

Manganese and Developmental Neurotoxicity

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Abstract Manganese (Mn) is an essential metal that plays a fundamental role for brain development and functioning. Environmental exposure to Mn may lead to accumulation in the basal ganglia and development of Parkinson-like disorders. The most recent research is focusing on early-life overexposure to Mn and the potential vulnerability of younger individuals to Mn toxicity also in regard to cognitive and executive functions through the involvement of the frontal cortex.

Neurodevelopmental disturbances are increasing in the society, and understanding the potential role of environmental determinants is a key for prevention. Therefore, assessing the environmental sources of Mn exposure and the mechanisms of developmental neurotoxicity and defining appropriate biomarkers of exposure and early functional alterations represent key issues to improve and address preventive strategies. These themes will be reviewed in this chapter.

Keywords Basal ganglia • Vehicle emissions • Methylcyclopentadienyl Mn tricarbonyl (MMT) • Fungicides • Deposited dust • Revised Conners' Teacher Rating Scale • Wechsler Intelligence Scale for Children (WISC) • Olfactory loss

Manganese in the Environment

The assessment of Mn occupational or environmental exposure is a key factor in order to investigate Mn toxicity. While in the occupational contexts personal air monitoring to different particles' granulometry (respirable vs inhalable) is essential to control and prevent Mn excessive exposure, an increasing variety of natural and anthropogenic sources of Mn in the environment can increase pre- and postnatal early-life exposure:

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(i) groundwater contamination, as a consequence of the weathering and leaching of Mn-bearing minerals and rocks into aquifers; (ii) use of the fungicides maneb and mancozeb, which contain approximately 21% Mn by weight; and (iii) emission from ferromanganese and iron industry (FAO 1979; Gulson et al. 2006; Wasserman et al. 2006; Menezes-Filho et al. 2009a, 2009b; Bouchard et al. 2011; ATSDR 2012; Lucchini et al. 2012b; Borgese et al. 2013; Gunier et al. 2013). Early-life exposure to Mn may be caused also by contamination of houses and cars used by Mn workers in various occupations, including welders and agricultural workers (Gunier et al. 2013). Manganese concentration in airborne particles is also higher in areas with intense traffic (Poulakis et al. 2015), showing a contribution of vehicle emissions in relation to non-exhaust sources such as road dust resuspension, break and tire wear, and road-wear abrasion (Thorpe and Harrison 2008) and to exhaust of potential combustion of the gasoline additive methylcyclopentadienyl Mn tricarbonyl (MMT) (Walsh 2007).

In order to investigate all the different ways in which Mn moves from the surrounding environment inside the human body, many studies have been conducted in various locations around the world during the last 30 years, targeting different environmental matrices: airborne particles, drinking water, deposited dust, soil, and vegetables.

Airborne Particles

Industrial activities, agricultural use of fungicides (maneb, mancozeb), and vehicle traffic can increase the ambient levels of Mn. Average air concentrations have been reported to range between 220 and 300 ng/m³ near industrial sources, whereas in urban and rural areas without point sources have been reported to range from 10 to 70 ng/m³ (WHO 2011).

Sampling for ambient levels and personal exposures provides direct measures of Mn exposure, but it may be difficult to obtain many data since such samples are time-consuming and expensive. Additionally, sampling only captures levels of exposure associated with the location and environmental conditions during the time of sampling, and this represents a limitation when the concern is cumulative exposure. Proximity measures used as surrogates for Mn exposure are inexpensive and easy to obtain but are limited in their ability to capture other factors that impact ambient air Mn concentrations such as wind direction, precipitation, and terrain. Air dispersion modeling may provide a viable alternative to ambient Mn exposure assessment: the AERMOD model (USEPA 2005) from the US Environmental Protection Agency, for example, estimates ambient air Mn values accounting for Mn emissions, terrain, and weather within a spatial and temporal context, all factors that influence the magnitude of exposure to an air pollutant (Fulk et al. 2016).

The inhalation of airborne particulate matter is the primary source of early-life exposure to Mn in the USA. Populations living in close proximity to industrial and agricultural sources may be at higher risk for developmental effects among children.

Deposited Dust

Deposited dust in houses and schools is another relevant potential source of pediatric Mn exposure, through both ingestion of contaminated hands and foods and inhalation of resuspended particles (Lioy et al. 2002; Zota et al. 2011). Dust sampling yields information on Mn concentration and loading. Samples are generally collected from a given measured surface of the main living area and of furniture or floor, sieved to the desired particle size (e.g., <250 μm), microwave-digested with HNO_3 , and analyzed using ICP-MS or XRF techniques. If the dust sample has sufficient mass (>0.1 g), this procedure has detection limits of 0.2 $\mu\text{g/g}$ for Mn concentration. Dust loadings ($\mu\text{g/m}^2$) are usually calculated as [(concentration \times mass collected)/area vacuumed].

