure and neurotoxicity. Toxicology 2012; 291(1–3):73–82. [PubMed: 22085607]
42. Liu Y, Byrne P, Wang H, et al. A compact DD neutron generator–based NAA system to quantify manganese (Mn) in bone in vivo. Physiol Meas 2014;35(9):1899. [PubMed: 25154883]
43. O’Neal SL, Hong L, Fu S, et al. Manganese accumulation in bone following chronic exposure in rats: steady-state concentration and half-life in bone. Toxicol Lett 2014;229(1):93–100. [PubMed: 24930841]
44. Viana GF, de Carvalho CF, Nunes LS, et al. Noninvasive biomarkers of manganese exposure and neuropsychological effects in environmentally exposed adults in Brazil. Toxicol Lett 2014;231(2):169–78. [PubMed: 24992226]
45. Rolle-McFarland D, Liu Y, Mostafaei F, et al. The association of bone, fingernail and blood manganese with cognitive and olfactory function in Chinese workers. Sci Total Environ 2019;666:1003–10. [PubMed: 30970467]
46. Palzes VA, Sagiv SK, Baker JM, et al. Manganese exposure and working memory-related brain activity in smallholder farmworkers in Costa Rica: Results from a pilot study. Environ Res 2019;173:539–48. [PubMed: 30991177]

47. Ward EJ, Edmondson DA, Nour MM, et al. Toenail manganese: a sensitive and specific biomarker of exposure to manganese in career welders. Ann Work Expo Health 2017;62(1):101–11. [PubMed: 29186301]
48. Wells EM, Liu Y, Rolle-McFarland D, et al. In vivo measurement of bone manganese and association with manual dexterity: A pilot study. Environ Res 2018; 160:35–8. [PubMed: 28961467]
49. Finley JW, Johnson PE, Johnson LK. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. Am J Clin Nutr 1994; 60(6):949–55. [PubMed: 7985639]
50. Finley JW. Manganese absorption and retention by young women is associated with serum ferritin concentration. Am J Clin Nutr 1999;70(1):37–43. [PubMed: 10393136]
51. Haynes EN, Heckel P, Ryan P, et al. Environmental manganese exposure in residents living near a ferromanganese refinery in Southeast Ohio: a pilot study. Neurotoxicology 2010;31(5):468–74. [PubMed: 19879291]
52. Thompson K, Molina RM, Donaghey T, et al. Olfactory uptake of manganese requires DMT1 and is enhanced by anemia. FASEB J 2007;21(1):223–30. [PubMed: 17116743]
53. Claus Henn B, Kim J, Wessling-Resnick M, et al. Associations of iron metabolism genes with blood manganese levels: a population-based study with validation data from animal models. Environ Health 2011;10:97. [PubMed: 22074419]
54. Anagianni S, Tuschl K. Genetic disorders of manganese metabolism. Curr Neurol Neurosci Rep 2019;19(6):33. [PubMed: 31089831]
55. Deveau M, Maier A, Krewski D. Application of a framework for the selection of an appropriate occupational exposure limit for manganese. Neurotoxicology 2017; 58:249–56. [PubMed: 27663849]
56. Racette BA, Criswell SR, Lundin JI, et al. Increased risk of parkinsonism associated with welding exposure. Neurotoxicology 2012;33(5):1356–61. [PubMed: 22975422]
57. Al-Lozi A, Nielsen SS, Hershey T, et al. Cognitive control dysfunction in workers exposed to manganese-containing welding fume. Am J Ind Med 2017;60(2): 181–8. [PubMed: 27862095]
58. Bouchard M, Mergler D, Baldwin M, et al. Neurobehavioral functioning after cessation of manganese exposure: a follow-up after 14 years. Am J Ind Med 2007;50(11):831–40. [PubMed: 17096374]
59. Park RM, Bouchard MF, Baldwin M, et al. Respiratory manganese particle size, time-course and neurobehavioral outcomes in workers at a manganese alloy production plant. Neurotoxicology 2014;45:276–84. [PubMed: 24721790]
60. Bowler RM, Gocheva V, Harris M, et al. Prospective study on neurotoxic effects in manganese-exposed bridge construction welders. Neurotoxicology 2011;32(5): 596–605. [PubMed: 21762725]
61. Wastensson G, Sallsten G, Bast-Pettersen R, et al. Neuromotor function in ship welders after cessation of manganese exposure. Int Arch Occup Environ Health 2012;85(6):703–13. [PubMed: 22038089]
62. Bowler RM, Harris M, Gocheva V, et al. Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure. Int J Hyg Environ Health 2012;215(3):393–405. [PubMed: 22112744]
63. Bowler RM, Kornblith ES, Gocheva VV, et al. Environmental exposure to manganese in air: Associations with cognitive functions. Neurotoxicology 2015;49: 139–48. [PubMed: 26096496]
64. Li SJ, Jiang L, Fu X, et al. Pallidal index as biomarker of manganese brain accumulation and associated with manganese levels in blood: a meta-analysis. PLoS One 2014;9(4):e93900. [PubMed: 24718592]
65. Criswell SR, Nielsen SS, Warden MN, et al. MRI signal intensity and parkinsonism in manganese-exposed workers. J Occup Environ Med 2019;61(8):641–5. [PubMed: 31348423]
66. Soldin OP, Aschner M. Effects of manganese on thyroid hormone homeostasis: potential links. Neurotoxicology 2007;28(5):951–6. [PubMed: 17576015]
67. Lee EY, Flynn MR, Du G, et al. T1 relaxation rate (R1) indicates nonlinear Mn accumulation in brain tissue of welders with low-level exposure. Toxicol Sci 2015;146(2):281–9. [PubMed: 25953701]

