

Brain manganese and the balance between essential roles and neurotoxicity

Published, Papers in Press, March 18, 2020, DOI 10.1074/jbc.REV119.009453

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Edited by Paul E. Fraser

Manganese (Mn) is an essential micronutrient required for the normal development of many organs, including the brain. Although its roles as a cofactor in several enzymes and in maintaining optimal physiology are well-known, the overall biological functions of Mn are rather poorly understood. Alterations in body Mn status are associated with altered neuronal physiology and cognition in humans, and either overexposure or (more rarely) insufficiency can cause neurological dysfunction. The resultant balancing act can be viewed as a hormetic U-shaped relationship for biological Mn status and optimal brain health, with changes in the brain leading to physiological effects throughout the body and vice versa. This review discusses Mn homeostasis, biomarkers, molecular mechanisms of cellular transport, and neuropathological changes associated with disruptions of Mn homeostasis, especially in its excess, and identifies gaps in our understanding of the molecular and biochemical mechanisms underlying Mn homeostasis and neurotoxicity.

Manganese is essential for numerous vital processes including nerve and brain development and cognitive functioning. For most people, dietary consumption generally fulfills the requisite Mn intake (1). Even though Mn is crucial for maintaining optimal physiology, several aspects of the biology of the homeostatic control and toxicity of Mn remain unclear (2, 3). Unanswered questions include the subcellular and organelle distribution of Mn and the nature of cellular events that occur when deviations from Mn homeostasis occur (e.g. with exposure to chronic low levels of Mn). Mn has been implicated in the metabolism of proteins, lipids, and carbohydrates and acts as a cofactor for numerous kinases and other enzymes (4, 5). Because magnesium (Mg) and Mn share a resemblance in their

physicochemical properties, a vast majority of enzymes can use Mg in lieu of Mn for their activation (3).

Mn also plays unique roles that cannot be replaced by other metals, such as in Mn-dependent enzymes, including arginase, agmatinase, glutamine synthetase, and Mn superoxide dismutase (MnSOD).³ As a result, its presence at optimal levels to support these functions is required, and the lack of this essential micronutrient can give rise to cognitive deficits (6). Excess cellular levels of Mn are also detrimental, and this aspect of Mn-induced disease has gained attention in the field of toxicology. Mn accumulates in specific regions of the brain to selectively alter neurophysiology. Elevated brain Mn levels usually occur only following overexposure, which can result from numerous sources, including environmental sources, occupational exposures, or dietary exposures to Mn such as from contaminated drinking water.

The consequences of Mn overexposure occur throughout the nervous system and can affect both motor function and higher-order cognitive functions. Motor control is disrupted via disruption of dopaminergic (DAergic) function (7). This includes clinical expression of parkinsonism in occupationally exposed workers (8, 9). Occupational exposure to Mn has been linked to other unfavorable outcomes, including learning deficits and neurodegeneration (10). The consequences of Mn overexposure occur throughout the nervous system and affect motor functions. This review is focused on neurotoxicity and presents evidence that Mn plays a key role in the maintenance of brain physiological homeostasis and is a primary target of this metal (11). Recent identification of genetic disorders of Mn metabolism combined with studies providing insights into the mechanisms of Mn neurotoxicity make a comprehensive review on this topic timely. This review illuminates the unfavorable outcomes Mn exposure causes. There is urgency to explore and address the potential changes that are occurring at a molecular level, as these unfavorable outcomes are leading to increased risk of diseases. This attempt requires an interdisci-

This work was supported by NIEHS, National Institutes of Health, Grants R01 ES024812 (to S. M.), R01 ES016931 (to A. B. B.), R01 ES010563 (to A. B. B. and M. A.), R01 ES031401 (to F. E. H. and A. B. B.), and R01 ES026446 (to E. N. H.) and by Veterans Affairs Grant I01 CX001610-01 (to F. E. H.). The authors declare that they have no conflicts of interest with the contents of this article. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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³ The abbreviations used are: SOD, superoxide dismutase; DAergic, dopaminergic; PD, Parkinson's disease; MRI, magnetic resonance imaging; GABA, γ -aminobutyric acid; TH, tyrosine hydroxylase; DA, dopamine; D1R and D2R, DA subtype 1 and 2 receptor, respectively; DAT, dopamine transporter; IGF, insulin-like growth factor; AD, Alzheimer's disease.

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6312 *J. Biol. Chem.* (2020) 295(19) 6312–6329

plinary approach where scientists with expertise in neuroscience, biology, and chemistry to come together to think about the problem at hand.

Routes of manganese exposure and accumulation in the brain

Beyond occupational exposures, excessive dietary or drinking water uptake of Mn is another source of overexposure. The World Health Organization recommends that the daily Mn consumption for an adult be between 0.7 and 10.9 mg (12). Although use of Mn dietary supplementation containing greater than 20 mg of Mn has been reported in cases of osteoarthritis and osteoporosis (13, 14), to our knowledge, naturally occurring Mn deficiency has never been reported in humans. Ingested Mn has an absorption rate of 3–5% through the gastrointestinal tract and is subject to tight homeostatic control *in vivo* (15, 16). Systemic homeostatic control of Mn is a balance between transport across the enterocytes lining the intestinal wall and removal by the liver (17). Several factors can influence the oral uptake of Mn, including iron (Fe) status, dietary matrix, bioavailability, and existing body burden of Mn (18). Following oral intake, Mn is distributed widely to tissues, and its metabolism may also involve cycling between Mn²⁺ and Mn³⁺, although only a small fraction is found in the 3+ oxidation state (19). The oxidation state of Mn exposure is a critical determinant of Mn toxicokinetics, tissue toxicodynamics, and toxicity (20). Contaminated drinking water is another source of Mn exposure (21, 22). Metal concentrations in water vary by location, with Mn ranging from 0.0001 to 0.1 mg/liter (18). Although the United States Environmental Protection Agency does not consider Mn to be a primary drinking water contaminant, the standard concentration of allowable Mn is 0.05 mg/liter (23, 24). There are arguments that the current Mn reference concentration guidelines need to be re-evaluated to consider Mn as a potential contaminant (25), specifically when using water for infant formulas that already contain high levels of Mn (26). Inhalation is the predominant route of exposure associated with the toxic effects of Mn in adults. Current data suggest that Mn exposure via drinking water in children/adolescents is as important as inhalation exposure under environmental and occupational settings (27). Excess environmental exposure may arise from air pollution (28–31), gasoline enhanced with methylcyclopentadienyl manganese tricarbonyl (MMT) (32, 33), and agricultural fungicides (34, 35). Many of the initial epidemiologic studies of Mn and health outcomes examined occupational inhalation exposures within industries such as ferromanganese welding, mining, and refining (36–40). Inhaled Mn enters the circulatory system through the nasal mucosa, bypasses the biliary excretion mechanism, and can cross the blood-brain barrier via several pathways, including facilitated diffusion and active transport from the olfactory bulb to the cerebral cortex (41–44). Mn accumulates in Fe-rich brain regions of the basal ganglia: caudate, putamen, globus pallidus, substantia nigra, and subthalamic nuclei of the brain (43, 45, 46). Under normal conditions, estimated concentrations of Mn in the human brain range from 5.32 to 14.03 ng of Mn/mg of protein, with 15.96–42.09 ng of Mn/mg of protein being the estimated pathophysiological threshold (47). Based on occupa-

tional studies of Mn exposure, the Occupational Safety and Health Administration exposure limit for general industry, construction industry, and shipyard employment is 5 mg/m³ (RRID:SCR_018203). However, even with Mn airborne levels near the Environmental Protection Agency's reference concentration of 0.05 μg/m³ (23), exposure can result in deficits in postural balance and neuropsychological and motor functions (49–51) and increased risk for physician diagnosis of Parkinson's disease (PD) (52). Deficits in neuromotor function are similar among adult Mn-exposed workers (53, 54) and older PD patients (55). Longitudinal and cross-sectional environmental exposure studies link low-level Mn exposure to deficits in intellectual development (6), neurobehavior (56), neuromotor function (57), and neuropsychiatric changes with respect to attention and mood (58).

Using magnetic resonance imaging (MRI), several studies have shown that significant brain accumulation of Mn in both humans and other animal models is associated with increased risk of neurotoxicity. These subjects often show a characteristic accumulation of manganese in the basal ganglia, particularly in the globus pallidus (59–61). Mn accumulation was also observed in the frontal cortex (Fig. 1) (59). Although recovery upon cessation is possible (62), this rarely happens in cases of occupational exposures, which are prolonged and cumulative. In rodent studies, areas of notable accumulation include the olfactory bulb, cerebellum, hippocampus and dentate gyrus, and pituitary gland in addition to the basal ganglia (63, 64). Other studies in nonhuman primates have shown that inhaled ultrafine Mn particles translocate and accumulate in the olfactory bulb in addition to the striatum, frontal cortex, and cerebellum (43). In addition to using MRI to analyze brain Mn levels, other noninvasive methods of measuring total body Mn burden based on bone levels are being used based on neutron activation analysis (65). The next section details the biomarkers that are currently being used to assess Mn biological status.

Biomarkers of brain and body Mn status

Blood Mn levels are the most used indicator of exposure and can characterize the difference between exposed and unexposed subjects (66). Blood Mn is reflective of recent exposure rather than total body burden due to the short half-life of Mn in blood, which is less than 2 h owing to rapid hepatic clearance (67–69). Hair Mn levels have been widely used to quantify chronic low levels of exposure, such as those commonly associated with deficits in cognition in children (28–30, 70, 71), but evidence that the hair Mn levels reflect internal exposure dose *versus* external exposure dose is lacking. Mn levels in dentin of deciduous teeth have also been used to quantify both prenatal and postnatal accumulation (34, 35). Fingernails and toenails are noninvasive indicators of internal Mn exposure and hold the potential to quantify long-term exposure for up to a year (72, 73). Due to the high rate of Mn elimination through bile to feces (>95%) and short half-life, urine Mn concentration is not recommended as an optimal medium for internal Mn exposure assessment (69, 73, 74). Only limited research is available on saliva and the hormone prolactin as alternate biomarkers for Mn exposure (68, 74, 75).

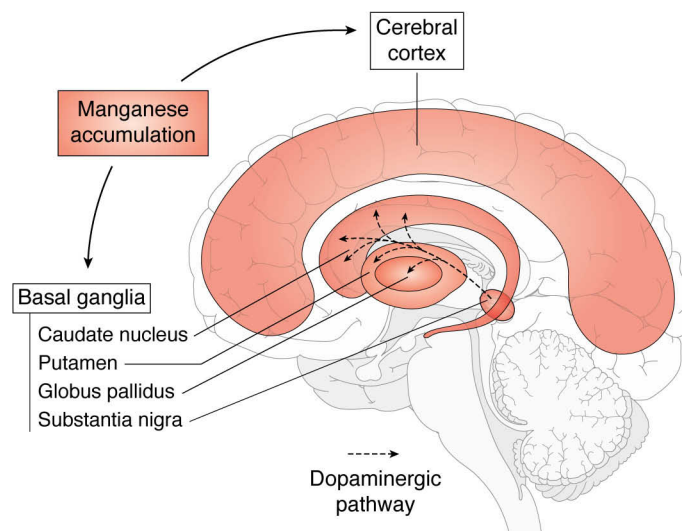


Figure 1. Schematic showing the sagittal section of human brain showing the brain regions where Mn predominantly accumulates (48, 200). Dopamine is a key neurotransmitter that is produced in the substantia nigra, and the dopaminergic neurotransmitters project to the basal ganglia region.

Biphasic relationship

Mn exhibits negative health effects at both deficient and excess exposures (6, 76, 77). In 1999, Mergler *et al.* (78) coined the term “a continuum of dysfunction” to describe the manifestations of Mn neurotoxicity along three toxicological outcomes: manganism, a neurological disorder in response to high exposures of Mn; neuropsychological abnormalities; and idiopathic Parkinson’s disease. Vollet *et al.* (6) describe this dose-response relationship of Mn focusing on neurocognitive outcomes (Fig. 2). In recent years, an inverse U-shaped association has been reported between Mn exposure and adverse neurodevelopmental effects in infants and children, suggesting adverse effects of both low and high Mn exposures (Fig. 2). This pattern is consistent with Mn acting as both an essential nutrient and a toxicant (6, 28, 79). This biphasic dose response between Mn exposure and neurotoxic effects is observed in both human and animal studies (28, 80, 81). Additional studies are needed to determine the full extent of Mn exposure effects on health outcomes. Future prospective field-based exposure studies can provide substantial insights regarding chronic low-level impacts and eventual progression in terms of disability and disease (78). Future biochemical research should include examination of mechanisms of nonlinear relationships and cell/molecular consequences of exposures across the lifespan, particularly during critical developmental windows.

Effects of Mn on neurotransmitters

Accumulation of Mn in the brain could potentially alter multiple neurotransmitter systems and their activity in the brain. Mn predominantly accumulates in the basal ganglia region of the brain, including the substantia nigra, striatum, and pallidum, when in excess (82–85). The basal ganglia have an intricate network of neurotransmitters that could potentially be altered and cause deviations in optimal physiology and behavior.

γ -Aminobutyric acid (GABA) is an inhibitory neurotransmitter seen in abundance in globus pallidus and substantia nigra pars reticulata that receives inputs from the striatum

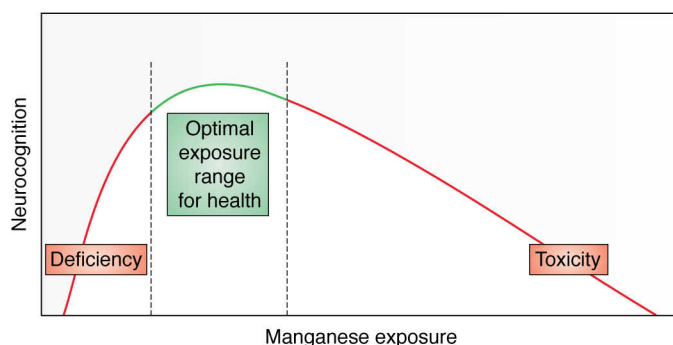


Figure 2. Mn exhibits hormetic dose response, which means an inverted “U-shaped” curve. Deficits in neurocognition are seen at both lower and higher doses, with maximum function being at the top of the inverted U-shaped curve. Adapted from Vollet *et al.* (6). This research was originally published in Current Environmental Health Reports. Vollet, K., Haynes, E. N., and Dietrich, K. N. Manganese exposure and cognition across the lifespan: contemporary review and argument for biphasic dose-response health effects. *Curr. Environ. Health Rep.* 2016; 3:392–404. © Springer.

(caudate nucleus and putamen) (86, 87). Mn exposures, even at levels that are not cytotoxic to neurons (*e.g.* 100 μ M), cause early and profound changes in neurite length and integrity, thus subsequently altering GABA levels (86). These deviations in GABAergic neurotransmission cause disinhibition of excitatory neurotransmitters. Stanwood *et al.* (86) showed that acute Mn treatment was neurotoxic *in vitro*, causing death in tyrosine hydroxylase (TH)-positive, presumptive dopamine (DA) neurons, along with loss of glutamic acid decarboxylase–positive neurons in the basal ganglia. Dopaminergic neurons present in the basal ganglia express TH, which is the rate-limiting enzyme for the synthesis of dopamine. Their study indicates that Mn toxicity acts on the neurocircuitry of this brain region to alter homeostasis and mediate neurodegeneration in the brain (86). Mn also inhibited GABA transport in the rat forebrain, confirming that Mn neurotoxicity perturbs the GABAergic neurotransmission (88).

Glutamate is the primary excitatory neurotransmitter and a critical signaling molecule. Mn can trigger neurotoxicity by release of excessive amounts of glutamate in the extracellular

space, potentially leading to activation of glutamate receptors and subsequent downstream processes (89). Mn exposure leads to altered synaptic neurotransmission via increased sensitivity of postsynaptic glutamate receptors and activation of neurons in the globus pallidus (90–92). Mn is also a cofactor for glutamine synthetase, and Mn disruption of astrocyte metabolism also leads to unavailability of the necessary components for neurotransmitter and GSH metabolism (93).