Zota et al. (2016) evaluated 53 infants at the Tar Creek Superfund site (Oklahoma, USA) in two points in time corresponding to developmental stages before and during initial ambulation (0–6 and 6–12 months). They measured Mn, lead (Pb), arsenic (As), and cadmium (Cd) in indoor air, house dust, tap water, and yard soil and found that except for Cd, metals were detected in all dust samples and at a lesser extent in indoor air, tap water, and soil. They found hair Mn, Pb, and Cd associated to the dust levels, concluding that deposited dust may represent a better measurement of infant exposure to Mn and Pb, compared to air and soil. In fact, infants spend most of their time indoors, and therefore risk assessments and exposure mitigation strategies should prioritize intervention on house dust for early-life prevention.

Gulson et al. (2014) conducted a 5-year longitudinal study to assess potential changes to the environment and exposure of young children associated with the introduction of MMT into Australia in 2001 and its cessation of use in 2004. They evaluated a cohort of 108 children aged 0–5 in Sydney collecting longitudinal samples of Mn and Pb blood, soil, duplicate diet samples, and several types of house dust samples: interior house and day-care dust fall accumulation using Petri dishes, exterior dust fall accumulation, and exterior dust sweepings. Although they did not stratify their results for age, they found dust accumulation ($\mu\text{g/m}^2/30$ day) being the only significant predictor for blood Pb, while no medium predicted blood Mn. More recently, Menezes-Filho et al. (2016) measured Mn and Pb dust fall accumulation on Petri dishes in 15 elementary schools, located between 1.25 and 6.48 km from a Mn alloy production plant in the municipality of Simões Filho, Bahia, Brazil. Their sampling method was similar to the one adopted by Gulson et al. (2014), but they found that the interior school environments, located within a 2-km radius from the plant, showed loading rates on average 190 times higher than the Mn levels measured in the day-care centers in Sydney, while Pb loading rates were not associated with distance from the plant and were lower than the rates observed in the same day-care centers in Sydney.

Surface Soil

Exposure through soil is especially relevant for children playing in contaminated playground or environment, due to their hand-to-mouth behavior and maximized gastrointestinal absorption. Manganese is in soils both in organic and inorganic forms and oxidation states, i.e., 0, +2, +3, +4, +6, and +7. Its mobility is extremely sensitive to soil conditions such as acidity, wetness, organic matter content, and biological activity (Nadaska et al. 2012). Research emphasis has been placed on the toxic effects of compounds containing inorganic Mn^{2+} , Mn^{3+} , and Mn^{4+} ions since these are the forms most commonly encountered in biological systems (Millaleo et al. 2010). With decreasing pH, the amount of exchangeable Mn – mainly Mn^{2+} form – increases in the soil solution. This Mn form is available for plants and can be readily transported into the root cells and translocated to the shoots, where it is finally accumulated. In contrast, other forms of Mn predominate at higher pH values, such as Mn(III) and Mn(IV), which are not available and cannot be accumulated in plants (Millaleo et al. 2010). Different techniques have been applied to laboratory determination of total Mn in soil, including spectrophotometry, polarography, atomic absorption spectrometry (AAS), and inductively coupled plasma atomic emission spectrometry (ICP-AES) or mass spectrometry (ICP-MS) (Pearson and Greenway 2005). Field portable x-ray fluorescence (XRF) is an exemplary field method, offering extremely rapid, cost-effective screening of total heavy metal concentration in soil by in situ measurement.

The total Mn content in soils is variable. Some authors reported small amounts of Mn in soils, ranging from 20 to 10,000 mg/kg soil, whereas other authors have registered total Mn contents between 450 and ~4000 mg Mn/kg soil (Adriano 2001). Potential bioavailability may not be properly addressed by the measure of total soil and can be investigated by means of sequential chemical extraction procedures, where a soil sample is divided into its composing fractions: metal compounds present in the first fraction are those that are weakly bound at cation exchange sites in the matrix and hence chemically very labile. Subsequent processing steps typically extract metals from the carbonate phase, organic matter, etc. Metals in the water/acid soluble and exchangeable fractions are considered the most mobile and potentially bioavailable forms present in soils and may best capture the anthropogenic contribution of greatest possible concern for children exposure, followed by the carbonate phase (Borgese et al. 2013).

Metal soil contamination resulting from anthropogenic activities is associated to increased health risks among children in the surrounding of smelters (Carrizales et al. 2006) and mines (Pruvot et al. 2006). A significant positive association between soil Mn exposure and both impaired motor coordination and odor discrimination was observed among Italian adolescents (Lucchini et al. 2012b,) and elderly (Zoni et al. 2012; Lucchini et al. 2014) residing near ferroalloy emission sites.