68. Pesch B, Dydak U, Lotz A, et al. Association of exposure to manganese and iron with relaxation rates R1 and R2*- magnetic resonance imaging results from the WELDOX II study. Neurotoxicology 2018;64:68–77. [PubMed: 28847517]
69. Lewis MM, Flynn MR, Lee EY, et al. Longitudinal T1 relaxation rate (R1) captures changes in short-term Mn exposure in welders. Neurotoxicology 2016;57:39–44. [PubMed: 27567731]
70. Edmondson DA, Ma RE, Yeh CL, et al. Reversibility of neuroimaging markers influenced by lifetime occupational manganese exposure. Toxicol Sci 2019; 172(1):181–90.
71. Baker MG, Criswell SR, Racette BA, et al. Neurological outcomes associated with low-level manganese exposure in an inception cohort of asymptomatic welding trainees. Scand J Work Environ Health 2015;41(1):94–101. [PubMed: 25380186]
72. Dydak U, Jiang YM, Long LL, et al. In vivo measurement of brain GABA concentrations by magnetic resonance spectroscopy in smelters occupationally exposed to manganese. Environ Health Perspect 2011;119(2):219–24. [PubMed: 20876035]
73. Seo J, Chang Y, Jang KE, et al. Altered executive function in the welders: A functional magnetic resonance imaging study. Neurotoxicol Teratol 2016;56:26–34. [PubMed: 27208889]
74. Lewis MM, Lee EY, Jo HJ, et al. Synergy as a new and sensitive marker of basal ganglia dysfunction: A study of asymptomatic welders. Neurotoxicology 2016;56: 76–85. [PubMed: 27373673]
75. Chang Y, Jin SU, Kim Y, et al. Decreased brain volumes in manganese-exposed welders. Neurotoxicology 2013;37:182–9. [PubMed: 23685157]
76. Chen P, Miah MR, Aschner M. Metals and neurodegeneration. F1000Res 2016;5: 366. 10.12688/f1000research.7431.1.
77. Bowman AB, Kwakye GF, Herrero Hernandez E, et al. Role of manganese in neurodegenerative diseases. J Trace Elem Med Biol 2011;25(4):191–203. [PubMed: 21963226]
78. Guilarte TR. Manganese and Parkinson’s disease: a critical review and new findings. Environ Health Perspect 2010;118(8):1071–80. [PubMed: 20403794]
79. Du K, Liu MY, Pan YZ, et al. Association of circulating manganese levels with Parkinson’s disease: A meta-analysis. Neurosci Lett 2018;665:92–8. [PubMed: 29191695]
80. Harischandra DS, Ghaisas S, Zenitsky G, et al. Manganese-induced neurotoxicity: new insights into the triad of protein misfolding, mitochondrial impairment, and neuroinflammation. Front Neurosci 2019;13:654. [PubMed: 31293375]
81. Guilarte TR. Manganese neurotoxicity: new perspectives from behavioral, neuroimaging, and neuropathological studies in humans and non-human primates. Front Aging Neurosci 2013;5:23. [PubMed: 23805100]
82. Guilarte TR, Gonzales KK. Manganese-induced parkinsonism is not idiopathic parkinson’s disease: environmental and genetic evidence. Toxicol Sci 2015; 146(2):204–12. [PubMed: 26220508]
83. Organization; WH. Dementia. 2019. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed October, 10, 2019.
84. Tong Y, Yang H, Tian X, et al. High manganese, a risk for Alzheimer’s disease: high manganese induces amyloid-beta related cognitive impairment. J Alzheimers Dis 2014;42(3):865–78. [PubMed: 24961945]
85. Du K, Liu M, Pan Y, et al. Association of serum manganese levels with alzheimer’s disease and mild cognitive impairment: a systematic review and meta-analysis. Nutrients 2017;9(3):231.
86. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer’s disease: assessing sex and gender differences. Clin Epidemiol 2014;6:37–48. [PubMed: 24470773]
87. Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson’s disease. J Neurol Neurosurg Psychiatry 2007;78(8):819–24. [PubMed: 17098842]
88. Sen S, Flynn MR, Du G, et al. Manganese accumulation in the olfactory bulbs and other brain regions of "asymptomatic" welders. Toxicol Sci 2011;121(1):160–7. [PubMed: 21307282]
89. Pappas RS, Gray N, Gonzalez-Jimenez N, et al. Triple Quad-ICP-MS measurement of toxic metals in mainstream cigarette smoke from spectrum research cigarettes. J Anal Toxicol 2016;40(1):43–8. [PubMed: 26359486]