The effects of Mn on brain cholinergic systems could add to the understanding of Mn neurotoxicity. Mn binds to the choline transporter and reduces choline uptake. Additionally, Mn influences regional choline uptake in the hippocampus, the frontal and parietal cortices, the caudate, and the putamen. These results suggest that choline uptake across the blood-brain barrier is likely inhibited by Mn (94). The deficit of choline, a key component needed for the synthesis of the neurotransmitter acetylcholine, could potentially contribute to deficits in both behavior and physiology. Mn has a greater neurotoxic effect on cholinergic neurons in the developing brain, as there is decrease in the enzyme choline acetyltransferase specifically in the midbrain and the cerebellar region (95). In adult rats, Mn may further contribute to regional specific (*e.g.* striatum and cerebellum) increases in the acetylcholine-degrading enzyme acetylcholinesterase (95–97). Further study is needed to corroborate the neurotoxic effects of Mn on cholinergic neurons and the interactions it has with the other neurotransmitter systems in the brain.

The current body of literature has predominantly focused on the effects of Mn neurotoxicity on DA. As discussed earlier in this work, Mn accumulates in the basal ganglia, a DA-rich region. This accumulation has been shown to correlate inversely with DA levels in both neonates (98) and adult rats (99). Research has predominantly focused on DA subtype 2 receptor (D2R) and the DA transporter (DAT) responsible for Mn transport into DA neurons (100). Nelson *et al.* showed that D2R are involved in Mn toxicity, at the receptor level or at a point downstream in the signaling cascade that does not involve adenylyl cyclase (101). MnCl₂ exposure can lead to DA depletion and blunt the efficacy of DAergic neurotransmission, leading to up-regulation of the post-synaptic dopamine receptors and causing behavioral alterations including hypoactivity, cognitive impairments, and altered sensorimotor function (102). DA release kinetics in rat striatum are also impacted by sub-acute exposure to Mn due to accumulation within the striatum, with decreased basal levels and lower stimulated release observed up to 3 weeks post-treatment (103).

DAT density is highest in the caudate, putamen, and nucleus accumbens, and this density increases with age under normal physiological conditions. Examination of DAT in Mn-intoxicated patients revealed a slight decrease in DAT density (104). The authors also noted significantly greater DAT in striatum of patients with Parkinson's disease compared with those with Mn intoxication. Nonhuman primate studies have shown that DAT in striatum is a target for Mn and could potentially indicate an early event in the damage of DAergic neurons by increased uptake of DA and/or Mn (105). Low doses of Mn do not kill DAergic neurons *in vitro* but can impair TH activity through activation of protein kinase C δ and protein phosphatase 2A

even in the absence of frank toxicity (106). Mn exposure *in vivo* increased DA and the DA metabolite 3,4-dihydroxyphenylacetic acid in adult rats (107). Tran *et al.* (108) showed that dietary Mn exposure caused disruption to the DA system that subsequently altered executive function. Developmental exposure of Mn caused cognitive deficits that implicate DA and brain-derived neurotrophic factor (109). Mn accumulation in the DAergic cells of the substantia nigra pars compacta in a rodent model points to a biological basis for deficits in motor skills seen in association with manganism (84). Reported effects of Mn neurotoxicity on DA include decreased DA levels (110–112), increased DA levels (113), or no modification (114) in the substantia nigra or striatum. These differences may be due to the specific exposure paradigm, including route of exposure, concentration, duration, Mn compound, animal model, species age, and sex of the subjects (115). An alternate mode of cytotoxicity is by promoting oxidation of DA and other catecholamines and altering the cellular protective mechanisms that cause the formation of ROS due to higher Mn dosages (116). Mn may directly contribute to dopaminergic cell death by disturbing mitochondrial respiration and antioxidant systems following accumulation within mitochondria (117). Cellular DA also potentiates the cytotoxicity caused by Mn through the oxidative stress-dependent NF- κ B signaling cascade (118). Related to this, antioxidants like taurine may provide neuroprotective effects against Mn neurotoxicity (119).

Mn transporters and deviations of Mn homeostasis

Nongenetic influences on Mn toxicity

Mn and Fe share common absorption and transport pathways (120). The absorption of Mn is closely linked with absorption of Fe (121–123). Fe-deficient diets lead to increased absorption of Mn (124), and conversely, large amounts of dietary Fe have been shown to inhibit Mn absorption (125–127). This observation was confirmed by a study that showed that as Fe content increased, absorption of Mn decreased (128). Fe supplementation of 60 mg/day over 4 months was associated with decreased blood Mn levels and an overall reduction in Mn nutritional status as shown by decreased Mn superoxide dismutase activity in white blood cells (129). In addition, individual Fe body concentrations affect Mn bioavailability. Fe deficiency increases intestinal absorption of Mn, and increased Fe storage measured by ferritin levels is associated with a decrease in Mn absorption (122). Men generally have higher Fe stores than women, in part due to the loss of Fe during menstruation. This may be why men generally absorb less Mn than women (15). Further, Fe deficiency has been linked to increased risk of Mn accumulation in the brain (130).

Genetic modifiers of Mn toxicity

Whereas some mammalian Mn transporters were characterized over the last 2 decades, the recent identification of three hereditary disorders of Mn metabolism is beginning to provide a clearer understanding of the mechanisms that regulate Mn homeostasis in mammalian cells and organisms. Loss-of-function mutations in the Mn efflux transporter SLC30A10 or the Mn influx transporter SLC39A14 increase Mn levels in the body to induce neurotoxicity. In contrast, loss-of-function

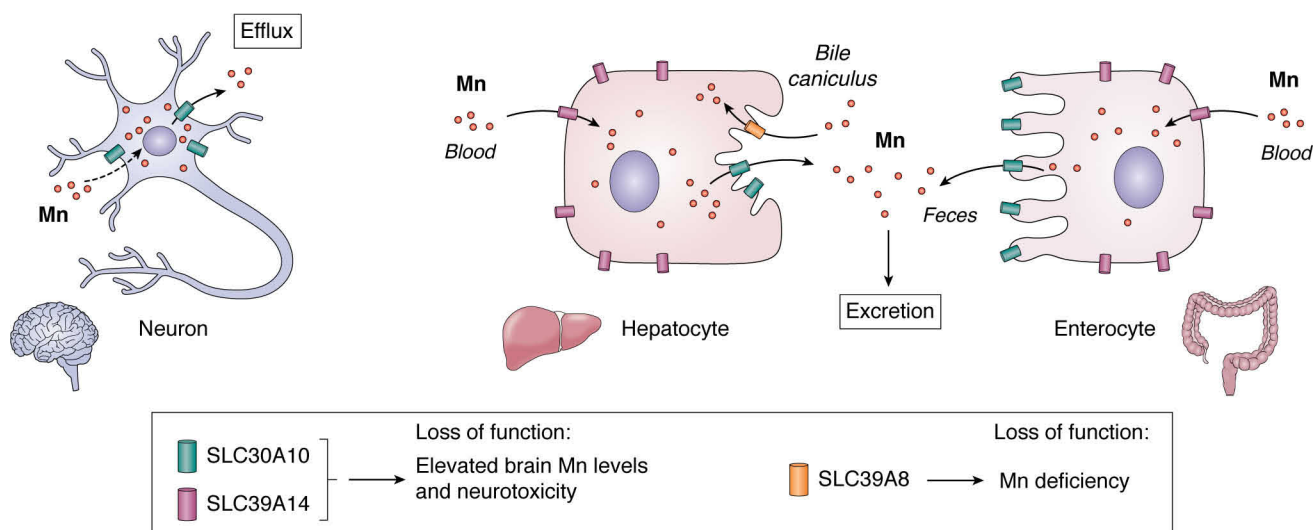


Figure 3. Function of SLC30A10, SLC39A14, and SLC39A8. SLC30A10 and SLC39A14 synergistically mediate Mn excretion. SLC39A14 transports Mn from blood into hepatocytes and enterocytes for subsequent excretion by SLC30A10 into bile and feces. SLC30A10 also mediates Mn efflux from neuronal cells. In contrast, SLC39A8 reclaims Mn lost in bile. Elevated brain Mn levels and neurotoxicity evident on loss-of-function of SLC30A10 or SLC39A14 is a consequence of an inhibition of Mn excretion and, for SLC30A10, a block in Mn efflux from neurons. Loss-of-function of SLC39A8, in contrast, produces Mn deficiency.

mutations in another Mn influx transporter, SLC39A8, induce Mn deficiency. The function of these transporters and the underlying disease mechanisms are described below (Fig. 3).

SLC30A10

Results from human patients

A detailed clinical description of a patient who harbored homozygous loss-of-function mutations in *SLC30A10* was first reported in 2008 (131). The patient was born to consanguineous parents, which was suggestive of an autosomal recessive disorder. On clinical examination, notable findings were that the patient exhibited motor abnormalities that influenced gait and fine movements of hands and dystonia that affected all four limbs. Blood Mn levels were ~10-fold higher than normal. MRI was indicative of basal ganglia Mn deposition. Additionally, there was evidence of cirrhosis and increased liver Mn levels on biopsy. The patient was not environmentally exposed to high Mn, and plasma copper and zinc (Zn) levels were normal (131).

Subsequent studies reported on additional individuals with the above-described clinical features (132, 133). MRI provided evidence for the accumulation of manganese in numerous brain regions, including the caudate and lentiform nuclei, thalamus, cortico-spinal tract, and substantia nigra (132). Accumulation in areas beyond the basal ganglia may reflect the substantial elevations in body manganese levels in the genetic disease. Through whole-genome homozygosity mapping and exome sequencing, homozygous mutations in *SLC30A10* were identified in affected patients. As expected, the disease exhibited an autosomal recessive form of inheritance (132, 133). Additional cases of patients harboring homozygous mutations in *SLC30A10* and suffering from Mn toxicity were later identified (134–136). Autopsy findings from a patient with homozygous *SLC30A10* mutations revealed marked elevations in Mn levels in the brain and liver with normal brain Zn and Fe levels (137). There was loss of neurons in the globus pallidus, which is also a characteristic feature of Mn toxicity secondary to occupational

overexposure (60, 138); depigmentation without neuronal loss in the substantia nigra; and hepatomegaly and cirrhosis (139). Overall, the major implication of the human studies is that loss-of-function mutations in *SLC30A10* alter Mn homeostasis in a manner that leads to the retention of Mn in the body. Accumulation of Mn in the brain, particularly in the basal ganglia, and liver likely cause neurotoxicity and hepatic damage, respectively. Notably, whereas the above discussion relates to rare homozygous mutations in *SLC30A10*, more recently, widely prevalent SNPs in *SLC30A10* associated with altered blood manganese and neurological function have been identified (140, 141), suggesting that changes in *SLC30A10* function likely influence Mn neurotoxicity in the general population as well.

Characterization of SLC30A10 as a Mn efflux transporter from cell culture assays

Determination of the molecular mechanism of action of SLC30A10 came from studies in cell culture. SLC30A10 is a member of the SLC30 family of metal transporters that usually transport Zn (142). Initial studies also characterized SLC30A10 as a Zn efflux transporter (143). However, doubts were raised by the fact that human patients had elevated Mn, but not Zn, levels. Evidence generated over the last few years indicates that SLC30A10 is a specific Mn efflux transporter. In multiple different cell types, WT SLC30A10 localized to the cell surface, decreased cellular Mn levels, and protected against Mn-induced toxicity (144). Disease-causing SLC30A10 mutants were retained in the endoplasmic reticulum and did not mediate Mn efflux (144). In GABAergic primary mouse midbrain neurons, expression of SLC30A10_{WT}, but not a disease-causing mutant, protected against Mn-induced neurotoxicity (144). In neuronal AF5 cells, knockdown of SLC30A10 elevated cellular Mn levels and increased sensitivity to Mn toxicity (144). Importantly, overexpression of SLC30A10_{WT} did not impact intracellular Zn levels or protect against Zn-induced cell death (144, 145). Mechanisms that confer Mn transport specificity to SLC30A10

are unclear, but analyses of the predicted structure of SLC30A10 and mutational assays suggest that the metal-binding site within its transmembrane domain is substantially different from that of related Zn transporters (145, 146). Orientation of amino acids within the transmembrane domain of SLC30A10 may favor Mn binding while simultaneously disfavoring association of other metals, such as Zn. Notably, mutations in residues required for, or adjacent to those required for, the Mn transport activity of SLC30A10 have been identified to induce disease in humans (136, 145). Liposome-based transport assays and crystallization may provide the information necessary to better understand the mechanisms that confer specific Mn transport capability to SLC30A10.

Understanding the function of SLC30A10 at the organism level using mouse, nematode, and zebrafish models

Full-body *Slc30a10* knockout mice were generated and characterized in 2017 (147). Knockout animals had ~20–60-fold increases in brain, liver, and blood Mn levels (147). Other essential metals (Zn, Cu, and Fe) were largely unaffected (147). The full-body knockouts exhibited a failure-to-thrive phenotype and died between 7 and 8 weeks of age (147). Histological analyses provided signs of thyroid dysfunction, and hormone assays demonstrated that the animals suffered from severe hypothyroidism (147). Further analyses revealed that the knockouts accumulated high levels of Mn in the thyroid, which blocked thyroxine biosynthesis (147, 148). The phenotype was rescued when animals were fed a low-Mn diet, which decreased tissue Mn levels (147). Additionally, knockout of the Mn importer SLC39A14 in the *Slc30a10* knockouts (*i.e.* *Slc30a10/Slc39a14* double knockouts; see below for a more detailed description of these double knockouts) reduced thyroid Mn levels and also rescued the hypothyroidism phenotype (148). The novel phenotype of *Slc30a10* knockout mice raises the hypothesis that thyroid dysfunction may be an understudied aspect of Mn-induced disease that exacerbates the direct neurotoxic effects of Mn. At least one human patient with homozygous *SLC30A10* mutations has now been reported to also have hypothyroidism (149).

As detailed below, further understanding of the mechanisms leading to Mn retention upon loss-of-function of SLC30A10 are derived from analyses of tissue-specific *Slc30a10* knockout mice. Mn is excreted by the liver and intestines into bile and feces, with biliary excretion being the predominant route of Mn elimination (17, 150–153). In mice and humans, strong expression of SLC30A10 was detectable in the liver and intestines (132, 139, 147, 148, 154, 155). Moreover, SLC30A10 localized to the apical/canalicular aspect of polarized HepG2 cells that model hepatocytes (148) and CaCO₂ cells that model enterocytes (154), raising the hypothesis that the transport activity of SLC30A10 mediates hepatic and intestinal Mn excretion. Consistent with this, tissue-specific *Slc30a10* knockout mice lacking SLC30A10 in both the liver and intestines (generated using an endoderm-specific *Cre*) exhibited marked increases in blood and brain Mn levels and had reduced fecal Mn levels (154). The above data suggest that loss-of-function of SLC30A10 blocks Mn excretion, which leads to a build-up of Mn within the body, and the retained Mn accumulates in the brain to induce neuro-

toxicity (Fig. 3). The excretory function of SLC30A10 was validated in 2019 using radioactive Mn excretion and surgical approaches (156).

In addition to its role in Mn excretion, SLC30A10 has an additional neuroprotective function in the brain (Fig. 3) (154). Robust expression of SLC30A10 was detected in the human and mouse brain, including neurons of the basal ganglia (132, 139, 147, 148, 154, 155). Mn levels in the basal ganglia of pan-neuronal/glia *Slc30a10* knockout mice, lacking SLC30A10 in all neurons and glia, were comparable with littermate controls (154). However, exposure to a sub-chronic Mn regimen produced larger increases in basal ganglia Mn levels of the pan-neuronal-glia knockouts than littermates. These findings suggest that activity of SLC30A10 in the brain is likely important to reduce Mn levels and protect against neurotoxicity when body Mn levels become elevated (Fig. 3). In totality, the data available to date suggest that neurotoxicity on loss-of-function of SLC30A10 is a consequence of an inhibition of hepatic and intestinal Mn excretion combined with a block in the efflux of Mn from vulnerable basal ganglia neurons (Fig. 3).