Edible Vegetables

Manganese occurs naturally in many food sources, such as leafy vegetables, nuts, grains, and animal products. For vegetables and vegetable products, mean concentrations range between 0.42 and 6.64 mg/kg (IOM 2002). The Food and Nutrition Board of the Institute of Medicine set adequate intake levels for Mn at 2.3 mg/day for adult men and 1.8 mg/day for adult women (IOM 2002). Adequate intake levels for Mn were also set for other age groups; the values were 0.003 mg/day for infants from birth to 6 months, 0.6 mg/day for infants from 7 months to 1 year, 1.2 mg/day for children aged 1–3 years, 1.5–1.9 mg/day for children aged 4–13 years, and 1.6–2.3 mg/day for adolescents and adults (WHO 2011). Higher levels on Mn were measured in lattice, but not in *Cichorium* spp. or turnip, cultivated in the vicinities of ferroalloy emissions (Ferri et al. 2012, 2015).

Drinking Water

The detection of Mn in groundwater in the USA is approximately 70% of the sites due to the ubiquity of Mn in soil and rock, although the levels detected are generally not considered of public health concern (USEPA 2002). ATSDR (2012) reported Mn levels from <11 to >51 µg/l in a river water survey in the USA. Higher levels found in aerobic waters are usually associated with industrial pollution. Concentrations in seawater have been reported from 0.4 to 10 µg/l, averaging 2 µg/l, whereas in freshwater, they typically range from 1 to 200 µg/l (ATSDR 2012).

Manganese intake from drinking water is substantially lower than the food intake. At the median drinking water level of 10 µg/l determined by the National Inorganic and Radionuclide Survey, the intake of Mn would be 20 µg/day for an adult, assuming a daily water intake of 2 liters. In Germany, the drinking water supplied to 90% of all households contains less than 20 µg/l of Mn (WHO 2011). Gonzalez-Merizalde et al. (2016) investigated the case of artisanal and small-scale gold mining activities performed in mountain areas of the southern Ecuadorian Amazon, which contaminated the aquatic system of the Nangaritza River Basin with mercury (Hg) and Mn, posing health risks for the populations living in the adjacent zones. Children living in alluvial areas showed the highest Mn concentrations in hair, whereas greater values of urinary Hg were found in children living in the high mountain areas, where the ore processing takes place inside or close to houses and schools. This suggests that Hg vapors impact directly the area where they are produced, while waterborne Mn can travel significant distances before impacting the population.

Studies about high level of Mn in drinking water in Quebec reported that the Revised Conners' Teacher Rating Scale oppositional and hyperactivity subscales (Bouchard et al. 2007) were inversely related to hair Mn. Among Bangladeshi children drinking tube-well water, it was found that IQ (Wasserman et al. 2006) and academic achievement (Khan et al. 2012) were inversely related to the level of Mn

in drinking water. In the fourth edition of Guidelines for Drinking-Water Quality (WHO 2011), the 400- $\mu\text{g/L}$ drinking-water guideline for manganese (Mn) was discontinued. Concentrations $> 400 \mu\text{g/L}$ are found in a substantial number of countries worldwide and may have been too high to adequately protect public health (Ljung and Vahter 2007). Toxic effects and geographic distribution of Mn in drinking-water supplies require reevaluation by the WHO of its decision to discontinue its drinking-water guideline for Mn (Frisbie et al. 2012).

Toxicology and Biomarkers

Metabolism

Manganese is a naturally occurring trace element essential for human development and function of the brain and other biological processes. As a trace element, Mn is assumed with the diet (mainly with grains, fruits, vegetables, tea) and, once ingested, is absorbed through the small intestine in a proportion of about 3–4%. Gastrointestinal absorption is influenced by the iron metabolism: a deficiency of iron increases the absorption of Mn through some transport proteins, like DMT1 and TFR, which both of these metals have in common (DeWitt et al. 2013).

Manganese is highly needed for the developing brain, and therefore the transplacental absorption is maximized during pregnancy (Guan et al. 2014). When exposure occurs through inhalation, Mn is absorbed through the alveolar-capillary membrane in percentage between 40 and 70%, depending on the size of the particles, and by their water solubility. Another possible route of absorption is the olfactory tract, especially for small particles, that, through the olfactory mucosa, can reach directly sensory areas of the brain (Elder et al. 2006; Lucchini et al. 2012c). An important exposure route for the children is inhalation/ingestion of resuspended soil particulates (Harris and Davidson 2005) or deposited house and school dust (Pavilonis et al. 2014; Lucas et al. 2015) and consumption of contaminated locally grown vegetables (Hough et al. 2004; Ferri et al. 2012, 2015).

Manganese is subjected to an efficient homeostatic control of gastrointestinal absorption and urinary excretion, based on the ratio between absorbed amount and concentration of Mn in the tissues. The absorbed Mn is conveyed in the blood bound to proteins (transferrin, alpha-2-macroglobulin) and in the proportion of 85% to red blood cells. It is deposited mainly in the liver, pancreas, and kidneys and less in bone and adipose tissue. The brain has a small proportion of Mn deposit, but the retention times are long. The Mn values in the adult population not occupationally exposed are between 3.0 and 8.0 $\mu\text{g/l}$ in whole blood and between 0.1 and 1.2 $\mu\text{g/l}$ in the serum (SIVR 2011). Much higher levels are measured during pregnancy and at birth, as shown by Mn in umbilical cord, and gradually decrease postnatally (Claus Henn et al. 2010).