90. Neal AP, Guilarte TR. Mechanisms of lead and manganese neurotoxicity. Toxicol Res (Camb) 2013;2(2):99–114. [PubMed: 25722848]

91. Bouchard M, Laforest F, Vandelac L, et al. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ Health Perspect 2007;115(1):122–7.

KEY POINTS

- Chronic increased manganese (Mn) exposure is associated with cognitive and motor impairments in both occupational and community settings.
- Numerous biomarkers are used to ascertain Mn exposure.
- Neuroimaging is an innovate tool used as both a biomarker of Mn exposure and a biomarker of effect.
- Older adults are a novel population that can provide insight into the impacts of chronic Mn exposure and the role of Mn in the development and progression of neurodegenerative diseases.

Future Directions

- Elucidating the optimal biomarker of Mn exposure
- Leveraging novel methods, such as neuroimaging, to directly measure Mn exposure and characterize effects
- Considering individual variability with regard to both Mn accumulation and neurotoxicity
- Understanding the role of Mn in neurodegenerative diseases and ultimately developing intervention methods

CLINICS CARE POINTS

- Environmental exposures should be considered when assessing neurodevelopmental deficits and neurodegenerative diseases.
- Those with increased susceptibility to Mn accumulation (ie. individuals with liver diseases, patients receiving parenteral nutrition) should be carefully monitored for Mn associated effects.
- Efforts to mitigate elevated environmental Mn exposure, especially in vulnerable populations, should be taken.