Results in other organisms support findings obtained in mice. As examples, in *Caenorhabditis elegans*, SLC30A10_{WT} protected DAergic neurons against Mn toxicity, rescued a Mn-induced behavioral defect, and increased viability on exposure to elevated levels of Mn, whereas a disease-causing mutant failed to exert these protective effects (144). There was no effect of SLC30A10_{WT} expression on Zn toxicity in the nematodes (157). Additionally, depletion of SLC30A10 in zebrafish also induced Mn toxicity (158).

SLC39A14

Results from human patients

In 2016, homozygous loss-of-function mutations in *SLC39A14* were reported to induce another inherited form of Mn neurotoxicity (159). SLC39A14 is a member of the SLC39 family of metal transporters (160). Unlike SLC30 proteins, members of the SLC39 family mediate metal influx; most members mediate Zn influx, but SLC39A14 can also mediate influx of Mn, Fe, and cadmium (Cd). Within the first decade of life, affected patients exhibited severe neurological dysfunction, including developmental deficits, dystonia, bulbar defects, spasticity, scoliosis, and loss of independent ambulatory activity (159). Parkinsonian features were evident in some (159). Blood Mn levels of patients were elevated, but importantly, Fe, Zn, and Cd in blood were within normal limits when tested (159). MRI indicated that there was accumulation of Mn in the brain, including in the globus pallidus and striatum (159). An important distinction from disease induced by *SLC30A10* mutations was the lack of deposition of Mn in the liver and, consequently, lack of liver dysfunction (159). This clinical finding provided the first clue that activity of SLC39A14 may be necessary to transport Mn from blood into hepatocytes (Fig. 3). Post-mortem analyses of one patient showed evidence of neuronal degeneration in the globus pallidus (159). Additional descriptions of patients suffering from Mn toxicity due to mutations in *SLC39A14* were reported in 2018 (161, 162).

Mechanistic in vivo and in vitro assays

Studies performed prior to discovery of the genetic disease had already demonstrated that SLC39A14 could mediate influx of Zn, Mn, Fe, and Cd (160, 163–168). SLC39A14_{WT} and disease-causing mutants localized to the cell surface, but the Mn transport capacity of the mutants was lower than for the WT protein (159). Combined with the fact that levels of Fe, Cd, and Zn were unaltered in patients, these results suggested that a defect in Mn influx underlies the observed disease phenotype.

Findings from *Slc39a14* knockout mice were first reported in 2010 and 2011 (169, 170), but changes in Mn homeostasis were identified in 2017 by three independent groups (171–173). Consistent with observations in human patients, knockout mice exhibited increased Mn levels in blood and brain, but this increase was not evident in the liver (171–173). These findings were also consistent with results in zebrafish depleted in SLC39A14 in which Mn levels in the brain, but not abdominal viscera, were elevated (159).

A straightforward hypothesis emerged from the above-described findings in human patients and model systems lacking SLC30A10 or SLC39A14: SLC39A14 and SLC30A10 likely function cooperatively to mediate Mn excretion, with SLC39A14 transporting Mn from blood into hepatocytes and enterocytes and SLC30A10 transporting Mn into bile and feces (Fig. 3). This hypothesis supported two important predictions. First, SLC39A14 and SLC30A10 should localize to the basolateral and apical domains of polarized hepatocytes and enterocytes, respectively (Fig. 3). Second, liver and intestine Mn levels of *Slc30a10/Slc39a14* double knockouts should not be elevated (148). As mentioned above, in polarized HepG2 cells, SLC30A10 was detected in the apical/luminal domain (148). In the same system, SLC39A14 localized to the basolateral aspect (148). Basolateral localization of SLC39A14 in polarized HepG2 cells was consistent with earlier observations in rat liver sections (174). A similar localization of SLC30A10 and SLC39A14 was also reported in Caco-2 enterocytes (154, 175). Analyses of *Slc30a10/Slc39a14* double-knockout mice provided direct support for the above hypothesis. In *Slc30a10/Slc39a14* double knockouts, liver Mn levels were not elevated (148). This effect was specific because, in the same experiment, liver Mn levels of *Slc30a10* single knockouts were substantially higher than WT, but no change was evident in *Slc39a14* single knockouts (148). Furthermore, blood and brain Mn levels of the double knockouts were higher than WT controls and both single knockouts (148). Results from the double knockouts imply that activity of SLC39A14 is necessary to transport Mn into hepatocytes for subsequent excretion by SLC30A10 (Fig. 3). Whereas intestinal Mn levels were not analyzed in the double knockouts, the differential localization of SLC30A10 and SLC39A14 in enterocytes described above, data from tissue-specific *Slc30a10* knockout mice (154, 156), and recent findings showing that SLC39A14 is required for the transport of Mn from blood into enterocytes (176), put together, suggest that SLC30A10 and SLC39A14 likely also act cooperatively to mediate intestinal Mn excretion (Fig. 3). We note an additional interesting feature of the *Slc30a10/Slc39a14* double knockouts. SLC39A14, but not SLC30A10, was detected in the thyroid

(148). Consequently, thyroid Mn levels of *Slc39a14* single and *Slc30a10/Slc39a14* double knockouts were lower than *Slc30a10* single knockouts, and both *Slc39a14* single and *Slc30a10/Slc39a14* double knockouts had functioning thyroid hormone (148). In sum, available data support the model presented in Fig. 3 and suggest that the neurotoxicity evident in patients with *SLC39A14* mutations is an effect of a defect in Mn excretion.

SLC39A8**Results from human patients**

In 2015, two companion papers reported that mutations in another member of the SLC39 family, SLC39A8, induce an inherited disorder of Mn deficiency (177, 178). SLC39A14 mediates influx of several metals: Zn, Mn, Fe, and Cd as well as cobalt (160, 164, 179). One of the papers reported detailed findings from an infant who had cranial asymmetry, severe infantile spasms with hypsarrhythmia, and disproportionate dwarfism (178). Atrophic changes were seen in the brain on computerized tomography and MRI (178). Plasma and urine Mn levels were below detection, but serum Zn levels and Fe metabolism parameters were unaffected (178). As part of the clinical analyses, glycosylation of serum transferrin (a common biomarker used to screen for congenital disorders of glycosylation) was found to be defective (178). Sequencing revealed that the patient carried homozygous mutations in *SLC39A8*. Subsequent examination of additional patients with unexplained defects in transferrin glycosylation led to the identification of a second infant with homozygous mutations in *SLC39A8*, severe neurological deficits, and undetectable Mn levels in whole blood and urine (178).

The second paper described findings from six children who belonged to the genetically isolated Hutterite ethnoreligious group and two other siblings born to consanguineous parents (177). Clinical features included severe intellectual and developmental disabilities, atrophy of the cerebellum, cross-eyed features, and hypotonia with signs being evident as early as birth (177). Sequencing identified homozygous mutations in *SLC39A8* (177). Of the eight patients, Mn levels in blood or erythrocytes were decreased in four, at the lower end of the normal range in three, and not determined in one (177). Authors of the first paper performed glycosylation assays on some of the patients described in the second study and discovered that glycosylation of transferrin was defective (178). Overall, the clinical studies suggest that mutations in *SLC39A8* induce Mn deficiency, which leads to deficits in glycosylation as several Golgi-localized enzymes involved in the glycosylation pathway require Mn for activity (180–182). Defective glycosylation, in turn, induces neurological disease.

Mechanistic in vivo and in vitro assays

In HeLa cells, SLC39A8_{WT} localized to the cell surface (183). In contrast, disease-causing mutations trapped the transporter in the endoplasmic reticulum and blocked its capability to mediate Mn influx (183). Further mechanistic insights came from analyses of *Slc39a8* knockout mice. Full-body depletion of *Slc39a8*, using a tamoxifen-inducible system, decreased tissue Mn levels and induced glycosylation defects, but did not impact

Zn or Fe levels (184). Constitutive liver-specific *Slc39a8* knockouts exhibited reductions in Mn levels not only in the liver but also in other tissues, such as the brain and intestines, and overexpression of *Slc39a8* in the liver increased Mn levels in the liver as well as in extrahepatic organs (184). Microscopy assays revealed that SLC39A8 localized to the apical surface of polarized hepatocytes (184). Together, these results suggest that SLC39A8 regulates Mn homeostasis by primarily acting in the liver, where it transports Mn from bile into hepatocytes, thereby reclaiming Mn that would otherwise be excreted (Fig. 3). When SLC39A8 function is compromised, Mn is lost in bile, which subsequently induces Mn deficiency and leads to glycosylation deficits that result in neurological dysfunction (Fig. 3) (177, 178). The means by which blocking glycosylation produces specific neurological changes observed in patients with *SLC39A8* mutations remain to be elucidated. Overall, SLC39A10, SLC39A14, and SLC39A8 have emerged as the critical regulators of Mn homeostasis in mammals. Much of the on-going work relates to using tissue-/cell-specific knockouts of these genes in mice to better understand how Mn homeostasis in specific neuronal populations and other peripheral organs is regulated and how changes in the homeostatic control of Mn induce neurotoxicity. This line of research, as well as work on other transporters that mediate transport of Mn into intracellular organelles (e.g. SPCA1 into the Golgi apparatus (185)), is expected to substantially improve understanding of Mn-induced neurological disease.

Pathogenic conditions linked to alteration in brain Mn status

Exposure to Mn can have detrimental effects on the brain at any stage of life, causing neurobehavioral and neuromotor deficits and/or neuropsychiatric illness (6, 78). Early life exposure to Mn has been shown to cause neurotoxic effects of concern in susceptible subgroups such as children and adolescents as their brains are undergoing developmental processes involving differentiation, apoptosis, and pathway direction. Each of these processes is vulnerable to deviations from normal physiology caused by exposure to Mn (186). A South Korean cohort-based study showed an inverted U-shaped association between blood Mn concentrations and infant mental development (187). A Taiwanese study showed a significant inverse association between Mn and Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) scores at 2 years of age (188). Yet another cohort showed decreased cognitive scores on Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) when they were subjected to pre- and postnatal exposure (81, 189).

Adolescence is the next critical period where the brain is undergoing transformative changes. Exposure to Mn during this time can potentially alter continuing myelination and may affect intellectual and cognitive abilities, as adolescence is a crucial time for brain maturation and pruning (190, 191). Additionally, adolescence is also a time when there are structural and functional changes happening in the prefrontal cortex (192–194). A study in children aged 8–11 years showed that both lower and higher concentration of Mn altered cognition and other behavioral measures on a battery of tests (81). A study

in a cohort of children living near a ferromanganese factory in Ohio showed a nonlinear U-shaped relationship between two Mn biomarkers, hair and blood, with pediatric intelligence quotient (28).

Adult populations are also vulnerable to inhaled Mn that enters the brain through the olfactory system (195). This can happen in both occupational and nonoccupational settings. Biomarkers, including scalp hair, axillary hair, fingernails, and saliva, were examined in 89 Brazilian men and women and showed that elevated levels of Mn were associated with lower visual scores in visual working memory (196). Another Brazilian study of 82 mothers and children showed that high Mn concentration in hair was associated with poor cognitive performance, particularly in the verbal domain (197). Studies that investigated biomarkers in people exposed to Mn in an occupational setting also showed deficits in cognition, specifically in working memory, compared with the control subjects (198). A cohort of Mn-exposed workers and their control counterparts were subjected to the Montreal Cognitive Assessment (MoCA) test, where the control group showed better cognition than the Mn-exposed group. This study also investigated the effects of Mn exposure on plasma brain-derived neurotrophic factor, which was lower in the Mn-exposed group (199). Increased Mn exposure in these human studies was investigated further with imaging studies to better identify the brain regions where Mn accumulated. These studies consistently identified the globus pallidus, frontal cortex, and striatum as brain regions that showed higher accumulation of Mn in exposed populations (59, 200, 201).

Neurobiology and neuronal metabolic pathways linked to Mn status

As an essential metal, it follows that deficient or excessive levels of Mn could result in biological dysfunction and disease. For example, enzymes that require Mn for their function may be expected to become dysfunctional in cases of insufficiency or overexposure. Key enzymes such as arginase and argininosuccinate lyase, which are a part of the urea cycle in the brain, require Mn as a cofactor, providing a direct link between Mn status and enzymatic function (18). An Mn-deficient diet in rats caused decreased insulin production mimicking a diabetic-like state, and pancreatic insulin following glucose stimulus was also affected (202–205). A Mn-deficient diet also led to decreased circulating IGF-1 and insulin (206). Mn and physiologically relevant levels of IGF synergistically regulate IGF/insulin activity in the cell lines tested (207). Taken together, these studies point to a connection between Mn and the regulation of IGF-1/insulin level. The reader is referred to recent reviews that discuss changes in the neuronal urea cycle, insulin signaling, and the cellular process of autophagy that are linked to Mn health and dysfunction associated with changes in brain Mn levels in depth (105, 132, 208–213).

Mn neurotoxicity and parkinsonism

PD is a progressive motor disorder characterized by selective neurodegeneration of DAergic neurons in the substantia nigra (214). Under conditions of Mn neurotoxicity, Mn has been shown to accumulate in the subcortical structures of the basal

ganglia, particularly the substantia nigra pars compacta, pallidum, and striatum (60, 215–217). As these brain regions are particularly sensitive to oxidative injury, a supported mechanism for Mn neurotoxicity, it is thought that this combination explains the relative involvement of these brain structures in Mn neurotoxicity (117, 217–220). The accumulation of Mn in basal ganglia occurs across multiple routes of exposure and genetic bases for elevated systemic Mn levels, including chronic oral exposure from contaminated water (218), inhalation of Mn particulates from ferromanganese plants (28), patients receiving parenteral nutrition (221, 222), or direct intravenous delivery (*i.e.* ephedrone users), as well as genetic alterations in the Mn efflux transporters as described earlier in this review (219, 223–226). In recently identified cases, manganese toxicity was caused by ephedrone abuse, which leads to manifestation of parkinsonian symptoms due to accumulation of Mn (227, 228). To further understand the underlying mechanism by which ephedrone leads to parkinsonian symptoms, imaging studies were performed in humans and nonhuman primates. These studies consistently show a lack of degeneration of dopamine neurons (224, 227, 228). Even though there is minimal degeneration of the neurons, ephedrone acts as a stimulant and induces the release of monoamines, thus causing a deviation from the normal physiology (229).

Excess brain Mn accumulation causes manganism (60, 216, 217, 230). Given that there are some similarities between the symptoms of manganism and idiopathic PD (231), although key differences exist as well (217, 232), research has predominantly focused on dysfunction and degeneration of dopaminergic neurons of the substantia nigra, although arguments for the involvement of other brain regions are also substantiated (138, 217, 233–235). A 1-week systemic Mn exposure trial in mice showed sex-dependent changes in dendritic spine density for medium spiny neurons (a subtype of GABAergic inhibitory neurons) of the striatum 3 weeks after exposure (Fig. 4). This may be evidence of damage either to these neurons directly or to the cortical glutamatergic or nigral dopaminergic presynaptic neurons that synapse onto the medium spiny neurons (83). In favor of a role for the presynaptic nigral dopaminergic neurons, Mn exposure is associated with a decrease in striatal dopamine and dopamine metabolite levels, although other neurotransmitters are also affected (82). It is noteworthy that deficits that are seen in motor function are associated with a marked decrease of *in vivo* DA release (103, 212, 236). Whereas these data do not report significant deficits in levels of TH or other structural markers of DA terminals, it is possible that chronic exposures and/or repeated deficits of *in vivo* DA release have long-term detrimental effects on DA structural markers. However, these data also suggest key differences between idiopathic PD and the neurotoxic effects of Mn. Further investigations with long-term exposure studies are needed to definitively determine the role of changes to DA systems in chronic Mn neurotoxicity.