Manganese is eliminated via the gastrointestinal tract through the bile, the intestinal mucosa, and pancreatic secretion. The main excretion of Mn is carried in the feces regardless of route of introduction, while the portion excreted in the urine is low, about 6% of the total, but with a high individual variability depending on age, sex, smoking, and alcohol intake.

Pediatric Absorption

Children are exposed to Mn through the mother during pregnancy and after birth through breastfeeding or formulas; in the neonatal period, during childhood and adolescence, the primary sources of exposure are potentially through drinking water, inhalation of airborne particles, and ingestion of particles from dust and soil. Exposure to Mn by ingestion or inhalation poses higher risks compared to adults, in relation to the different mechanisms of absorption and elimination: the intestinal absorption rate of ingested Mn in children is higher; the high demand for Fe linked to growth can further enhance the absorption of ingested Mn; the excretion rate is lower than in adults because of the poorly developed biliary excretion mechanism; the ratio of inhaled air/body weight is substantially higher (Menezes-Filho et al. 2009a, b).

Biomarkers

A variety of potential biomarkers are available to evaluate Mn exposure in children, including maternal/cordonal blood, blood, serum, plasma, urine, nails, saliva, and hair (Zheng et al. 2011). Blood and urinary Mn reflect exposure over a short and recent period of time (from hours to days), whereas nails and hair longer periods up to several months (Smith et al. 2007; Zheng et al. 2011). Nails and in particular toenails show higher accumulation related to longer-term cumulative exposure (Laohaudomchok et al. 2011). Hair Mn is considered the most consistent and valid biomarker for pediatric exposure and has been found to be associated to intelligence quotient (IQ) decrement by most studies (Coetzee et al. 2016). Hair grows 1 cm per month and provides exposure information for a period of 1–6 months, with variability due to hair pigmentation and potential external contamination (Eastman et al. 2013; Haynes et al. 2015).

A new biomarker, Mn in deciduous teeth, can estimate the exposure windows during prenatal development and early childhood. Deciduous teeth accumulate metals and their mineralization proceeds in an incremental pattern spanning the prenatal and early postnatal periods, commencing gestational week 13–16 for incisors, and concluding postnatal age 10–11 months for molars. Therefore, the distribution

of Mn in deciduous teeth can provide information on environmental Mn exposure during fetal development and early childhood. Usually, deciduous teeth are replaced by permanent teeth from the age of 6–12 years. The deposit of metals in teeth has been correlated with exposure in pre- and postnatal period, measuring Mn in the house dust and in the blood and bone of the mother prenatally and cord blood and blood in the postnatal period (Arora et al. 2012; Gunier et al. 2015). This biomarker can provide information about exposure timing and intensity over the fetal period, in particular second and third trimesters, and during early childhood and cumulative early-life exposure (Andra et al. 2015).

Effects on Cognitive Functions

An increasing number of studies have focused on the potential impact of early-life exposure to Mn on cognitive functions (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; Haynes et al. 2010, 2012, 2015). Manganese plays a vital role in brain growth and development, and therefore children are more vulnerable than adults to Mn dysfunction (Zoni and Lucchini 2013) in a U-shaped relationship where both insufficiency and excessive absorption can cause adverse effects (Claus Henn et al. 2010). Since brain susceptibility varies during the different phases of development, exposure windows are critical for neurotoxicity (Grandjean and Landrigan 2014). Prenatal and early postnatal periods are sensitive developmental windows for Mn exposure (Claus Henn et al. 2010; Lin et al. 2013; Liu et al. 2014) that can act as essential or toxic element as a function of exposure timing and dose (Sanders et al. 2015; Claus Henn et al. 2010; Chung et al. 2015).

Manganese is transported through the placenta (Erikson et al. 2007), and an elevated maternal exposure during pregnancy can lead to excessive fetal overload (Takser et al. 2004), with accumulation in the developing brain and changes in different neurological structures, which may be responsible of motor, cognitive, and behavioral impairment postnatally. Basal ganglia are the main target of Mn accumulation (Kim et al. 1999) and are involved in the regulation of inhibitory and disinhibitory processes at a cellular and behavioral level throughout the body, via dopaminergic pathways connecting to the frontal lobes (Lezak et al. 2012). These pathways are responsible for the coordination of higher-level cognitive functions including cognitive flexibility, response inhibition, and planning (Miller and Cummings 2007).