Table 1

Biomarkers of manganese exposure

Acute Exposures			Cumulative Exposures		
Blood	**Urine**	**Saliva**	**Hair**	**Nails**	**Bone**
Most widely used biomarker of Mn exposure[38]	Poor correlation between Mn exposure and Mn levels in urine[39]	Although levels are present at concentrations similar to blood, saliva is an alternative noninvasive biomarker for Mn exposure[39]	Quantifies longer-term cumulative exposures transpiring over several months[40]	Fingernails and toenails are noninvasive measures that represent aggregate exposures spanning from several months to approximately 1 y[37]	Approximately 40% of Mn is stored in bone[45]
Mn in blood has a short half-life of hours[10]	Past studies have not made significant observations using urine as a Mn biomarker[38]	Saliva Mn levels seem to linearly increase with exposure[39]	Exogenous contamination is a significant concern[40]	Mn concentrations quantified in nails have been associated with levels of Mn in the striatum and midbrain regions[41,42] of the brain	Estimated half-life of Mn in bone is 8 y[10]
Optimal for acute exposures[37] such as occupational settings	The future use of urine as a marker of Mn exposure is not recommended[30]	Use of saliva as a Mn biomarker is questionable[10,38,39]	Used as a noninvasive biomarker in many studies[40]		Bone Mn concentrations have been correlated with Mn levels in the brain, specifically the striatum, hippocampus, and choroid plexus[43]

Table 2

Epidemiologic studies investigating occupational exposure to manganese

Author	Location	Study Design	Participants Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
Bouchard et al,[58] 2007	Canada	Prospective cohort	Exposed n = 69 Referents n = 68 Mean age 58.1 y	Mn ferroalloy plant	Dust (mg Mn/m^3 years) n = 69	Age, education, alcohol, and smoking	Motor Scale of the Luria-Nebraska, finger tapping, Dynamometer, 9-hole Hand Steadiness Test	Exposed had poorer scores compared with referents both in the initial and follow-up examinations for the Luria-Nebraska test. Increasing levels of CEI were significantly associated with poorer scores on the Luria Motor Scale and the Hand Steadiness Test
Shin et al, 2007[26]	Korea	Cross-sectional study	350 workers Age not specified	Manufacturing factories	Air (mg/m^3) n = 121 Blood (μg/dL) n = 121 Duration of work (years) n = 121 CEV n = 121 PI n = 111	Age, alanine aminotransferase, and educational level	WHO-NCTB and computerized finger tapping	The proportion of workers with increased signals increased with all the Mn exposure variables. The PI was significantly associated with a correct score of pursuit aiming II tests and finger tapping of the dominant hand
Cowan et al,[27] 2009	Guizhou, China	Cross sectional study	Smelters n = 26 18–56 y	Ferroalloy plant	Air (mg/m^3) Blood MIR n = 136 Plasma MIR n = 143 Mn concentration in erythrocytes n = 144	Age, years of education, sex, income, and years of employment	Groove-type steadiness tester, 9-hole tests, and Purdue Pegboard Coordination Test	Plasma MIR was significantly correlated with pegboard scores. Age-related decline in fine-movement coordination was observed among all study participants regardless of Mn exposure
Chang et al,[24] 2009	Korea	Cross-sectional study	Welders n = 43 Controls n = 29 40–57 y	Steel block factory	Air (mg/m^3) Blood (μg/dL) n = 72 PI n = 73	Age, educational level, alcohol consumption, and smoking	Grooved pegboard, finger-tapping test, CATSYS, hand pronation/supination test	Grooved-pegboard and finger-tapping tests showed significant differences between the 2 groups. Blood Mn levels were shown to be significantly associated with grooved pegboard (dominant hand)
Chang et al,[32] 2010	Korea	Cross-sectional study	Welders n = 42 Controls n = 26 40–57 y	Steel block factory	Air (mg/m^3) n = 73 Blood (μg/dL) n = 73	Age, educational level, alcohol	Grooved pegboard, finger-tapping test,	Hand pronation/ supination and finger-tapping tests were