There is strong evidence of a decrease of *in vivo* DA release for both acute and chronic Mn exposure and limited evidence showing lack of degeneration of D1R and D2R in various models. Furthermore, studying the long-term effect on DA neuron viability with chronic Mn overexposure to understand the neu-

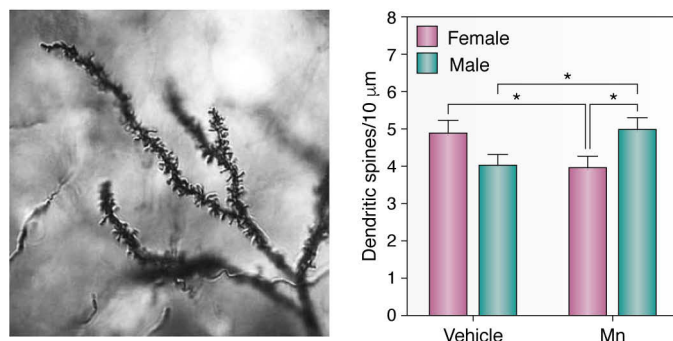


Figure 4. Mn exposure alters synaptic spine density in striatal MSNs. *Left*, representative mouse MSN dendritic segment impregnated by the rapid Golgi method, reproduced here with permission (83). Dendritic branching is clearly visualized as well as dendritic spines. Image obtained in 2010 by Jennifer Madison, Ph.D. in the Aaron Bowman laboratory at Vanderbilt University. *Right*, total spine density was the only measure of neuron morphology to have a significant gender difference 3 weeks post-exposure. Mn-exposed (Mn) male mice had a higher total spine density than Mn-exposed female mice, whereas Mn exposure decreased spine density in female mice. More studies need to be done to establish the spine density levels between sexes under control conditions to consistently better-establish the differences caused by exposure to contaminants. Data are plotted as mean ± S.E. (error bars); *, $p < 0.05$, post hoc *t* test. Data were originally published in Ref. 83. This research was originally published in Neurotoxicology. Madison, J. L., Wegrzynowicz, M., Aschner, M., and Bowman, A. B. Gender and manganese exposure interactions on mouse striatal neuron morphology. *Neurotoxicology*. 2011; 32:896–906.

rotoxic effects of Mn is vital. Long-term consequences of decreasing DA release on the neurons of the substantia nigra remain to be addressed. There are limited studies suggesting that changes in D2R occur with increasing Mn exposure (237).

In further support of a link between Mn biology and PD, exposure to Mn has been suggested as a PD environmental risk factor (238–240). Further, a dose dependence between Mn-containing welding fumes and advancement of parkinsonism-like features has been observed (40). Indeed, parkinsonism is clinically distinguishable only by age of onset (46 *versus* 63 years, respectively) in welders *versus* nonwelders, and there is an increased prevalence of PD among welders compared with an age-matched population (9, 233, 241). A study done in Taiwanese ferromanganese factory workers showed that there was Mn accumulation in the globus pallidus and substantia nigra par reticulata, caudate nucleus, and putamen with minimal effects on the sub-thalamic nucleus and substantia nigra pars compacta. One of the points to keep in mind regarding the studies that point to the lack of degeneration of the neuronal terminals is that the imaging studies were done immediately after exposure. A better understanding of long-term and delayed effects of Mn neurotoxicity is still needed to provide clarity on the mechanisms at play (40, 232, 234). Last, transporters such as DMT-1 (divalent metal transporter-1) have been implicated in parkinsonian-like neurodegeneration in animal models (242). More investigation is needed to understand how transporters like DMT-1 could also give rise to parkinsonian symptoms due to Mn neurotoxicity as DMT-1 is involved in transport of Mn (243).

Potential role for Mn dyshomeostasis in Alzheimer's disease (AD) and other degenerative disorders

The relationship between Mn toxicology and AD needs to be further explored. Importantly for AD, Mn is required as a co-

factor in enzymatic reactions including neurotransmitter metabolism (glutamine synthetase) and antioxidant status (MnSOD) (18). Glutamine synthetase is required for recycling of glutamate to glutamine within the astrocyte and as such plays a key role in glutamate clearance from the synapse, whereas MnSOD protects oxidative status in the mitochondria. Whereas Mn deficiency could thus impair glutamine synthetase enzymatic function, Mn exposure in cultured astrocytes was associated with increased intra- and extracellular glutamate, impairment of gap junctions, and cell death (244). As such, Mn sufficiency is key to brain health and protection from excitotoxicity and oxidative stress, particularly in neurodegenerative disorders (245). Nevertheless, evidence suggests that both deficiency and excess Mn can contribute to the development of AD, although more work is necessary to clarify potentially contradictory findings in the literature.

In a study of >2,000 Chinese elders, serum Mn levels were lower in AD and mild cognitive impairment (MCI) cases than in healthy controls (246). Epidemiological data from human AD and MCI studies are more equivocal and dependent on methods and sample type but support the role for altered Mn accumulation in AD brains (247, 248). In earlier studies, decreased Mn in AD and MCI were closely related to changes in other transition metals, including Fe and aluminum (249), and were dependent on sample type (*e.g.* serum but not erythrocytes (250)), which may also explain the lack of clarity in the literature. MnSOD RNA expression was decreased in lymphocytes in AD patients (251). In contrast, MnSOD expression was determined to be 3–11-fold greater in the hippocampus of AD patients than controls (252). In post-mortem AD tissue, MnSOD was localized to astrocytes associated with β -amyloid plaques in cortex and hippocampus, suggesting a response to a pathological stressor (253). In the Tg19959 mouse model of AD, decreased expression of MnSOD exacerbated β -amyloid pathology, whereas increased expression led to a 33% decrease in β -amyloid plaque burden and was associated with improvement in spatial memory (254, 255). MnSOD, a key antioxidant enzyme, is one target of tyrosine nitration causing degradation of the enzyme. Activity but not overall expression decreased in 5-month-old APP and PSEN1 knock-in mice due to increased nitration in transgenic mice, which worsened with age and β -amyloid accumulation (256) and contributed to decreased mitochondrial respiration. Even though studies have demonstrated that altered Mn exposure or handling may directly impact neuropathology through altered enzymatic function, there is no evidence that this happens at this age.

Exposure to Mn and other potential neurotoxicants through particulate matter in air pollution has been studied in post-mortem tissues from young adults in Mexico City (257) compared with controls in low-pollution cities. Although neither lung Mn levels nor lung nor cortical Fe levels increased significantly, an ~50% increase in frontal cortex Mn was observed by MS in the pollution-exposed population. Mn was significantly correlated with IL-1 β gene expression, suggesting inflammatory response changes. Neuropathological changes were noted in young adults from the Mexico City cohort that were not evident in control brains, including diffuse amyloid plaques (51%) and hyperphosphorylated tau (40%), suggesting a direct

impact on development of AD even in young adults (258). The role of chronic exposure to modest levels of Mn in the development of AD pathology was assessed directly in cynomolgous macaques (236, 259). Mn sulfate (3.3–5.0 mg/kg) given intravenously for 40 weeks increased Mn levels in the frontal cortex nearly 50% with no concomitant change in Fe levels. Strikingly, expression of β -amyloid-like protein 1 mRNA (APLP1, a member of the amyloid precursor protein family) was strongly up-regulated in the frontal cortex in Mn-treated animals, and this was confirmed with immunohistochemistry (236). Mn-treated animals also showed evidence of diffuse β -amyloid plaques that were not evident in control animals, as well as degenerating and apoptotic cells. A similar duration of Mn treatments also led to a modest decrease in cognitive function, including impaired spatial working memory and fine motor skills, and increased compulsive-like behaviors (259). Together, these results suggest a direct role for Mn in activating a cellular stress response and in driving AD neuropathology. Most AD cases cannot be attributed to a single gene or mutation. AD age of onset and speed of decline of both cognitive and pathological markers of disease is therefore far more susceptible to environmental influences, likely including changes in brain Mn status. An important role for dysfunction in Mn homeostasis is suggested by Mn exposure studies in rodents and nonhuman primates and correlational studies in human populations, as elucidated in this review. Both Mn deficiency and toxicity are implicated in AD-related changes through inflammatory response, oxidative stress, and degenerative pathways as well as direct effects on neuropathological markers. Nevertheless, the role(s) of altered Mn needs to be clarified in AD, particularly regarding genetic variation and Mn exposure levels within different human populations or communities.

Summary

Although essential for cellular metabolic signaling, exposures to high Mn levels cause neurotoxicity. This review of the available data suggests that Mn toxicity is multifaceted, yet genetic modulation of its transport (uptake and efflux) plays a major role in governing both health and disease. Numerous studies have pointed to a link between Mn homeostasis and Fe, and the ensuing oxidative stress secondary to impaired mitochondrial function and energy failure is a proven mediator of Mn-induced neurotoxicity. Despite growing awareness of the association between Mn exposure and adverse neurological outcomes, studies have yet to fully elucidate the underlying molecular mechanisms involved in its neurotoxicity. Mn also has an important role as an enzymatic cofactor, especially in insulin and insulin growth factor signaling pathways, along the continuum of biological Mn deficiency through neurotoxic Mn overexposure. Multiple kinases and phosphatases are known Mn-dependent (or Mn-preferring) enzymes, and as such, future experimental studies should identify their role in the etiology of neurodegenerative diseases vis-à-vis alterations in Mn brain levels. Whereas studies carried out in the last few decades have been highly instrumental in adding novel information on molecular aspects involved in Mn-induced neurotoxicity, further research on the role of Mn in health and disease as well as effective treatment strategies to reverse its neurolog-

ical consequences are warranted. Additionally, it is important to draw attention to the fact that there are also differences in how individual research studies (sometimes with conflicting findings) have utilized either different animal species or formulations of Mn to treat/expose the subjects. The inconsistencies in reported observations could also be due to difference in the duration of exposure. Whereas standardizing protocols may eliminate the variation in results, it is nonetheless still important to learn the effects of Mn caused by different exposure durations and compositions. It would also be pertinent to model studies based on mixtures of other toxicants with Mn that human populations are exposed to in the environment, reflecting real-life scenarios of exposure. Importantly, these future studies should also consider age and sex, in addition to genetic factors, in modulating Mn-induced neurotoxicity.

Author contributions—R. C. B., S. M., D. M., J. V., F. E. H., E. N. H., and A. B. B. writing-original draft; R. C. B., S. M., D. M., M. A., E. N. H., and A. B. B. writing-review and editing; A. B. B. conceptualization; A. B. B. data curation; A. B. B. supervision; A. B. B. funding acquisition.

Acknowledgments—We thank Dr. Jennifer Madison for the rapid Golgi stain image and Dr. Andrey Selyunin (University of Texas, Austin) for initial drafts of Fig. 3.

References

- Aschner, J. L., and Aschner, M. (2005) Nutritional aspects of manganese homeostasis. *Mol. Aspects Med.* **26**, 353–362 [CrossRef Medline](#)
- Underwood, M. J., More, R. S., Thompson, M. M., and Gershlick, A. H. (1993) Reduction of vein graft intimal hyperplasia by *ex vivo* treatment with desferrioxamine manganese. *J. Vasc. Res.* **30**, 239–240 [CrossRef Medline](#)
- Takeda, A. (2003) Manganese action in brain function. *Brain Res. Rev.* **41**, 79–87 [CrossRef Medline](#)
- Wedler, F. C. (1993) Biological significance of manganese in mammalian systems. *Prog. Med. Chem.* **30**, 89–133 [CrossRef Medline](#)
- Keen, C. L., Ensunsa, J. L., and Clegg, M. S. (2000) Manganese metabolism in animals and humans including the toxicity of manganese. *Met. Ions Biol. Syst.* **37**, 89–121 [Medline](#)
- Vollet, K., Haynes, E. N., and Dietrich, K. N. (2016) Manganese exposure and cognition across the lifespan: contemporary review and argument for biphasic dose-response health effects. *Curr. Environ. Health Rep.* **3**, 392–404 [CrossRef Medline](#)
- Guilarte, T. R. (2013) Manganese neurotoxicity: new perspectives from behavioral, neuroimaging, and neuropathological studies in humans and non-human primates. *Front. Aging Neurosci.* **5**, 23 [CrossRef Medline](#)
- Gonzalez-Cuyar, L. F., Nelson, G., Criswell, S. R., Ho, P., Lonzanida, J. A., Checkoway, H., Seixas, N., Gelman, B. B., Evanoff, B. A., Murray, J., Zhang, J., and Racette, B. A. (2014) Quantitative neuropathology associated with chronic manganese exposure in South African mine workers. *Neurotoxicology* **45**, 260–266 [CrossRef Medline](#)
- Racette, B. A., Tabbal, S. D., Jennings, D., Good, L., Perlmutter, J. S., and Evanoff, B. (2005) Prevalence of parkinsonism and relationship to exposure in a large sample of Alabama welders. *Neurology* **64**, 230–235 [CrossRef Medline](#)
- Caito, S., and Aschner, M. (2015) Neurotoxicity of metals. *Handb. Clin. Neurol.* **131**, 169–189 [CrossRef Medline](#)
- Roh, E., Song, D. K., and Kim, M. S. (2016) Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. *Exp. Mol. Med.* **48**, e216 [CrossRef Medline](#)
- World Health Organization (2011) Manganese in drinking-water: background document for development of WHO *Guidelines for Drinking-water Quality*, pp. 5–6, WHO Press, Geneva
- Lehmann, T., and Lämmle, B. (1999) IFN α treatment in systemic mastocytosis. *Ann. Hematol.* **78**, 483–484 [CrossRef Medline](#)
- Das, A., Jr., and Hammad, T. A. (2000) Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. *Osteoarthritis Cartilage* **8**, 343–350 [CrossRef Medline](#)
- Finley, J. W., Johnson, P. E., and Johnson, L. K. (1994) Sex affects manganese absorption and retention by humans from a diet adequate in manganese. *Am. J. Clin. Nutr.* **60**, 949–955 [CrossRef Medline](#)
- Davis, C. D., Zech, L., and Greger, J. L. (1993) Manganese metabolism in rats: an improved methodology for assessing gut endogenous losses. *Proc. Soc. Exp. Biol. Med.* **202**, 103–108 [CrossRef Medline](#)
- Papavasiliou, P. S., Miller, S. T., and Cotzias, G. C. (1966) Role of liver in regulating distribution and excretion of manganese. *Am. J. Physiol.* **211**, 211–216 [CrossRef Medline](#)
- Horning, K. J., Caito, S. W., Tipps, K. G., Bowman, A. B., and Aschner, M. (2015) Manganese is essential for neuronal health. *Annu. Rev. Nutr.* **35**, 71–108 [CrossRef Medline](#)
- Gibbons, R. A., Dixon, S. N., Hallis, K., Russell, A. M., Sansom, B. F., and Symonds, H. W. (1976) Manganese metabolism in cows and goats. *Biochim. Biophys. Acta* **444**, 1–10 [CrossRef Medline](#)
- Reaney, S. H., Bench, G., and Smith, D. R. (2006) Brain accumulation and toxicity of Mn(II) and Mn(III) exposures. *Toxicol. Sci.* **93**, 114–124 [CrossRef Medline](#)
- Wasserman, G. A., Liu, X., Parvez, F., Ahsan, H., Levy, D., Factor-Litvak, P., Kline, J., van Geen, A., Slavkovich, V., Lofacono, N. J., Cheng, Z., Zheng, Y., and Graziano, J. H. (2006) Water manganese exposure and children's intellectual function in Araihasar, Bangladesh. *Environ. Health Perspect.* **114**, 124–129 [CrossRef Medline](#)
- Khan, K., Wasserman, G. A., Liu, X., Ahmed, E., Parvez, F., Slavkovich, V., Levy, D., Mey, J., van Geen, A., Graziano, J. H., and Factor-Litvak, P. (2012) Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology* **33**, 91–97 [CrossRef Medline](#)
- National Center for Environmental Assessment (2012) Manganese (CASRN 7439-96-5). in *Integrated Risk Information System*, Environmental Protection Agency, Washington, D. C.
- Environmental Protection Agency (2020) *Secondary Drinking Water Standards: Guidance for Nuisance Chemicals*. Environmental Protection Agency, Washington, D. C.
- Ljung, K., and Vahter, M. (2007) Time to re-evaluate the guideline value for manganese in drinking water? *Environ. Health Perspect.* **115**, 1533–1538 [CrossRef Medline](#)
- Collipp, P. J., Chen, S. Y., and Maitinsky, S. (1983) Manganese in infant formulas and learning disability. *Ann. Nutr. Metab.* **27**, 488–494 [CrossRef Medline](#)
- Leonhard, M. J., Chang, E. T., Loccisano, A. E., and Garry, M. R. (2019) A systematic literature review of epidemiologic studies of developmental manganese exposure and neurodevelopmental outcomes. *Toxicology* **420**, 46–65 [CrossRef Medline](#)
- Haynes, E. N., Sucharew, H., Kuhnell, P., Alden, J., Barnas, M., Wright, R. O., Parsons, P. J., Aldous, K. M., Praamsma, M. L., Beidler, C., and Dietrich, K. N. (2015) Manganese exposure and neurocognitive outcomes in rural school-age children: the communities actively researching exposure study (Ohio, U.S.A.). *Environ. Health Perspect.* **123**, 1066–1071 [CrossRef Medline](#)
- Torres-Agustín, R., Rodríguez-Agudelo, Y., Schilman, A., Solís-Vivanco, R., Montes, S., Riojas-Rodríguez, H., Cortez-Lugo, M., and Ríos, C. (2013) Effect of environmental manganese exposure on verbal learning and memory in Mexican children. *Environ. Res.* **121**, 39–44 [CrossRef Medline](#)
- Carvalho, C. F., Menezes-Filho, J. A., de Matos, V. P., Bessa, J. R., Coelho-Santos, J., Viana, G. F., Argollo, N., and Abreu, N. (2014) Elevated airborne manganese and low executive function in school-aged children in Brazil. *Neurotoxicology* **45**, 301–308 [CrossRef Medline](#)
- Solís-Vivanco, R., Rodríguez-Agudelo, Y., Riojas-Rodríguez, H., Ríos, C., Rosas, I., and Montes, S. (2009) Cognitive impairment in an adult