Intellectual Ability

A variety of tests and test batteries are used to detect and quantify cognitive effects of Mn exposure in children mostly with the Wechsler Intelligence Scale for Children (WISC) but also with other mental developmental indices (BSID, CDIIT,

etc.). A relevant number of studies have now reported effects on the reduction of IQ, using hair Mn as exposure biomarker. Children aged 7–9 years were examined in Marietta (Ohio), home to the largest operating ferromanganese industry in North America. Both low and high Mn concentrations in both blood and hair were negatively associated with the total IQ scores (Haynes et al. 2015). Other studies were conducted in various geographic locations, with moderate sample size, although usually higher than 200 subjects, and adjusted for several covariates including maternal education and intellectual ability, child age, child gender, and nutritional status (Bouchard et al. 2011; Menezes-Filho et al. 2011; Lin et al. 2013; Chung et al. 2015). A few cross-sectional studies in adolescents reported no significant association with IQ using blood Mn (Lucchini et al. 2012a; Bhang et al. 2013), although one of these reported significant associations with deficits on the Learning Disability Evaluation Scale (LDES) (Bhang et al. 2013). Despite limited sample size, a cross-sectional study of 1–4-year-old Uruguayan children reported also significant inverse associations of hair Mn with cognition and language (Rink et al. 2014). Taken all together, these studies support the conclusion that elevated early-life Mn exposure adversely impacts childhood cognition with particularly consistent associations with the IQ (Sanders et al. 2015).

The WISC battery is also used to assess cognitive effects caused by interaction between Mn and other developmental neurotoxicants such as Pb and As. Interaction between Pb or As and Mn and their co-exposure is associated with neurodevelopmental deficiencies that are more severe than expected based on the effects of exposure to each metal alone (Claus Henn et al. 2012; Rodrigues et al. 2016). Similarly, in utero exposure to high Pb and high Mn was associated with larger deficits in cognition and language development compared to low exposure to both metals or to exposure to high levels of only one metal at a time (Lin et al. 2013). In contrast, no statistical interaction was found between Pb and Mn on IQ in 11- to 14-year-old Italian children (Lucchini et al. 2012a).

The WISC has been used to assess both children's general cognitive abilities (IQ) and more specific cognitive functions through its subtests. A study by Rahman et al. (2016) aimed to evaluate potential adverse effects of elevated exposure to Mn in drinking water (W-Mn) from fetal life to school age in a large cohort of boys and girls during 10 years in Bangladesh. Gender was strongly influential in the models of prenatal exposure to W-Mn, with the different cognitive ability measures and the interaction between gender and W-Mn resulting significant for full IQ scale and sub-scales of verbal comprehension, working memory, and processing speed. Elevated prenatal W-Mn exposure was positively associated with cognitive function in girls, while boys appeared unaffected. This gender influence is observed in several children studies, although the underlying mechanism is still unclear. Several hypotheses have been suggested such as gender-related differences in epigenetic and/or hormonal factors (Barker et al. 2013; Tarrade et al. 2015) or different kinetics (Berglund et al. 2011; Oulhote et al. 2014). In experimental studies, postnatal exposure to Mn has been shown to alter the levels of monoamines and corticosterone in a sex-dependent manner (Vorhees et al. 2014) and cause more morphological changes in striatal medium spiny neurons in male than in female mice (Madison et al. 2011).

Executive Function

Manganese exposure during childhood can impact the executive function (FE), a set of cognitive processes including attentional and inhibitory control, working memory and cognitive flexibility, reasoning, problem-solving, and planning, necessary for cognitive control of behavior (Diamond 2013). Data from experimental study corroborate epidemiological research in children and suggest that exposure to Mn during neurodevelopment significantly alters dopaminergic synaptic environments in brain nuclei and in fronto-striatal circuits that mediate the control of executive function (Kern et al. 2010; Carvalho et al. 2014).

Children aged 6–12 years showed a significant association between Mn in blood and impaired visual attention, while Mn in hair was related to impaired performance of working memory. High levels of Mn from drinking water can affect inhibitory control (Nascimento et al. 2016). Similarly, in Brazilian children living near a ferromanganese alloy plant, airborne Mn exposure was associated to lower IQ and neuropsychological performance in tasks of inhibition responses, strategic visual formation, and verbal working memory (Carvalho et al. 2014).

All together, these results confirm a negative association between executive function and high Mn exposures reported also in a large body of occupational literature (Bowler et al. 2015).

Memory

Significant associations between Mn exposure and cognitive function have been observed also in the domains of learning and memory skills. A group of 174 Mexican children aged 7–11 years was evaluated with the Children's Auditory Verbal Learning Test (CAVLT). Compared to nonexposed subjects, they showed higher hair and blood Mn ($p < 0.001$) as well as lower scores ($p < 0.001$) for all the CAVLT subscales. Hair Mn was inversely associated with most CAVLT subscales, especially those evaluating long-term memory and learning. Blood Mn showed also a negative but nonsignificant association with the CAVLT scores (Torres-Agustín et al. 2013). This study confirmed the findings by Wright et al. (2006) based on the California Verbal Learning Test-Children (CVLTC) and the Wide Range Assessment of Memory and Learning (WRAML) scales. Children with higher Mn levels in that study recalled fewer words on the learning trials of the CVLTC as well as on both the short delay free recall and long delay free recall trials and fewer elements on the WRAML stories.