Author	Location	Study Design	Participants Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
					Pallidal index n = 73	consumption, and smoking	CATSYS, hand pronation/supination test	significantly lower among the welders than among the controls
Bowler et al,[60] 2011	California	Prospective cohort	Welders n = 26 32–65 y	Mn-containing welding fumes	Blood (μg/L) n = 24	Age, ethnicity, duration of welding, type of welding, blood Pb, and smoking	UPDRS3 and the CATSYS Tremor system	Rigidity, dominant postural hand tremor, and body sway increased significantly at follow-up
Sen et al,[88] 2011	United States	Cross-sectional study	Welders n = 7 Controls n = 7 Mean age 48 y	Not specified	CEI (Mg Mn/m^3) n=7	Age	Grooved pegboard; MRI	The welders scored worse than the controls on the grooved-pegboard test for both dominant and nondominant hand
Laohaudomchok et al,[30] 2011	United States	Cross-sectional study	Welders n = 46 Mean age 37.4 y	Welding school	Air (μg/m^3) n = 46	Age, race, education, income, dietary Mn, and BMI	Neuroskill device and finger tapping	Mn exposure over a work shift was significantly associated with worse stability of handwriting
Kim et al,[33] 2011	Korea	Cross-sectional study	Welders n = 30 Controls n = 19 40–58 y	Factory	Air (μg/m^3) n = 100 Blood (μg/L) n = 191	Age, educational level, smoking status, and alcohol consumption status	Finger-tapping tests and the grooved-pegboard test	Fractional anisotropy and radial diffusivity were significantly associated with grooved-pegboard (dominant and nondominant hand) and finger-tapping (dominant and nondominant hand) test outcomes
Racette et al,[56] 2012	United States	Prospective cohort	389 welders 40–58 y	Factories and shipyards	CEI (Mg Mn/m^3) n = 886	Age at baseline, sex, race, tobacco smoking, alcohol consumption, and occupational pesticide exposure	UPDRS3	Exposure was most strongly associated with progression of upper limb bradykinesia, upper and lower limb rigidity
Wastensson et al,[61] 2012	Sweden	Cross-sectional study	Welders n = 17 Referents n = 21 Mean age 69 y	Shipyard	CEI (mA/m^2) n = 17	Age and smoking habits	The Kløve-Matthews static steadiness test, CATSYS, finger-tapping test, grooved-pegboard test, eurythmokinesimeter, diadochokinesimeter, and Jamar dynamometer	Former welders performed less well than referents in the grooved-pegboard test, and poorer performance was associated with CEI
Chang et al,[75] 2013	Korea	Cross-sectional study	Welders n = 40 Controls n = 26 40–58 y	Steel block factory	Air (mg/m^3) Blood (μg/dL) n = 66	Age, educational level, alcohol	MRI, Grooved-pegboard, and finger-tapping test	Significant brain volume reductions were found in