- Mexican population non-occupationally exposed to manganese. *Environ. Toxicol. Pharmacol.* **28**, 172–178 [CrossRef Medline](#)
32. Davis, J. M. (1998) Methylcyclopentadienyl manganese tricarbonyl: health risk uncertainties and research directions. *Environ. Health Perspect.* **106**, 191–201 [CrossRef Medline](#)
 33. Gulson, B., Mizon, K., Taylor, A., Korsch, M., Stauber, J., Davis, J. M., Louie, H., Wu, M., and Swan, H. (2006) Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline—preliminary results. *Environ. Res.* **100**, 100–114 [CrossRef Medline](#)
 34. Mora, A. M., Arora, M., Harley, K. G., Kogut, K., Parra, K., Hernández-Bonilla, D., Gunier, R. B., Bradman, A., Smith, D. R., and Eskenazi, B. (2015) Prenatal and postnatal manganese teeth levels and neurodevelopment at 7, 9, and 10.5 years in the CHAMACOS cohort. *Environ. Int.* **84**, 39–54 [CrossRef Medline](#)
 35. Gunier, R. B., Arora, M., Jerrett, M., Bradman, A., Harley, K. G., Mora, A. M., Kogut, K., Hubbard, A., Austin, C., Holland, N., and Eskenazi, B. (2015) Manganese in teeth and neurodevelopment in young Mexican-American children. *Environ. Res.* **142**, 688–695 [CrossRef Medline](#)
 36. Rodier, J. (1955) Manganese poisoning in Moroccan miners. *Br. J. Ind. Med.* **12**, 21–35 [CrossRef Medline](#)
 37. Zoni, S., Albini, E., and Lucchini, R. (2007) Neuropsychological testing for the assessment of manganese neurotoxicity: a review and a proposal. *Am. J. Ind. Med.* **50**, 812–830 [CrossRef Medline](#)
 38. Iregren, A. (1990) Psychological test performance in foundry workers exposed to low levels of manganese. *Neurotoxicol. Teratol.* **12**, 673–675 [CrossRef Medline](#)
 39. Roels, H., Lauwerys, R., Buchet, J. P., Genet, P., Sarhan, M. J., Hanotiau, I., de Fays, M., Bernard, A., and Stanescu, D. (1987) Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. *Am. J. Ind. Med.* **11**, 307–327 [CrossRef Medline](#)
 40. Racette, B. A., Searles Nielsen, S., Criswell, S. R., Sheppard, L., Seixas, N., Warden, M. N., and Checkoway, H. (2017) Dose-dependent progression of parkinsonism in manganese-exposed welders. *Neurology* **88**, 344–351 [CrossRef Medline](#)
 41. Aschner, M. (2006) The transport of manganese across the blood-brain barrier. *Neurotoxicology* **27**, 311–314 [CrossRef Medline](#)
 42. Davis, J. M. (1999) Inhalation health risks of manganese: an EPA perspective. *Neurotoxicology* **20**, 511–518 [Medline](#)
 43. Elder, A., Gelein, R., Silva, V., Feikert, T., Opanashuk, L., Carter, J., Potter, R., Maynard, A., Ito, Y., Finkelstein, J., and Oberdörster, G. (2006) Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ. Health Perspect.* **114**, 1172–1178 [CrossRef Medline](#)
 44. Dorman, D. C., Struve, M. F., and Wong, B. A. (2002) Brain manganese concentrations in rats following manganese tetroxide inhalation are unaffected by dietary manganese intake. *Neurotoxicology* **23**, 185–195 [CrossRef Medline](#)
 45. Bock, N. A., Paiva, F. F., Nascimento, G. C., Newman, J. D., and Silva, A. C. (2008) Cerebrospinal fluid to brain transport of manganese in a non-human primate revealed by MRI. *Brain Res.* **1198**, 160–170 [CrossRef Medline](#)
 46. Eriksson, H., Gillberg, P. G., Aquilonius, S. M., Hedström, K. G., and Heilbronn, E. (1992) Receptor alterations in manganese intoxicated monkeys. *Arch. Toxicol.* **66**, 359–364 [CrossRef Medline](#)
 47. Williams, M., Todd, G. D., Roney, N., Crawford, J., Coles, C., McClure, P. R., Garey, J. D., Zaccaria, K., and Citra, M. (2012) *Toxicological Profile for Manganese*, Agency for Toxic Substances and Disease Registry, Atlanta, GA
 48. Blomlie, V., Sivanandan, R., and Jynge, P. (2020) Manganese uptake and accumulation in the human brain. *AJNR Am. J. Neuroradiol.* **41**, E3 [CrossRef Medline](#)
 49. Hernández-Bonilla, D., Schilman, A., Montes, S., Rodríguez-Agudelo, Y., Rodríguez-Dozal, S., Solís-Vivanco, R., Ríos, C., and Riojas-Rodríguez, H. (2011) Environmental exposure to manganese and motor function of children in Mexico. *Neurotoxicology* **32**, 615–621 [CrossRef Medline](#)
 50. Standridge, J. S., Bhattacharya, A., Succop, P., Cox, C., and Haynes, E. (2008) Effect of chronic low level manganese exposure on postural balance: a pilot study of residents in southern Ohio. *J. Occup. Environ. Med.* **50**, 1421–1429 [CrossRef Medline](#)
 51. Lucchini, R. G., Guazzetti, S., Zoni, S., Donna, F., Peter, S., Zacco, A., Salmistraro, M., Bontempi, E., Zimmerman, N. J., and Smith, D. R. (2012) Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. *Neurotoxicology* **33**, 687–696 [CrossRef Medline](#)
 52. Finkelstein, M. M., and Jerrett, M. (2007) A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. *Environ. Res.* **104**, 420–432 [CrossRef Medline](#)
 53. Huang, C. C. (2007) Parkinsonism induced by chronic manganese intoxication—an experience in Taiwan. *Chang Gung Med. J.* **30**, 385–395 [Medline](#)
 54. Huang, C. C., Chu, N. S., Lu, C. S., Chen, R. S., Schulzer, M., and Calne, D. B. (2007) The natural history of neurological manganese over 18 years. *Parkinsonism Relat. Disord.* **13**, 143–145 [CrossRef Medline](#)
 55. Revilla, F. J., Larsh, T. R., Mani, A., Duker, A. P., Cox, C., Succop, P., Gartner, M., Jarrin Tejada, C., and Bhattacharya, A. (2013) Effect of dopaminergic medication on postural sway in advanced Parkinson's disease. *Front. Neurol.* **4**, 202 [CrossRef Medline](#)
 56. Oulhote, Y., Mergler, D., Barbeau, B., Bellinger, D. C., Bouffard, T., Brodeur, M. È., Saint-Amour, D., Legrand, M., Sauvè, S., and Bouchard, M. F. (2014) Neurobehavioral function in school-age children exposed to manganese in drinking water. *Environ. Health Perspect.* **122**, 1343–1350 [CrossRef Medline](#)
 57. Rugless, F., Bhattacharya, A., Succop, P., Dietrich, K. N., Cox, C., Alden, J., Kuhnell, P., Barnas, M., Wright, R., Parsons, P. J., Praamsma, M. L., Palmer, C. D., Beidler, C., Wittberg, R., and Haynes, E. N. (2014) Childhood exposure to manganese and postural instability in children living near a ferromanganese refinery in Southeastern Ohio. *Neurotoxicol. Teratol.* **41**, 71–79 [CrossRef Medline](#)
 58. Laohadomchok, W., Lin, X., Herrick, R. F., Fang, S. C., Cavallari, J. M., Shrairman, R., Landau, A., Christiani, D. C., and Weisskopf, M. G. (2011) Neuropsychological effects of low-level manganese exposure in welders. *Neurotoxicology* **32**, 171–179 [CrossRef Medline](#)
 59. Ma, R. E., Ward, E. J., Yeh, C. L., Snyder, S., Long, Z., Gokalp Yavuz, F., Zauber, S. E., and Dydak, U. (2018) Thalamic GABA levels and occupational manganese neurotoxicity: association with exposure levels and brain MRI. *Neurotoxicology* **64**, 30–42 [CrossRef Medline](#)
 60. Olanow, C. W. (2004) Manganese-induced parkinsonism and Parkinson's disease. *Ann. N.Y. Acad. Sci.* **1012**, 209–223 [CrossRef Medline](#)
 61. Criswell, S. R., Perlmutter, J. S., Huang, J. L., Golchin, N., Flores, H. P., Hobson, A., Aschner, M., Erikson, K. M., Checkoway, H., and Racette, B. A. (2012) Basal ganglia intensity indices and diffusion weighted imaging in manganese-exposed welders. *Occup. Environ. Med.* **69**, 437–443 [CrossRef Medline](#)
 62. Han, J. H., Chung, Y. H., Park, J. D., Kim, C. Y., Yang, S. O., Khang, H. S., Cheong, H. K., Lee, J. S., Ha, C. S., Song, C. W., Kwon, I. H., Sung, J. H., Heo, J. D., Kim, N. Y., Huang, M., et al. (2008) Recovery from welding-fume-exposure-induced MRI T1 signal intensities after cessation of welding-fume exposure in brains of cynomolgus monkeys. *Inhal. Toxicol.* **20**, 1075–1083 [CrossRef Medline](#)
 63. Finkelstein, Y., Zhang, N., Fitsanakis, V. A., Avison, M. J., Gore, J. C., and Aschner, M. (2008) Differential deposition of manganese in the rat brain following subchronic exposure to manganese: a T1-weighted magnetic resonance imaging study. *Isr. Med. Assoc. J.* **10**, 793–798 [Medline](#)
 64. Fitsanakis, V. A., Zhang, N., Anderson, J. G., Erikson, K. M., Avison, M. J., Gore, J. C., and Aschner, M. (2008) Measuring brain manganese and iron accumulation in rats following 14 weeks of low-dose manganese treatment using atomic absorption spectroscopy and magnetic resonance imaging. *Toxicol. Sci.* **103**, 116–124 [CrossRef Medline](#)
 65. Liu, Y., Rolle-McFarland, D., Mostafaei, F., Zhou, Y., Li, Y., Zheng, W., Wells, E., and Nie, L. H. (2018) *In vivo* neutron activation analysis of bone manganese in workers. *Physiol. Meas.* **39**, 035003 [CrossRef Medline](#)