Imaging research on nonhuman primates has also shown that in addition to the basal ganglia, Mn affects the frontal cortex (Guilarte 2013), an area associated with strategic encoding, organization, and retrieval of verbal and visual memories (Stuss and Alexander 2007).

Academic Achievement

Although adverse effects of Mn on cognitive function raise concern about potential repercussion on children academic achievement, little scientific evidence is available on this aspect. In a rural area of Bangladesh, a cross-sectional study was conducted in 840 children, to investigate associations between the levels of Mn and As in drinking water and academic achievement in mathematics and languages among elementary school children aged 8–11 years. The annual scores of the study children in languages (Bangla and English) and mathematics were obtained from the academic achievement records of the elementary schools. No significant relation was observed between W-Mn and academic achievement in either language. Neither W-As was significantly related to any of the three academic achievement scores. Diversely, W-Mn at levels above the WHO standard of 400 µg/L was associated with a 6.4% score loss in the mathematics achievement test scores, after adjustment for W-As and other sociodemographic variables. These results suggest that deficits in mathematics may be induced by high concentrations of Mn in drinking water (Khan et al. 2012).

Effects on Motor Functions

Although a high number of studies have historically investigated the relation between Mn exposure and motor impairment in workers and adults, little research has focused on these issues in children. In a recent study of Rodrigues et al. (2016), a sample of Bangladeshi children aged 20–40 months were assessed using a translated, culturally adapted version of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Age-adjusted z-scores were calculated for the five test's domains (i.e., cognitive, receptive language, expressive language, fine motor, and gross motor). The results indicated that most associations between As, Pb, and Mn exposures and the BSID-III z-scores were linear, with the exception of W-Mn concentrations and fine motor scores, for which an inverse U-shaped curve was observed. The interpretation of an inverse U relationship is that at W-Mn <400 µg/L, Mn is beneficial to fine motor development, whereas at W-Mn >400 µg/L, Mn exposure is detrimental for motor function. These results differ from a previous study conducted on 375 Canadian children (Oulhote et al. 2014) that showed a significant association between the estimated Mn intake from water consumption and decreased performance at motor function tests. In the same study, no significant association was also observed between hair Mn and motor function.

A sample of 55 children, aged 7–9 years, was enrolled to determine the association between Mn and Pb exposure with neuromotor function in children. All measures of Mn exposure (blood, hair, and time-weighted distance from a ferromanganese emission) were significantly associated with poor postural balance. Low-level blood Pb was also negatively associated with balance outcomes (Rugless et al. 2014). In a previous study, adolescents aged 11–14 years were recruited in Val Camonica, a region impacted by

ferroalloy plants emissions for a century until 2001 and the reference area of Lake Garda (Italy). Several motor tasks were used including the Luria-Nebraska Motor Battery, finger tapping, visual simple reaction time, pursuit aiming, tremor test, and body sway. Regression models showed a significant impairment of motor coordination (Luria-Nebraska test), hand dexterity (pursuit aiming), and odor identification (Sniffin' task), as associated with soil Mn measured at the participants' house. Tremor intensity was directly associated with blood and hair Mn concentrations (Lucchini et al. 2012b).

However, few prospective studies have looked at the effects of both prenatal and postnatal Mn exposure on child cognitive and motor functions. Recently, a cohort of 248 children living near agricultural fields treated with Mn-containing fungicides in Salinas, California, have been studied longitudinally (Mora et al. 2015). Manganese levels was measured in prenatal and early postnatal dentine of shed teeth and confronted to behavior, cognition, memory, and motor functioning examined at the ages of 7, 9, and/or 10.5 years. Motor functions were assessed using finger tapping, the Pegboard tests, and five subtests of the Luria-Nebraska Motor Battery that have shown sensitivity to Mn exposure (Lucchini et al. 2012b). Results showed that higher prenatal and early postnatal Mn levels in dentine of deciduous teeth were adversely associated with behavioral outcomes in school-aged boys and girls. In contrast, higher Mn levels in prenatal and postnatal dentine were associated with better memory abilities and cognitive and motor abilities in school-aged boys (Mora et al. 2015). Hernández-Bonilla et al. (2011) assessed the association between Mn exposure and motor function in 195 children (100 exposed and 95 not exposed), aged 7–11 years, living in Mexico near a Mn mine. Motor functions were assessed with the Grooved Pegboard, the Finger Tapping, and the Santa Ana Test. Comparing exposed and not-exposed groups, a significant difference emerged in the number of errors on the Grooved Pegboard, where exposed subjects made errors more frequently during the test; no differences were observed between groups in the other two motor tests. An inverse association was observed between MnB and Finger Tapping performance for each hand.

The effects of As and Mn ingestion through drinking water, on children's motor functions, were further studied by Parvez et al. (2011). They investigated the association of W-As and W-Mn with motor function in a population of 304 children (8–11 years) from Bangladesh. They assessed motor functions using the Bruininks-Oseretsky test, generating a summary score (total motor composite, TMC) and four subscales: fine manual control (FMC), manual coordination, body coordination, and strength and agility. Adjusted model found an inverse association between As in blood and three motor scales: TMC, FMC, and BC. No associations were observed between MnB or PbB and motor function.