Author	Location	Study Design	Participants Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
						consumption, and smoking		welders compared with controls, and these volume reductions are associated with motor deficits
Ellingsen et al,[28] 2014	Russia	Cross-sectional study	Welders n = 137 Referents n = 137 19–70 y	Shipyard	Air (μg/m^3) n = 130 Blood (μg/L) n = 123 Urine (μg/g) n = 126	Age, tobacco smoking, the concentration of carbohydrate-deficient transferrin in serum, self-reported mild head injury, shift work, duration of education, coffee consumption	Finger-tapping, foot-tapping, grooved-pegboard, dynamometer, CATSYS 2000, Kløve-Matthews Static Steadiness and Hand Pronation-Supination tests	Welders had poorer performance on motor tests compared with nonwelder referents
Park et al,[59] 2014	Quebec, Canada	Cross-sectional study	Referents n = 67 Alloy workers n = 68 Mean age 43.9 y	Silico-Mn and ferro-Mn production plant	CE (mg/m^3) n = 68	Age and educational level	Luria-Nebraska Neuropsychological Battery–Motor Scale and Finger Tapping	The duration of Mn exposure and Mn as small respirable particulates is strongly associated with the Luria-Nebraska Motor Scale
Long et al,[29] 2014	Guangxi, China	Cross-sectional study	Smelters n = 9 Controls n = 23 Mean age 39.3 y	Mn-iron alloy factory	Air (mg/m^3) n=9 Blood (mg/L) n = 32 Urine (μg/L) n = 32	Age	Purdue pegboard motor testing	Increase in GABA level was significantly associated with the duration of exposure and significant inverse associations between GABA levels and all Purdue Pegboard Test scores in the smelter workers
Baker et al,[71] 2015	Washington	Prospective cohort	Welders n = 56 Mean age 28 y	Welding	Air (μg/m^3) n = 56 TI-weighted indices n = 17	Smoking status, alcohol drinker, prior self-reported loss of consciousness, self-reported respirator use, and age at baseline	Grooved pegboard (Lafayette Instrument Evaluation, West Lafayette, IN), UPDRS3	There were no associations between cumulative exposure and UPDRS3 score or grooved-pegboard time
Lewis et al,[69] 2016	Pennsylvania	Cross-sectional study	Welders n = 20 Controls n = 13 Mean age 47.1 y	Not specified	hW (hours) n = 20 yW (years) n = 20	Age, education level, BMI, and respirator use	Maximal voluntary contraction tasks, single-finger ramp tasks, quick force pulse production tasks., UPDRS, and the grooved-pegboard test	There also were no significant differences between welders and controls on the grooved-pegboard test
Seo et al,[73] 2016	Korea	Cross-sectional study	Welders n = 53 Controls n = 44 40+ y	Factories for mild steel	Air (mg/m3) n = 53 Blood (μg/dL) n = 97	Age, education level, tobacco use, alcohol consumption, use of	fMRI, Wisconsin Card-sorting Task, Word-	Blood Mn level was significantly higher in welders than in

Author	Location	Study Design	Participants Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
				blocks and shipbuilding		medication, medical history, subjective symptoms, job type (type of welding and duration), work history	Color Test, Computerized Neuropsychological Test	controls. Reaction time for given tasks were not significantly different between groups even though welders took longer. Based on fMRI images, no specific regions had significant activity in welders while WCST was being completed
Al-Lozi et al,[57] 2017	United States	Cross-sectional study	Welders n = 82 Nonwelders n = 13 23–66 y	Welding	Exposure welding metrics (duration, intensity and total exposure)	Work history, cumulative Mn exposure, age, sex, race, ethnicity, medical history, history of head injury, previous exposures, alcohol/tobacco use	Assess cognitive control in response inhibition, working memory, fluency, verbal fluency, letter-number sequencing, Two Black Letter Task, Go-N-Go, Simon Task, Cognitive Control Summary was scored for those completing all 5 tasks, WAIS3- verbal/ matrix reasoning	Poorer performance in cognitive control tasks in relation to welding fume exposure. Welders had lower IQ and cognitive control scores
Zhang et al,[35] 2017	Qingdao City, China	Cross-sectional study	n = 505 19–54 y	Welding	Work history	Smoking habits, years of work, education level, age	Questionnaires assessing symptoms	Correlation between the highest level of symptom reports with highest level of air Mn measurements. Those with >15 y of welding reported high levels of tremor and motor disabilities
Bowler et al,[23] 2018	United States	Cross-sectional study	Welders n = 26 Controls n = 17 ≥18 y	Welding for semitruck manufacture	Air (mg/m^3) n = 43 MRI n = 43	Age, education, ethnicity, alcohol consumption, smoking habits	Rey-O Copy Trial, Trials B Test, Trails A, Digit Symbol Coding, WAIS3, WHO-AVLT, verbal fluency	Welders scored lower than controls in verbal fluency, Parallel Lines Test, and Digit Symbol Coding. Welders had shorter T1 relaxation times
Lee et al,[36] 2018	Pennsylvania	Cross-sectional study	Welders n = 43 Controls n = 32 Age not stated	Welding	Blood (ng/mL) n = 75	Recent hours welding, lifetime exposure, cumulative exposure inhaled over lifetime	Grooved-pegboard test, UPDRS3, single-finger/ multifinger pressing task, MRI	Results of Phonemic Fluency Test suggest that processes associated with phonemic fluency are among some of the earliest changes in welders with low Mn exposure