66. Baker, M. G., Simpson, C. D., Sheppard, L., Stover, B., Morton, J., Cocker, J., and Seixas, N. (2015) Variance components of short-term biomarkers of manganese exposure in an inception cohort of welding trainees. *J. Trace Elem. Med. Biol.* **29**, 123–129 [CrossRef Medline](#)
67. Baker, M. G., Simpson, C. D., Stover, B., Sheppard, L., Checkoway, H., Racette, B. A., and Seixas, N. S. (2014) Blood manganese as an exposure biomarker: state of the evidence. *J. Occup. Environ. Hyg.* **11**, 210–217 [CrossRef Medline](#)
68. O'Neal, S. L., and Zheng, W. (2015) Manganese toxicity upon overexposure: a decade in review. *Curr. Environ. Health Rep.* **2**, 315–328 [CrossRef Medline](#)
69. Smith, D., Gwiazda, R., Bowler, R., Roels, H., Park, R., Taicher, C., and Lucchini, R. (2007) Biomarkers of Mn exposure in humans. *Am. J. Ind. Med.* **50**, 801–811 [CrossRef Medline](#)
70. Betancourt, Ó., Tapia, M., and Méndez, I. (2015) Decline of general intelligence in children exposed to manganese from mining contamination in Puyango River Basin, Southern Ecuador. *Ecohealth* **12**, 453–460 [CrossRef Medline](#)
71. Rink, S. M., Ardoino, G., Queirolo, E. I., Cicariello, D., Mañay, N., and Kordas, K. (2014) Associations between hair manganese levels and cognitive, language, and motor development in preschool children from Montevideo, Uruguay. *Arch. Environ. Occup. Health* **69**, 46–54 [CrossRef Medline](#)
72. Hassani, H., Golbabaee, F., Shirkhanloo, H., and Tehrani-Doust, M. (2016) Relations of biomarkers of manganese exposure and neuropsychological effects among welders and ferroalloy smelters. *Ind. Health* **54**, 79–86 [CrossRef Medline](#)
73. Laohaudomchok, W., Lin, X., Herrick, R. F., Fang, S. C., Cavallari, J. M., Christiani, D. C., and Weisskopf, M. G. (2011) Toenail, blood and urine as biomarkers of manganese exposure. *J. Occup. Environ. Med.* **53**, 506–510 [CrossRef Medline](#)
74. Zheng, W., Fu, S. X., Dydak, U., and Cowan, D. M. (2011) Biomarkers of manganese intoxication. *Neurotoxicology* **32**, 1–8 [CrossRef Medline](#)
75. Marreilha Dos Santos, A. P., Lopes Santos, M., Batoréu, M. C., and Aschner, M. (2011) Prolactin is a peripheral marker of manganese neurotoxicity. *Brain Res.* **1382**, 282–290 [CrossRef Medline](#)
76. Kang, J. O. (2001) Chronic iron overload and toxicity: clinical chemistry perspective. *Clin. Lab. Sci.* **14**, 209–219 [Medline](#)
77. Ghosh, K. (2006) Non haematological effects of iron deficiency—a perspective. *Indian J. Med. Sci.* **60**, 30–37 [CrossRef Medline](#)
78. Mergler, D., Baldwin, M., Bélanger, S., Larribe, F., Beuter, A., Bowler, R., Panisset, M., Edwards, R., de Geoffroy, A., Sassine, M. P., and Hudnell, K. (1999) Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. *Neurotoxicology* **20**, 327–342 [Medline](#)
79. Claus Henn, B., Ettinger, A. S., Schwartz, J., Téllez-Rojo, M. M., Lama-drid-Figueroa, H., Hernández-Avila, M., Schnaas, L., Amarasiriwardena, C., Bellinger, D. C., Hu, H., and Wright, R. O. (2010) Early postnatal blood manganese levels and children's neurodevelopment. *Epidemiology* **21**, 433–439 [CrossRef Medline](#)
80. Beaudin, S. A., Strupp, B. J., Strawderman, M., and Smith, D. R. (2017) Early postnatal manganese exposure causes lasting impairment of selective and focused attention and arousal regulation in adult rats. *Environ. Health Perspect.* **125**, 230–237 [CrossRef Medline](#)
81. Bhang, S. Y., Cho, S. C., Kim, J. W., Hong, Y. C., Shin, M. S., Yoo, H. J., Cho, I. H., Kim, Y., and Kim, B. N. (2013) Relationship between blood manganese levels and children's attention, cognition, behavior, and academic performance—a nationwide cross-sectional study. *Environ. Res.* **126**, 9–16 [CrossRef Medline](#)
82. Madison, J. L., Wegrzynowicz, M., Aschner, M., and Bowman, A. B. (2012) Disease-toxicant interactions in manganese exposed Huntington disease mice: early changes in striatal neuron morphology and dopamine metabolism. *PLoS ONE* **7**, e31024 [CrossRef Medline](#)
83. Madison, J. L., Wegrzynowicz, M., Aschner, M., and Bowman, A. B. (2011) Gender and manganese exposure interactions on mouse striatal neuron morphology. *Neurotoxicology* **32**, 896–906 [CrossRef Medline](#)
84. Robison, G., Sullivan, B., Cannon, J. R., and Pushkar, Y. (2015) Identification of dopaminergic neurons of the substantia nigra pars compacta as a target of manganese accumulation. *Metallomics* **7**, 748–755 [CrossRef Medline](#)
85. Park, J. D., Chung, Y. H., Kim, C. Y., Ha, C. S., Yang, S. O., Khang, H. S., Yu, I. K., Cheong, H. K., Lee, J. S., Song, C. W., Kwon, I. H., Han, J. H., Sung, J. H., Heo, J. D., Choi, B. S., et al. (2007) Comparison of high MRI T1 signals with manganese concentration in brains of cynomolgus monkeys after 8 months of stainless steel welding-fume exposure. *Inhal. Toxicol.* **19**, 965–971 [CrossRef Medline](#)
86. Stanwood, G. D., Leitch, D. B., Savchenko, V., Wu, J., Fitsanakis, V. A., Anderson, D. J., Stankowski, J. N., Aschner, M., and McLaughlin, B. (2009) Manganese exposure is cytotoxic and alters dopaminergic and GABAergic neurons within the basal ganglia. *J. Neurochem.* **110**, 378–389 [CrossRef Medline](#)
87. Fitsanakis, V. A., Au, C., Erikson, K. M., and Aschner, M. (2006) The effects of manganese on glutamate, dopamine and γ -aminobutyric acid regulation. *Neurochem. Int.* **48**, 426–433 [CrossRef Medline](#)
88. Wong, P. C. L., Lai, J. C. K., Lim, L., and Davison, A. N. (1981) Selective inhibition of L-glutamate and gammaaminobutyrate transport in nerve ending particles by aluminium, manganese, and cadmium chloride. *J. Inorg. Biochem.* **14**, 253–260 [CrossRef Medline](#)
89. Danbolt, N. C. (2001) Glutamate uptake. *Prog. Neurobiol.* **65**, 1–105 [CrossRef Medline](#)
90. Spadoni, F., Stefani, A., Morello, M., Lavaroni, F., Giacomini, P., and Sancesario, G. (2000) Selective vulnerability of pallidal neurons in the early phases of manganese intoxication. *Exp. Brain Res.* **135**, 544–551 [CrossRef Medline](#)
91. Takeda, A., Sotogaku, N., and Oku, N. (2002) Manganese influences the levels of neurotransmitters in synapses in rat brain. *Neuroscience* **114**, 669–674 [CrossRef Medline](#)
92. Takeda, A., Sotogaku, N., and Oku, N. (2003) Influence of manganese on the release of neurotransmitters in rat striatum. *Brain Res.* **965**, 279–282 [CrossRef Medline](#)
93. Zwingmann, C., Leibfritz, D., and Hazell, A. S. (2003) Energy metabolism in astrocytes and neurons treated with manganese: relation among cell-specific energy failure, glucose metabolism, and intercellular trafficking using multinuclear NMR-spectroscopic analysis. *J. Cereb. Blood Flow Metab.* **23**, 756–771 [CrossRef Medline](#)
94. Eriksson, H., Morath, C., and Heilbronn, E. (1984) Effects of manganese on the nervous system. *Acta Neurol. Scand. Suppl.* **100**, 89–93 [Medline](#)
95. Lai, J. C. K., Leung, T. K. C., and Lim, L. (1984) Differences in the neurotoxic effects of manganese during development and aging—some observations on brain regional neurotransmitter and non-neurotransmitter metabolism in a developmental rat model of chronic manganese encephalopathy. *Neurotoxicology* **5**, 37–47 [Medline](#)
96. Yousefi Babadi, V., Sadeghi, L., Shirani, K., Malekirad, A. A., and Rezaei, M. (2014) The toxic effect of manganese on the acetylcholinesterase activity in rat brains. *J. Toxicol.* **2014**, 946372 [CrossRef Medline](#)
97. Lai, J. C. K., Chan, A. W. K., Leung, T. K. C., Minski, M. J., and Lim, L. (1992) Neurochemical changes in rats chronically treated with a high-concentration of manganese chloride. *Neurochem. Res.* **17**, 841–847 [CrossRef Medline](#)
98. Tran, T. T., Chohanadisai, W., Crinella, F. M., Chicx-DeMet, A., and Lönnerdal, B. (2002) Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status. *Neurotoxicology* **23**, 635–643 [CrossRef Medline](#)
99. Seth, P. K., and Chandra, S. V. (1984) Neurotransmitters and neurotransmitter receptors in developing and adult rats during manganese poisoning. *Neurotoxicology* **5**, 67–76 [Medline](#)
100. Ingersoll, R. T., Montgomery, E. B., Jr., and Aposhian, H. V. (1999) Central nervous system toxicity of manganese. II: Cocaine or reserpine inhibit manganese concentration in the rat brain. *Neurotoxicology* **20**, 467–476 [Medline](#)
101. Nelson, M., Adams, T., Ojo, C., Carroll, M. A., and Catapane, E. J. (2018) Manganese toxicity is targeting an early step in the dopamine signal transduction pathway that controls lateral cilia activity in the bivalve mollusc *Crassostrea virginica*. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **213**, 1–6 [CrossRef Medline](#)
102. Vezér, T., Kurunczi, A., Náráy, M., Papp, A., and Nagymajtényi, L. (2007) Behavioral effects of subchronic inorganic manganese exposure in rats. *Am. J. Ind. Med.* **50**, 841–852 [CrossRef Medline](#)

103. Khalid, M., Aoun, R. A., and Mathews, T. A. (2011) Altered striatal dopamine release following a sub-acute exposure to manganese. *J. Neurosci. Methods* **202**, 182–191 [CrossRef Medline](#)
104. Huang, C. C., Weng, Y. H., Lu, C. S., Chu, N. S., and Yen, T. C. (2003) Dopamine transporter binding in chronic manganese intoxication. *J. Neurol.* **250**, 1335–1339 [CrossRef Medline](#)
105. Chen, M. K., Lee, J. S., McGlothlan, J. L., Furukawa, E., Adams, R. J., Alexander, M., Wong, D. F., and Guilarte, T. R. (2006) Acute manganese administration alters dopamine transporter levels in the non-human primate striatum. *Neurotoxicology* **27**, 229–236 [CrossRef Medline](#)
106. Zhang, D., Kanthasamy, A., Anantharam, V., and Kanthasamy, A. (2011) Effects of manganese on tyrosine hydroxylase (TH) activity and TH-phosphorylation in a dopaminergic neural cell line. *Toxicol. Appl. Pharmacol.* **254**, 65–71 [CrossRef Medline](#)
107. Amos-Kroohs, R. M., Davenport, L. L., Gutierrez, A., Hufgard, J. R., Vorhees, C. V., and Williams, M. T. (2016) Developmental manganese exposure in combination with developmental stress and iron deficiency: effects on behavior and monoamines. *Neurotoxicol. Teratol.* **56**, 55–67 [CrossRef Medline](#)
108. Tran, T. T., Chowanadisai, W., Lönnnerdal, B., Le, L., Parker, M., Chiczy-Demet, A., and Crinella, F. M. (2002) Effects of neonatal dietary manganese exposure on brain dopamine levels and neurocognitive functions. *Neurotoxicology* **23**, 645–651 [CrossRef Medline](#)
109. Bailey, R. A., Gutierrez, A., Kyser, T. L., Hemmerle, A. M., Hufgard, J. R., Seroogy, K. B., Vorhees, C. V., and Williams, M. T. (2019) Effects of preweaning manganese in combination with adult striatal dopamine lesions on monoamines, BDNF, TrkB, and cognitive function in Sprague-Dawley rats. *Neurotox. Res.* **35**, 606–620 [CrossRef Medline](#)
110. Autissier, N., Rochette, L., Dumas, P., Beley, A., Loireau, A., and Bralet, J. (1982) Dopamine and norepinephrine turnover in various regions of the rat brain after chronic manganese chloride administration. *Toxicology* **24**, 175–182 [CrossRef Medline](#)
111. Eriksson, H., Mägiste, K., Plantin, L.-O., Fonnum, F., Hedström, K.-G., Theodorsson-Norheim, E., Kristensson, K., Stålberg, E., and Heilbronn, E. (1987) Effects of manganese oxide on monkeys as revealed by a combined neurochemical, histological and neurophysiological evaluation. *Arch. Toxicol.* **61**, 46–52 [CrossRef Medline](#)
112. Sistrunk, S. C., Ross, M. K., and Filipov, N. M. (2007) Direct effects of manganese compounds on dopamine and its metabolite Dopac: an *in vitro* study. *Environ. Toxicol. Pharmacol.* **23**, 286–296 [CrossRef Medline](#)
113. Tomás-Camardiel, M., Herrera, A. J., Venero, J. L., Cruz Sánchez-Hidalgo, M., Cano, J., and Machado, A. (2002) Differential regulation of glutamic acid decarboxylase mRNA and tyrosine hydroxylase mRNA expression in the aged manganese-treated rats. *Mol. Brain Res.* **103**, 116–129 [CrossRef Medline](#)
114. Gwiazda, R. H., Lee, D., Sheridan, J., and Smith, D. R. (2002) Low cumulative manganese exposure affects striatal GABA but not dopamine. *Neurotoxicology* **23**, 69–76 [CrossRef Medline](#)
115. Avila Costa, M. R., Gutierrez-Valdez, A., Anaya, V., Ordoñez Librado, J., Sanchez Betancourt, J., Montiel-Flores, E., Aley-Medina, P., Reynoso-Erazo, L., Espinosa-Villanueva, J., Tron-Alvarez, R., and Rodriguez Lara, V. (2018) Manganese inhalation induces dopaminergic cell loss: relevance to Parkinson's disease, pp. 59–83. In *Dopamine: Health and Disease*, InTechOpen Ltd., London
116. Stredrick, D. L., Stokes, A. H., Worst, T. J., Freeman, W. M., Johnson, E. A., Lash, L. H., Aschner, M., and Vrana, K. E. (2004) Manganese-induced cytotoxicity in dopamine-producing cells. *Neurotoxicology* **25**, 543–553 [CrossRef Medline](#)
117. Smith, M. R., Fernandes, J., Go, Y. M., and Jones, D. P. (2017) Redox dynamics of manganese as a mitochondrial life-death switch. *Biochem. Biophys. Res. Commun.* **482**, 388–398 [CrossRef Medline](#)
118. Prabhakaran, K., Ghosh, D., Chapman, G. D., and Gunasekar, P. G. (2008) Molecular mechanism of manganese exposure-induced dopaminergic toxicity. *Brain Res. Bull.* **76**, 361–367 [CrossRef Medline](#)
119. Ommati, M. M., Heidari, R., Ghanbarinejad, V., Abdoli, N., and Niknahad, H. (2019) Taurine treatment provides neuroprotection in a mouse model of manganese. *Biol. Trace Elem. Res.* **190**, 384–395 [CrossRef Medline](#)
120. Fitsanakis, V. A., Zhang, N., Garcia, S., and Aschner, M. (2010) Manganese (Mn) and iron (Fe): interdependency of transport and regulation. *Neurotox. Res.* **18**, 124–131 [CrossRef Medline](#)
121. Sandstrom, B., Davidsson, L., Cederblad, A., Eriksson, R., and Lonnerdal, B. (1986) Manganese absorption and metabolism in man. *Acta Pharmacol. Toxicol. (Copenh.)* **59**, 60–62 [CrossRef Medline](#)
122. Finley, J. W. (1999) Manganese absorption and retention by young women is associated with serum ferritin concentration. *Am. J. Clin. Nutr.* **70**, 37–43 [CrossRef Medline](#)
123. Thomson, A. B., Olatunbosun, D., and Valberg, L. S. (1971) Interrelation of intestinal transport system for manganese and iron. *J. Lab. Clin. Med.* **78**, 642–655 [Medline](#)
124. Rehnberg, G. L., Hein, J. F., Carter, S. D., Linko, R. S., and Laskey, J. W. (1982) Chronic ingestion of Mn₃O₄ by rats: tissue accumulation and distribution of manganese in two generations. *J. Toxicol. Environ. Health* **9**, 175–188 [CrossRef Medline](#)
125. Schroeder, H. A., Balassa, J. J., and Tipton, I. H. (1966) Essential trace metals in man: manganese. A study in homeostasis. *J. Chronic Dis.* **19**, 545–571 [CrossRef Medline](#)
126. Lutz, T. A., Schroff, A., and Scharrer, E. (1993) Effects of calcium and sugars on intestinal manganese absorption. *Biol. Trace Elem. Res.* **39**, 221–227 [CrossRef Medline](#)
127. McDermott, S. D., and Kies, C. (1987) Manganese usage in humans as affected by use of calcium supplements. in *Nutritional Bioavailability of Manganese* (Kies, C., ed) pp. 146–151, American Chemical Society, Washington, D. C.
128. Keen, C. L., and Zidenberg-Cherr, S. (1990) Manganese. In *Present Knowledge in Nutrition* (Brown, M. L., ed) pp. 279–286, International Life Science Institute, Nutrition Foundation, Washington, D. C.
129. Davis, C. D., and Greger, J. L. (1992) Longitudinal changes of manganese-dependent superoxide dismutase and other indexes of manganese and iron status in women. *Am. J. Clin. Nutr.* **55**, 747–752 [CrossRef Medline](#)
130. Aschner, M., and Dorman, D. C. (2006) Manganese: pharmacokinetics and molecular mechanisms of brain uptake. *Toxicol. Rev.* **25**, 147–154 [CrossRef Medline](#)
131. Tuschl, K., Mills, P. B., Parsons, H., Malone, M., Fowler, D., Bitner-Glindzicz, M., and Clayton, P. T. (2008) Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia—a new metabolic disorder. *J. Inher. Metab. Dis.* **31**, 151–163 [CrossRef Medline](#)
132. Quadri, M., Federico, A., Zhao, T., Breedveld, G. J., Battisti, C., Delnooz, C., Severijnen, L. A., Di Toro Mammarella, L., Mignarri, A., Monti, L., Sanna, A., Lu, P., Punzo, F., Cossu, G., Willemsen, R., et al. (2012) Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. *Am. J. Hum. Genet.* **90**, 467–477 [CrossRef Medline](#)
133. Tuschl, K., Clayton, P. T., Gospe, S. M., Jr., Gulab, S., Ibrahim, S., Singhi, P., Aulakh, R., Ribeiro, R. T., Barsottini, O. G., Zaki, M. S., Del Rosario, M. L., Dyack, S., Price, V., Rideout, A., Gordon, K., et al. (2012) Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. *Am. J. Hum. Genet.* **90**, 457–466 [CrossRef Medline](#)
134. Gulab, S., Kayyali, H. R., and Al-Said, Y. (2018) Atypical neurologic phenotype and novel SLC30A10 mutation in two brothers with hereditary hypermanganesemia. *Neuropediatrics* **49**, 72–75 [CrossRef Medline](#)
135. Quadri, M., Kamate, M., Sharma, S., Olgiati, S., Graafland, J., Breedveld, G. J., Kori, I., Hattiholi, V., Jain, P., Aneja, S., Kumar, A., Gulati, P., Goel, M., Talukdar, B., and Bonifati, V. (2015) Manganese transport disorder: novel SLC30A10 mutations and early phenotypes. *Mov. Disord.* **30**, 996–1001 [CrossRef Medline](#)
136. Zaki, M. S., Issa, M. Y., Elbendary, H. M., El-Karakasy, H., Hosny, H., Ghobrial, C., El Safty, A., El-Hennawy, A., Oraby, A., Selim, L., and Abdel-Hamid, M. S. (2018) Hypermanganesemia with dystonia, polycythemia and cirrhosis in 10 patients: six novel SLC30A10 mutations and further phenotype delineation. *Clin. Genet.* **93**, 905–912 [CrossRef Medline](#)
137. Gospe, S. M., Jr., Caruso, R. D., Clegg, M. S., Keen, C. L., Pimstone, N. R., Ducore, J. M., Gettner, S. S., and Kreutzer, R. A. (2000) Paraparesis, hypermanganesemia, and polycythaemia: a novel presentation of cirrhosis. *Arch. Dis. Child.* **83**, 439–442 [CrossRef Medline](#)