Behavior

Several studies showed an exposure-response relationship between Mn and neurobehavioral effects, but not conclusive. Most of the studies analyzed the exposure during childhood and fewer studies also during prenatal exposure.

Sanders et al. in an epidemiologic review (2015) about early-life Mn exposure identified seven studies that examined the association between early-life exposure to Mn and children/adolescent behavior. Taken together, these studies provide some evidence of a link between early-life Mn and ADHD (attention deficit hyperactivity disorder), ASD (autism spectrum disorder), and other adverse behavioral outcomes in children.

Attention Deficit Hyperactivity Disorder

ADHD is a neurodevelopmental disorder manifested by symptoms of inattention, hyperactivity, and impulsivity; it affects approximately 3–7% of school-aged children. Its persistence into adulthood may result in an approximately 1–4% prevalence of adult ADHD. Children with ADHD are at higher risk of developing psychiatric comorbidity (Hong et al. 2014; Sharma and Couture 2014). The exact etiology of ADHD is still unknown (Sharma and Couture 2014). The proposed neurotoxic mechanisms of Mn involve striatal dopamine neurotransmission, implicated in the pathophysiology of ADHD (Hong et al. 2014).

Sanders et al. (2015) considered a case-control study in the United Arab Emirates [although with the limits of a small case group (18 cases vs 74 controls) and not adjusted for any confounding variables] that reported increased odds of ADHD with increased blood Mn levels. They highlight also a large cross-sectional study of South Korean children where blood Mn levels were associated with poorer scores of commission on one of the three ADHD tests but with no association with doctor-diagnosed ADHD.

In addition, Mora et al. (2015) found that prenatal and early postnatal Mn levels in dentine of deciduous teeth were adversely associated with behavioral outcomes – namely, maternal reports of, using Conners' Rating Scales, internalizing and externalizing symptoms and hyperactivity problems, in school-aged boys and girls.

In a study by Benko et al. (2010), children with ADHD show significantly higher serum Mn concentrations. A cross-sectional study (Bouchard et al. 2007), using the Revised Conners' Teacher and Parent Rating Scales, demonstrated greater hyperactive and oppositional classroom behavior, associated with higher hair Mn from children, on average, 11 years old.

About remediation for ADHD, a case-cohort study in Brazil found that the treatment of adolescent ADHD with the common medication methylphenidate (Ritalin®) significantly reduced blood Mn levels (Farias et al. 2010). A recent study found that methylphenidate administered following chronic postnatal Mn exposure resulted in improved motor function in rats; however, there was no effect on Mn blood levels (Beaudin et al. 2015). If Mn metabolism is part of the underlying biologic pathway for ADHD, this finding may support the evidence for a biological role of Mn in the ADHD causation. Conversely, if methylphenidate alters Mn metabolism independently from its effect on ADHD, this may represent a source of bias. Further research is needed to replicate and understand this relationship.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impairs social interaction and communication. Currently, the etiology of ASD is still not well understood. A number of studies have indicated that ASD has a genetic factor. Others have suggested that there are combinations of factors that influence the etiology of ASD, including the interaction of genetic predisposition and environmental exposures (Rahbar et al. 2014; Rossignol et al. 2014).

Several studies examined the relationship between ASD and Mn exposure, as measured by air distribution, tooth enamel, hair, urine, and red blood cells, but with conflicting findings (Rahbar et al. 2014). Rossignol et al. (2014) supported the idea of an association between environmental toxicants and ASD. On the other side, they declare that many of the reviewed studies contain significant weaknesses and reveal a need for more high-quality epidemiological studies concerning e-relation between environmental toxicants and ASD. In particular, they highlight for Mn a study conducted with 325 children with ASD vs 22,101 controls. The study reported that perinatal exposure to the highest versus lowest quintile of air pollutants was significantly associated with an increased risk of ASD, including Mn (OR = 1.5; 95%), and an overall measure of metals was significantly associated with ASD suggesting that perinatal exposure to air pollutants may increase risk for ASD. Notably, a stronger association was observed in boys compared with girls for most pollutants, suggesting a sex-specific interaction (Roberts et al. 2013).

Comparing the blood Mn levels between ASD children and healthy Jamaican children, Rahbar et al. (2014) found no significant association between BMn and ASD, suggesting that there is no significant association between Mn exposures and ASD. The authors however underscore that blood Mn cannot be used to assess early exposure at potentially more susceptible time period.

Moreover, a case-control study of children in the USA with ASD found that cases had marginally significantly lower levels of tooth enamel Mn, representing postnatal exposure, compared to controls (Abdullah et al. 2012). These findings should be interpreted cautiously, however, because tooth enamel does not track early-life timing of exposure as well as tooth dentine, due to its longer maturation process (Arora et al. 2012).