Author	Location	Study Design	Participants Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
Ma et al,[31] 2018	United States	Cross-sectional study	Welders n = 39 Controls n = 22 Mean age 40 y	Mn fumes	Air (mg/m^3) n = 39	Age	UPDRS3	High exposure to Mn showed a significant increase of thalamic GABA levels, as well as significantly worse performance in general motor function
Wells et al,[48] 2018	United States	Cross-sectional study	Workers n = 7 Comparison n = 12 18–62 y	Trailer manufacturer	Bone Mn (μg/g) n = 19	Age and occupation	Purdue Pegboard Test	High MnBn was significantly associated with lower manual dexterity based on the Purdue pegboard assembly task
Criswell et al,[65] 2019	Midwest United States	Cross-sectional study	Mn-exposed welders n = 27 Other Mn-exposed workers n = 12 Nonexposed n = 29 22–69 y	Welding worksites	CEI n = 68 PI n = 68	Sex; age; imaging scan date; current consumption of cigarettes, caffeine or alcohol	UPDRS3	Cumulative Mn exposure is associated with increased PI. PI was associated with clinical parkinsonism
Palzes et al,[46] 2019	Zarcero County, Costa Rica	Cross-sectional study	Organic farmers n = 26 Conventional farmers n = 22 18+ y	Farmers from organic and conventional farms	Hair (μg/g) n = 33 Toenails (μg/g) n = 40	Sociodemographic characteristics, work history, medical history, computer literacy, age	Letter retrieving/working memory task, fNIR	Brain activity decreased with every 2-fold increase in nail and hair Mn concentration
Rolle-McFarland et al,[45] 2019	Zunyi, China	Cross-sectional study	Ferroalloy smelters n = 30 Manufacturing workers n = 30 ≥18 y	Equipment manufacturing and installation company (control) and ferroalloy smelting facility	Bone (μg/g) n = 60 Fingernail (μg/g) n = 55 Blood (μg/L) n = 60	Age, education, drinking status, smoking status	Animal naming, fruit naming, WHO/UCLA Verbal Learning Test (AVLT), UPenn Smell Identification Test	MnBn and MnFn are associated with decreased performance in cognitive function but not smell MnB had no association with cognitive function

Abbreviations: AVLT, auditory verbal learning test; BMI, body mass index; CEI, Cumulative Exposure Index; CEV, cumulative exposure variable; CATSYS, Coordination Ability Test System; GABA, gamma-aminobutyric acid; Ferro-Mn, ferromanganese; fMRI, functional MRI; fNIR, functional near infrared; IQ, intelligence quotient; hW, hours spent welding in the 90 day period preceding MRI; MnBn, Bone Mn; MnB, Blood Mn; MnFn, Fingernail Mn; NCTB, Neurobehavioral Core Test Battery; PI, pallidal index; UCLA, University of California, Los Angeles; UPDRS, Unified Parkinson Disease Rating Scale; UPenn, University of Pennsylvania; WAIS, Wechsler Adult Intelligence Scale; WHO, World Health Organization; yW, cumulative lifetime years welding.