138. Perl, D. P., and Olanow, C. W. (2007) The neuropathology of manganese-induced parkinsonism. *J. Neuropathol. Exp. Neurol.* **66**, 675–682 [CrossRef Medline](#)
139. Lechpammer, M., Clegg, M. S., Muzar, Z., Huebner, P. A., Jin, L. W., and Gospe, S. M., Jr. (2014) Pathology of inherited manganese transporter deficiency. *Ann. Neurol.* **75**, 608–612 [CrossRef Medline](#)
140. Wahlberg, K. E., Guazzetti, S., Pineda, D., Larsson, S. C., Fedrighi, C., Cagna, G., Zoni, S., Placidi, D., Wright, R. O., Smith, D. R., Lucchini, R. G., and Broberg, K. (2018) Polymorphisms in manganese transporters SLC30A10 and SLC39A8 are associated with children's neurodevelopment by influencing manganese homeostasis. *Front. Genet.* **9**, 664 [CrossRef Medline](#)
141. Wahlberg, K., Kippler, M., Alhamdow, A., Rahman, S. M., Smith, D. R., Vahter, M., Lucchini, R. G., and Broberg, K. (2016) Common polymorphisms in the solute carrier SLC30A10 are associated with blood manganese and neurological function. *Toxicol. Sci.* **149**, 473–483 [CrossRef Medline](#)
142. Huang, L., and Tepasamrondch, S. (2013) The SLC30 family of zinc transporters: a review of current understanding of their biological and pathophysiological roles. *Mol. Aspects Med.* **34**, 548–560 [CrossRef Medline](#)
143. Bosomworth, H. J., Thornton, J. K., Coneyworth, L. J., Ford, D., and Valentine, R. A. (2012) Efflux function, tissue-specific expression and intracellular trafficking of the Zn transporter ZnT10 indicate roles in adult Zn homeostasis. *Metallomics* **4**, 771–779 [CrossRef Medline](#)
144. Leyva-Illades, D., Chen, P., Zogzas, C. E., Hutchens, S., Mercado, J. M., Swaim, C. D., Morrisett, R. A., Bowman, A. B., Aschner, M., and Mukhopadhyay, S. (2014) SLC30A10 is a cell surface-localized manganese efflux transporter, and parkinsonism-causing mutations block its intracellular trafficking and efflux activity. *J. Neurosci.* **34**, 14079–14095 [CrossRef Medline](#)
145. Zogzas, C. E., Aschner, M., and Mukhopadhyay, S. (2016) Structural elements in the transmembrane and cytoplasmic domains of the metal transporter SLC30A10 are required for its manganese efflux activity. *J. Biol. Chem.* **291**, 15940–15957 [CrossRef Medline](#)
146. Nishito, Y., Tsuji, N., Fujishiro, H., Takeda, T. A., Yamazaki, T., Teranishi, F., Okazaki, F., Matsunaga, A., Tuschl, K., Rao, R., Kono, S., Miyajima, H., Narita, H., Himeno, S., and Kambe, T. (2016) Direct comparison of manganese detoxification/efflux proteins and molecular characterization of ZnT10 protein as a manganese transporter. *J. Biol. Chem.* **291**, 14773–14787 [CrossRef Medline](#)
147. Hutchens, S., Liu, C., Jursa, T., Shawlot, W., Chaffee, B. K., Yin, W., Gore, A. C., Aschner, M., Smith, D. R., and Mukhopadhyay, S. (2017) Deficiency in the manganese efflux transporter SLC30A10 induces severe hypothyroidism in mice. *J. Biol. Chem.* **292**, 9760–9773 [CrossRef Medline](#)
148. Liu, C., Hutchens, S., Jursa, T., Shawlot, W., Polishchuk, E. V., Polishchuk, R. S., Dray, B. K., Gore, A. C., Aschner, M., Smith, D. R., and Mukhopadhyay, S. (2017) Hypothyroidism induced by loss of the manganese efflux transporter SLC30A10 may be explained by reduced thyroxine production. *J. Biol. Chem.* **292**, 16605–16615 [CrossRef Medline](#)
149. Anagianni, S., and Tuschl, K. (2019) Genetic disorders of manganese metabolism. *Curr. Neurol. Neurosci. Rep.* **19**, 33 [CrossRef Medline](#)
150. Greenberg, D. M., Copp, D. H., and Cuthbertson, E. M. (1943) Studies in mineral metabolism with the aid of artificial radioactive isotopes. 7. The distribution and excretion, particularly by way of the bile, of iron, cobalt, and manganese. *J. Biol. Chem.* **147**, 749–756
151. Ballatori, N., Miles, E., and Clarkson, T. W. (1987) Homeostatic control of manganese excretion in the neonatal rat. *Am. J. Physiol.* **252**, R842–R847 [CrossRef Medline](#)
152. Klaassen, C. (1974) Biliary excretion of manganese in rats, rabbits, and dogs. *Toxicol. Appl. Pharmacol.* **29**, 458–468 [CrossRef Medline](#)
153. Bertinchamps, A. J., Miller, S. T., and Cotzias, G. C. (1966) Interdependence of routes excreting manganese. *Am. J. Physiol.* **211**, 217–224 [CrossRef Medline](#)
154. Taylor, C. A., Hutchens, S., Liu, C., Jursa, T., Shawlot, W., Aschner, M., Smith, D. R., and Mukhopadhyay, S. (2019) SLC30A10 transporter in the digestive system regulates brain manganese under basal conditions while brain SLC30A10 protects against neurotoxicity. *J. Biol. Chem.* **294**, 1860–1876 [CrossRef Medline](#)
155. Uhlén, M., Fagerberg, L., Hallström, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., Sivertsson, A., Kampf, C., Sjöstedt, E., Asplund, A., Olsson, I., Edlund, K., Lundberg, E., Navani, S., Szgyarto, C. A., *et al.* (2015) Proteomics: tissue-based map of the human proteome. *Science* **347**, 1260419 [CrossRef Medline](#)
156. Mercadante, C. J., Prajapati, M., Conboy, H. L., Dash, M. E., Herrera, C., Pettiglio, M. A., Cintron-Rivera, L., Salesky, M. A., Rao, D. B., and Bartnikas, T. B. (2019) Manganese transporter Slc30a10 controls physiological manganese excretion and toxicity. *J. Clin. Invest.* **129**, 5442–5461 [CrossRef Medline](#)
157. Chen, P., Bowman, A. B., Mukhopadhyay, S., and Aschner, M. (2015) SLC30A10: a novel manganese transporter. *Worm* **4**, e1042648 [CrossRef Medline](#)
158. Xia, Z., Wei, J., Li, Y., Wang, J., Li, W., Wang, K., Hong, X., Zhao, L., Chen, C., Min, J., and Wang, F. (2017) Zebrafish slc30a10 deficiency revealed a novel compensatory mechanism of Atp2c1 in maintaining manganese homeostasis. *PLoS Genet.* **13**, e1006892 [CrossRef Medline](#)
159. Tuschl, K., Meyer, E., Valdivia, L. E., Zhao, N., Dadsell, C., Abdulsada, A., Hung, C. Y., Simpson, M. A., Chong, W. K., Jacques, T. S., Woltjer, R. L., Eaton, S., Gregory, A., Sanford, L., Kara, E., *et al.* (2016) Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. *Nat. Commun.* **7**, 11601 [CrossRef Medline](#)
160. Jeong, J., and Eide, D. J. (2013) The SLC39 family of zinc transporters. *Mol. Aspects Med.* **34**, 612–619 [CrossRef Medline](#)
161. Juneja, M., Shamim, U., Joshi, A., Mathur, A., Uppili, B., Sairam, S., Ambawat, S., Dixit, R., and Faruq, M. (2018) A novel mutation in SLC39A14 causing hypermanganesemia associated with infantile onset dystonia. *J. Gene Med.* **20**, e3012 [CrossRef Medline](#)
162. Marti-Sanchez, L., Ortigoza-Escobar, J. D., Darling, A., Villaronga, M., Baide, H., Molero-Luis, M., Batllori, M., Vanegas, M. I., Muchart, J., Aquino, L., Artuch, R., Macaya, A., Kurian, M. A., and Dueñas, P. (2018) Hypermanganesemia due to mutations in SLC39A14: further insights into Mn deposition in the central nervous system. *Orphanet J. Rare Dis.* **13**, 28 [CrossRef Medline](#)
163. Girijashanker, K., He, L., Soleimani, M., Reed, J. M., Li, H., Liu, Z., Wang, B., Dalton, T. P., and Nebert, D. W. (2008) Slc39a14 gene encodes ZIP14, a metal/bicarbonate symporter: similarities to the ZIP8 transporter. *Mol. Pharmacol.* **73**, 1413–1423 [CrossRef Medline](#)
164. Jenkitkasemwong, S., Wang, C. Y., Mackenzie, B., and Knutson, M. D. (2012) Physiologic implications of metal-ion transport by ZIP14 and ZIP8. *Biomaterials* **25**, 643–655 [CrossRef Medline](#)
165. Liuzzi, J. P., Aydemir, F., Nam, H., Knutson, M. D., and Cousins, R. J. (2006) Zip14 (Slc39a14) mediates non-transferrin-bound iron uptake into cells. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 13612–13617 [CrossRef Medline](#)
166. Liuzzi, J. P., Lichten, L. A., Rivera, S., Blanchard, R. K., Aydemir, T. B., Knutson, M. D., Ganz, T., and Cousins, R. J. (2005) Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response. *Proc. Natl. Acad. Sci. U.S.A.* **102**, 6843–6848 [CrossRef Medline](#)
167. Pinilla-Tenas, J. J., Sparkman, B. K., Shawki, A., Illing, A. C., Mitchell, C. J., Zhao, N., Liuzzi, J. P., Cousins, R. J., Knutson, M. D., and Mackenzie, B. (2011) Zip14 is a complex broad-scope metal-ion transporter whose functional properties support roles in the cellular uptake of zinc and nontransferrin-bound iron. *Am. J. Physiol. Cell Physiol.* **301**, C862–C871 [CrossRef Medline](#)
168. Taylor, K. M., Morgan, H. E., Johnson, A., and Nicholson, R. I. (2005) Structure-function analysis of a novel member of the LIV-1 subfamily of zinc transporters, ZIP14. *FEBS Lett.* **579**, 427–432 [CrossRef Medline](#)
169. Hojyo, S., Fukada, T., Shimoda, S., Ohashi, W., Bin, B. H., Koseki, H., and Hirano, T. (2011) The zinc transporter SLC39A14/ZIP14 controls G-protein coupled receptor-mediated signaling required for systemic growth. *PLoS ONE* **6**, e18059 [CrossRef Medline](#)
170. Tang, T., Li, L., Tang, J., Li, Y., Lin, W. Y., Martin, F., Grant, D., Solloway, M., Parker, L., Ye, W., Forrest, W., Ghilardi, N., Oravec, T., Platt, K. A.,