The potential correlation between hair toxic metal concentrations and ASD severity was examined by Geier (2012) in a prospective cohort of participants diagnosed with moderate to severe ASD. Only hair Hg concentrations resulted significantly correlated with increased ASD severity, and for Mn, no significant correlations were observed for ASD severity.

Other Behavioral Outcomes

Neurobehavioral toxicities associated with Mn also include other behavioral aspects, often evaluated using checklist and questionnaires.

Sanders et al. (2015) analyze in their review three studies examining scales of adolescent behavior and reporting conflicting results. Firstly a cross-sectional study by Lucchini et al. (2012b) on 11- to 14-year-old Italian adolescents found that blood Mn was not associated with any of the other behavioral Conners' Rating Scale sub-scales. A second cross-sectional study of 8- to 11-year-olds in Bangladesh reported a significant association between drinking water Mn, but not blood Mn, with internalizing and externalizing behaviors (Khan et al, 2012). The third cross-sectional study of 7- to 12-year-old subjects in Brazil found significantly impaired performance on attention when comparing higher hair Mn tertiles to lower Mn but did not report a significant linear relationship (Carvalho et al. 2014).

Moreover, Rahman et al. (2016) assessed behavior problems in 1265 10-year-old children in rural Bangladesh. Elevated prenatal and early childhood exposure levels to W-Mn appeared to increase the risk of children's behavioral problems at 10 years of age. Behavioral problems were assessed using a specific questionnaire assessing conduct problems, hyperactivity/inattention, emotional symptoms, and peer relationship problems. Early-life W-Mn exposure appeared to adversely affect children's behavior. Results showed that W-Mn at all time points was significantly associated with increased risk of conduct problems. They found a significant interaction between gender and prenatal W-Mn for hyperactivity and between gender and W-Mn at 10 years of age for peer problems. Stratifying the models by gender indicated slightly stronger associations of prenatal W-Mn with conduct problems in boys (statistically significant) than in girls (not significant).

Menezes-Filho et al. (2014) verified externalizing behaviors and attention problems using Child Behavior Checklist (CBCL). For girls, CBCL was significantly associated with higher hair Mn.

Hong et al. (2014) demonstrated a correlation between blood Mn levels and behavioral problems like anxiety, social behavior, and aggression in ADHD.

Khan et al. (2011, 2012) in a cross-sectional study demonstrated a dose-response relationship between blood Mn levels and externalizing behavior problems like disruptive behavior and conduct problems and showed that higher water Mn concentrations are associated with lower achievement scores, IQ, and behavioral scores among children.

Effects on Olfactory Function

Elevated Mn exposure during pre-/early adolescence plays an important role in human neurotoxicity, and it is associated with olfactory function in children and elderly (Aschner et al. 2005; Lucchini et al. 2012b, Zoni and Lucchini 2013; Iannilli et al. 2016).

Inhalation of ultrafine particles represents one of the primary routes for neurotoxicity. Manganese exposure reduces significantly the surviving adult-born cells in the olfactory bulb and markedly inhibits their differentiation into mature neurons,

resulting in an overall decreased neurogenesis in this brain's region (Fu et al. 2016). Furthermore Mn, as other metals, is readily transported via olfactory pathways and may access to structures located within the brain (Zoni et al. 2012; Guarneros et al. 2013). Mn bypasses the blood-brain barrier and the homeostatic mechanisms that regulate absorption and excretion to keep Mn levels in the desired range. Through the inhalation route, Mn can reach the prefrontal cortex and the striatum altering monoaminergic signaling pathways, particularly dopaminergic transmission, in these two areas (Ye and Kim 2015).

The dopaminergic system plays a central role in the regulation of motor and olfactory function. Various clinical diseases which manifest in the adult life are known to present with olfactory loss, including Parkinson's disease (PD) and Alzheimer-type dementia (AD), which both present with significant smell loss in more than 70% of patients (Lucchini et al. 2014).

Olfactory deficit is an early sign of PD. Living in a Mn-affected environment area can cause impairment in the olfactory functions that may be potentially considered as an early warning for the onset of late neurodegenerative effects in the older age (Lucchini et al. 2012b).

Few studies explored the relation between olfactory functions and Mn exposure. Iannilli et al. (2016) in a pilot study comparing exposed preadolescent (who have spent their whole life span in contaminated areas) with not exposed controls assessed an fMRI experiment pointing at differences of brain activities. They found a generally lower sensory-odor response, and the decreased activity in the relevant brain olfactory areas suggests that young subjects exposed to Mn exhibit a significant reduction of subjective odor sensitivity and olfactory bulb volume. Moreover Mn exposure induces less activation of the limbic system, suggesting an alteration of brain network linked to odor perception and emotional responses (Iannilli et al. 2016).

Lucchini et al. (2012b) used the Sniffin' Sticks test (Hummel et al. 1997) to assess the response to a standardized odor source in 311 healthy adolescents living near a ferroalloy plant. They found a significant impairment of motor functions and of odor identification associated with soil Mn.

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