Data from Refs.[23,24,26–32,34–36,45,46,48,56,57,59–61,65,71,73–75,88,91]

Table 3

Epidemiologic studies investigating community-level manganese exposures

Author	Location	Study Design	Participants; Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
Kim et al,[33] 2011	Ohio	Cross-sectional study	Exposed n = 100 Reference n = 90 30–75 y	Ferro-Mn and silico-Mn smelter	Air (μg/m^3) n = 100 Blood (μg/L) n = 190	Age, sex, ethnicity, smoking status, drinking status, educational level, household income, insurance status, serum ferritin, ALT, and GGT; BMI; medication history, blood lead, cadmium, and mercury	UPDRS and CATSYS 2000	UPDRS motor and postural sway scores were significantly higher in the exposed group than in the comparison group. No significant difference between the exposed and comparison groups was evident as to MnB
Bowler et al,[62] 2012	Ohio	Cross-sectional study	Exposed n = 100 Reference n = 91 30–75 y	Ferro-Mn smelter	CEI air (μg/m^3) n = 100 Blood (μg/L) n = 190	Age, sex, education, diabetes, mental health medication, and health insurance status	Finger tapping, grooved pegboard, dynamometer, and UPDRS	MnB did not predict any motor outcomes either in the exposed or in the comparison group
Rentschler et al,[19] 2012	Italy	Cross-sectional study	255 adults 63–80 y	Ferroalloy smelters	Soil (ppm) Blood (μg/L) Urine (mg/L)	Age and gender	Luria-Nebraska Motor Battery, stylus and balance plate	For both adolescents and elderly, negative correlations between Mn in soil and motor coordination were shown
Lucchini et al,[16] 2014	Brescia, Italy	Cross-sectional study	Exposed n = 153 Reference n = 102 65–75 y	Ferroalloy plant	Air (ng/m^3) n = 254 soil (ppm) n = 255 Blood (μg/L) n = 238 Urine (μg/L) n = 239	Age, gender, alcohol, smoke, and distance from the nearest ferro-Mn plant	Luria-Nebraska Neuropsychological Battery	Air Mn was negatively associated with the motor coordination tests of the Luria-Nebraska Neuropsychological Battery
Viana et al,[44] 2014	Bahia, Brazil	Cross-sectional study	89 adults 15–55 y	Ferro-Mn refinery	Scalp hair (μg/g) n = 81 Fingernail (μg/g) n = 73 Axillary hair (μg/g) n = 18 Saliva (μg/g) n = 82	Age, gender, years of schooling, locale of residence, time in years of residence in the communities, drinking habits, and family income	Grooved-pegboard Test	MnH, MnFN, and MnAxH levels were positively correlated with motor function for the dominant hand
Bowler et al,[25] 2016	Ohio	Cross-sectional study	186 adults 30–75 y	Ferro-Mn smelter	Air (μg/m^3) n = 186	Sex, employment status, household income	Finger tapping, hand dynamometer, grooved pegboard, and the CATSYS tremor system	Tremor and motor function were associated with higher exposure to airborne Mn
Cabral Pinto et al,[18] 2018	Estarreja, Portugal	Cross-sectional study	N = 103 residents 55+ y	Industrial activity	Urine Water Soil	Years of residency, medical history, health status, work history, education, water used in irrigation and drinking, use of	MMSE, MoCA, CDR Scale	Association between mild dementia and moderate dementia with high contents of Cr, Mn, Cd, and Se. Stream water was associated with dementia and

Author	Location	Study Design	Participants; Age at Motor Assessment	Source of Mn Exposure	Biomarker/ Environmental Measures	Covariates	Outcome Measure	Results
						homegrown foods, daily habits		high levels of Cr, Mn, Cd and Se in urine
Kornblith et al,[20] 2018	Ohio	Cross-sectional study	N = 182 30–75 y	Ferro-Mn smelter	Air (μg/m3) n = 182	Age, gender, employment, race, and years of residence	CATSYS, UPDRS	Increased tremor and motor symptoms and executive dysfunction were observed, and TD and NTD symptom clusters were identified

Abbreviations: ALT, alanine transaminase; CDR, Clinical Dementia Rating; GGT, gamma-glutamyl transferase; MMSE, Mini-Mental State Examination; MnAxH, Auxiliary Hair Mn; MoCA, Montreal Cognitive Assessment; NTD, non-tremor dominant; TD, tremor dominant.