- Rice, D. S., *et al.* (2010) A mouse knockout library for secreted and transmembrane proteins. *Nat. Biotechnol.* **28**, 749–755 [CrossRef Medline](#)
171. Aydemir, T. B., Kim, M. H., Kim, J., Colon-Perez, L. M., Banan, G., Mareci, T. H., Febo, M., and Cousins, R. J. (2017) Metal transporter Zip14 (Slc39a14) deletion in mice increases manganese deposition and produces neurotoxic signatures and diminished motor activity. *J. Neurosci.* **37**, 5996–6006 [CrossRef Medline](#)
172. Jenkitkasemwong, S., Akinyode, A., Paulus, E., Weiskirchen, R., Hojyo, S., Fukada, T., Giraldo, G., Schrier, J., Garcia, A., Janus, C., Giasson, B., and Knutson, M. D. (2018) SLC39A14 deficiency alters manganese homeostasis and excretion resulting in brain manganese accumulation and motor deficits in mice. *Proc. Natl. Acad. Sci. U.S.A.* **115**, E1769–E1778 [CrossRef Medline](#)
173. Xin, Y., Gao, H., Wang, J., Qiang, Y., Imam, M. U., Li, Y., Wang, J., Zhang, R., Zhang, H., Yu, Y., Wang, H., Luo, H., Shi, C., Xu, Y., Hojyo, S., *et al.* (2017) Manganese transporter Slc39a14 deficiency revealed its key role in maintaining manganese homeostasis in mice. *Cell Discov.* **3**, 17025 [CrossRef Medline](#)
174. Nam, H., Wang, C. Y., Zhang, L., Zhang, W., Hojyo, S., Fukada, T., and Knutson, M. D. (2013) ZIP14 and DMT1 in the liver, pancreas, and heart are differentially regulated by iron deficiency and overload: implications for tissue iron uptake in iron-related disorders. *Haematologica* **98**, 1049–1057 [CrossRef Medline](#)
175. Guthrie, G. J., Aydemir, T. B., Troche, C., Martin, A. B., Chang, S. M., and Cousins, R. J. (2015) Influence of ZIP14 (slc39a14) on intestinal zinc processing and barrier function. *Am. J. Physiol. Gastrointest. Liver Physiol.* **308**, G171–G178 [CrossRef Medline](#)
176. Scheiber, I. F., Wu, Y., Morgan, S. E., and Zhao, N. (2019) The intestinal metal transporter ZIP14 maintains systemic manganese homeostasis. *J. Biol. Chem.* **294**, 9147–9160 [CrossRef Medline](#)
177. Boycott, K. M., Beaulieu, C. L., Kernohan, K. D., Gebril, O. H., Mhanni, A., Chudley, A. E., Redl, A. M., Hörtnagel, K., Biskup, S., Gleixner, E. M., Kurlemann, G., *et al.* (2015) SLC39A8 deficiency: a disorder of manganese transport and glycosylation. *Am. J. Hum. Genet.* **97**, 886–893 [CrossRef Medline](#)
178. Park, J. H., Hogrebe, M., Grüneberg, M., DuChesne, I., von der Heiden, A. L., Reunert, J., Schlingmann, K. P., Boycott, K. M., Beaulieu, C. L., Mhanni, A. A., Innes, A. M., Hörtnagel, K., Biskup, S., Gleixner, E. M., Kurlemann, G., *et al.* (2015) SLC39A8 deficiency: a disorder of manganese transport and glycosylation. *Am. J. Hum. Genet.* **97**, 894–903 [CrossRef Medline](#)
179. Wang, C. Y., Jenkitkasemwong, S., Duarte, S., Sparkman, B. K., Shawki, A., Mackenzie, B., and Knutson, M. D. (2012) ZIP8 is an iron and zinc transporter whose cell-surface expression is up-regulated by cellular iron loading. *J. Biol. Chem.* **287**, 34032–34043 [CrossRef Medline](#)
180. Wagner, R. R., and Cynkin, M. A. (1971) Glycoprotein metabolism: a UDP-galactose-glycoprotein galactosyltransferase of rat serum. *Biochem. Biophys. Res. Commun.* **45**, 57–62 [CrossRef Medline](#)
181. Schachter, H., McGuire, E. J., and Roseman, S. (1971) Sialic acids. 13. A uridine diphosphate D-galactose: mucin galactosyltransferase from porcine submaxillary gland. *J. Biol. Chem.* **246**, 5321–5328 [Medline](#)
182. Bendiak, B., and Schachter, H. (1987) Control of glycoprotein synthesis. Kinetic mechanism, substrate specificity, and inhibition characteristics of UDP-N-acetylglucosamine- α -D-mannoside β 1–2 N-acetylglucosaminyltransferase II from rat liver. *J. Biol. Chem.* **262**, 5784–5790 [Medline](#)
183. Choi, E. K., Nguyen, T. T., Gupta, N., Iwase, S., and Seo, Y. A. (2018) Functional analysis of SLC39A8 mutations and their implications for manganese deficiency and mitochondrial disorders. *Sci. Rep.* **8**, 3163 [CrossRef Medline](#)
184. Lin, W., Vann, D. R., Doulias, P. T., Wang, T., Landesberg, G., Li, X., Ricciotti, E., Scalia, R., He, M., Hand, N. J., and Rader, D. J. (2017) Hepatic metal ion transporter ZIP8 regulates manganese homeostasis and manganese-dependent enzyme activity. *J. Clin. Invest.* **127**, 2407–2417 [CrossRef Medline](#)
185. Mukhopadhyay, S., and Linstedt, A. D. (2011) Identification of a gain-of-function mutation in a Golgi P-type ATPase that enhances Mn²⁺ efflux and protects against toxicity. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 858–863 [CrossRef Medline](#)
186. Landrigan, P. J., and Miodovnik, A. (2011) Children’s health and the environment: an overview. *Mt. Sinai J. Med.* **78**, 1–10 [CrossRef Medline](#)
187. Chung, S. E., Cheong, H. K., Ha, E. H., Kim, B. N., Ha, M., Kim, Y., Hong, Y. C., Park, H., and Oh, S. Y. (2015) Maternal blood manganese and early neurodevelopment: the Mothers and Children’s Environmental Health (MOCEH) study. *Environ. Health Perspect.* **123**, 717–722 [CrossRef Medline](#)
188. Takser, L., Mergler, D., Hellier, G., Sahuquillo, J., and Huel, G. (2003) Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology* **24**, 667–674 [CrossRef Medline](#)
189. Rodrigues, E. G., Bellinger, D. C., Valeri, L., Hasan, M. O., Quamruzzaman, Q., Golam, M., Kile, M. L., Christiani, D. C., Wright, R. O., and Mazumdar, M. (2016) Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. *Environ. Health.* **15**, 44 [CrossRef Medline](#)
190. Frangou, S., Chitins, X., and Williams, S. C. (2004) Mapping IQ and gray matter density in healthy young people. *NeuroImage* **23**, 800–805 [CrossRef Medline](#)
191. Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., Evans, A., Rapoport, J., and Giedd, J. (2006) Intellectual ability and cortical development in children and adolescents. *Nature* **440**, 676–679 [CrossRef Medline](#)
192. Lewis, D. A. (1997) Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology* **16**, 385–398 [CrossRef Medline](#)
193. Weathers, J. D., Stringaris, A., Deveney, C. M., Brotman, M. A., Zarate, C. A., Jr., Connolly, M. E., Fromm, S. J., LeBourdais, S. B., Pine, D. S., and Leibenluft, E. (2012) A developmental study of the neural circuitry mediating motor inhibition in bipolar disorder. *Am. J. Psychiatry* **169**, 633–641 [CrossRef Medline](#)
194. Bourgeois, J. P., Goldman-Rakic, P. S., and Rakic, P. (1994) Synaptogenesis in the prefrontal cortex of rhesus monkeys. *Cereb. Cortex* **4**, 78–96 [CrossRef Medline](#)
195. Dorman, D. C., Brenneman, K. A., McElveen, A. M., Lynch, S. E., Roberts, K. C., and Wong, B. A. (2002) Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. *J. Toxicol. Environ. Health A* **65**, 1493–1511 [CrossRef Medline](#)
196. Viana, G. F., de Carvalho, C. F., Nunes, L. S., Rodrigues, J. L., Ribeiro, N. S., de Almeida, D. A., Ferreira, J. R., Abreu, N., and Menezes-Filho, J. A. (2014) Noninvasive biomarkers of manganese exposure and neuropsychological effects in environmentally exposed adults in Brazil. *Toxicol. Lett.* **231**, 169–178 [CrossRef Medline](#)
197. Menezes-Filho, J. A., Novaes Cde, O., Moreira, J. C., Sarcinelli, P. N., and Mergler, D. (2011) Elevated manganese and cognitive performance in school-aged children and their mothers. *Environ. Res.* **111**, 156–163 [CrossRef Medline](#)
198. Chang, Y., Lee, J. J., Seo, J. H., Song, H. J., Kim, J. H., Bae, S. J., Ahn, J. H., Park, S. J., Jeong, K. S., Kwon, Y. J., Kim, S. H., and Kim, Y. (2010) Altered working memory process in the manganese-exposed brain. *NeuroImage* **53**, 1279–1285 [CrossRef Medline](#)
199. Zou, Y., Qing, L., Zeng, X., Shen, Y., Zhong, Y., Liu, J., Li, Q., Chen, K., Lv, Y., Huang, D., Liang, G., Zhang, W., Chen, L., Yang, Y., and Yang, X. (2014) Cognitive function and plasma BDNF levels among manganese-exposed smelters. *Occup. Environ. Med.* **71**, 189–194 [CrossRef Medline](#)
200. Long, Z., Jiang, Y. M., Li, X. R., Fadel, W., Xu, J., Yeh, C. L., Long, L. L., Luo, H. L., Harezlak, J., Murdoch, J. B., Zheng, W., and Dydak, U. (2014) Vulnerability of welders to manganese exposure—a neuroimaging study. *Neurotoxicology* **45**, 285–292 [CrossRef Medline](#)
201. Pautler, R. G., Mongeau, R., and Jacobs, R. E. (2003) *In vivo* trans-synaptic tract tracing from the murine striatum and amygdala utilizing manganese enhanced MRI (MEMRI). *Magn. Reson. Med.* **50**, 33–39 [CrossRef Medline](#)
202. Baly, D. L., Lee, I., and Doshi, R. (1988) Mechanism of decreased insulinogenesis in manganese-deficient rats: decreased insulin mRNA levels. *FEBS Lett.* **239**, 55–58 [CrossRef Medline](#)

203. Baly, D. L., Keen, C. L., and Hurlley, L. S. (1986) Effects of manganese deficiency on pyruvate carboxylase and phosphoenolpyruvate carboxykinase activity and carbohydrate homeostasis in adult rats. *Biol. Trace Elem. Res.* **11**, 201–212 [CrossRef Medline](#)
204. Baly, D. L., Curry, D. L., Keen, C. L., and Hurlley, L. S. (1984) Effect of manganese deficiency on insulin secretion and carbohydrate homeostasis in rats. *J. Nutr.* **114**, 1438–1446 [CrossRef Medline](#)
205. Baly, D. L., Schneiderman, J. S., and Garcia-Welsh, A. L. (1990) Effect of manganese deficiency on insulin binding, glucose transport and metabolism in rat adipocytes. *J. Nutr.* **120**, 1075–1079 [CrossRef Medline](#)
206. Clegg, M. S., Donovan, S. M., Monaco, M. H., Baly, D. L., Ensuna, J. L., and Keen, C. L. (1998) The influence of manganese deficiency on serum IGF-1 and IGF binding proteins in the male rat. *Proc. Soc. Exp. Biol. Med.* **219**, 41–47 [CrossRef Medline](#)
207. Bryan, M. R., Nordham, K. D., Rose, D. I. R., O'Brien, M. T., Joshi, P., Foshage, A. M., Gonçalves, F. M., Nitin, R., Uhouse, M. A., Aschner, M., and Bowman, A. B. (2020) Manganese acts upon insulin/IGF receptors to phosphorylate AKT and increase glucose uptake in Huntington's disease cells. *Mol. Neurobiol.* **57**, 1570–1593 [CrossRef Medline](#)
208. Yamada, M., Ohno, S., Okayasu, I., Okeda, R., Hatakeyama, S., Watanabe, H., Ushio, K., and Tsukagoshi, H. (1986) Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain. *Acta Neuropathol.* **70**, 273–278 [CrossRef Medline](#)
209. Bryan, M. R., and Bowman, A. B. (2017) Manganese and the insulin-IGF signaling network in Huntington's disease and other neurodegenerative disorders. *Adv. Neurobiol.* **18**, 113–142 [CrossRef Medline](#)
210. Verity, M. A. (1999) Manganese neurotoxicity: a mechanistic hypothesis. *Neurotoxicology* **20**, 489–497 [Medline](#)
211. Pfalzer, A. C., and Bowman, A. B. (2017) Relationships between essential manganese biology and manganese toxicity in neurological disease. *Curr. Environ. Health Rep.* **4**, 223–228 [CrossRef Medline](#)
212. Guilarte, T. R., Chen, M. K., McGlothlan, J. L., Verina, T., Wong, D. F., Zhou, Y., Alexander, M., Rohde, C. A., Syversen, T., Decamp, E., Koser, A. J., Fritz, S., Gonczi, H., Anderson, D. W., and Schneider, J. S. (2006) Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human primates. *Exp. Neurol.* **202**, 381–390 [CrossRef Medline](#)
213. Aschner, M., Guilarte, T. R., Schneider, J. S., and Zheng, W. (2007) Manganese: recent advances in understanding its transport and neurotoxicity. *Toxicol. Appl. Pharmacol.* **221**, 131–147 [CrossRef Medline](#)
214. Hisahara, S., and Shimohama, S. (2011) Dopamine receptors and Parkinson's disease. *Int. J. Med. Chem.* **2011**, 403039 [CrossRef Medline](#)
215. Newland, M. C., Ceckler, T. L., Kordower, J. H., and Weiss, B. (1989) Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. *Exp. Neurol.* **106**, 251–258 [CrossRef Medline](#)
216. Cersosimo, M. G., and Koller, W. C. (2006) The diagnosis of manganese-induced parkinsonism. *Neurotoxicology* **27**, 340–346 [CrossRef Medline](#)
217. Guilarte, T. R. (2010) Manganese and Parkinson's disease: a critical review and new findings. *Environ. Health Perspect.* **118**, 1071–1080 [CrossRef Medline](#)
218. Lao, Y., Dion, L.-A. A., Gilbert, G., Bouchard, M. F., Rocha, G., Wang, Y., Leporé, N., and Saint-Amour, D. (2017) Mapping the basal ganglia alterations in children chronically exposed to manganese. *Sci. Rep.* **7**, 41804 [CrossRef Medline](#)
219. Aschner, J. L., Anderson, A., Slaughter, J. C., Aschner, M., Steele, S., Beller, A., Mouvery, A., Furlong, H. M., and Maitre, N. L. (2015) Neuroimaging identifies increased manganese deposition in infants receiving parenteral nutrition. *Am. J. Clin. Nutr.* **102**, 1482–1489 [CrossRef Medline](#)
220. Cordova, F. M., Aguiar, A. S., Jr., Peres, T. V., Lopes, M. W., Gonçalves, F. M., Pedro, D. Z., Lopes, S. C., Pilati, C., Prediger, R. D., Farina, M., Erikson, K. M., Aschner, M., and Leal, R. B. (2013) Manganese-exposed developing rats display motor deficits and striatal oxidative stress that are reversed by Trolox. *Arch. Toxicol.* **87**, 1231–1244 [CrossRef Medline](#)
221. Hsieh, C. T., Liang, J. S., Peng, S. S., and Lee, W. T. (2007) Seizure associated with total parenteral nutrition-related hypermanganesemia. *Pediatr. Neurol.* **36**, 181–183 [CrossRef Medline](#)
222. Iwase, K., Higaki, J., Mikata, S., Tanaka, Y., Kondoh, H., Yoshikawa, M., Hori, S., and Kamiike, W. (2002) Manganese deposition in basal ganglia due to perioperative parenteral nutrition following gastrointestinal surgeries. *Dig. Surg.* **19**, 174–183 [CrossRef Medline](#)
223. Rivera-Mancía, S., Ríos, C., and Montes, S. (2011) Manganese accumulation in the CNS and associated pathologies. *Biometals* **24**, 811–825 [CrossRef Medline](#)
224. Sikk, K., Haldre, S., Aquilonius, S. M., and Taba, P. (2011) Manganese-induced parkinsonism due to ephedrone abuse. *Parkinsons Dis.* **2011**, 865319 [CrossRef Medline](#)
225. Ohtake, T., Negishi, K., Okamoto, K., Oka, M., Maesato, K., Moriya, H., and Kobayashi, S. (2005) Manganese-induced parkinsonism in a patient undergoing maintenance hemodialysis. *Am. J. Kidney Dis.* **46**, 749–753 [CrossRef Medline](#)
226. Brna, P., Gordon, K., Dooley, J. M., and Price, V. (2011) Manganese toxicity in a child with iron deficiency and polycythemia. *J. Child Neurol.* **26**, 891–894 [CrossRef Medline](#)
227. Selikhova, M., Fedoryshyn, L., Matviyenko, Y., Komnatska, I., Kyrlychuk, M., Krolicki, L., Friedman, A., Taylor, A., Jäger, H. R., Lees, A., and Sanotsky, Y. (2008) Parkinsonism and dystonia caused by the illicit use of ephedrone—a longitudinal study. *Mov. Disord.* **23**, 2224–2231 [CrossRef Medline](#)
228. Iqbal, M., Monaghan, T., and Redmond, J. (2012) Manganese toxicity with ephedrone abuse manifesting as parkinsonism: a case report. *J. Med. Case Rep.* **6**, 52 [CrossRef Medline](#)
229. Ares-Santos, S., Granado, N., and Moratalla, R. (2013) The role of dopamine receptors in the neurotoxicity of methamphetamine. *J. Intern. Med.* **273**, 437–453 [CrossRef Medline](#)
230. Calne, D. B., Chu, N. S., Huang, C. C., Lu, C. S., and Olanow, W. (1994) Manganism and idiopathic parkinsonism: similarities and differences. *Neurology* **44**, 1583–1586 [CrossRef Medline](#)
231. Sulzer, D. (2007) Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. *Trends Neurosci.* **30**, 244–250 [CrossRef Medline](#)
232. Guilarte, T. R., and Gonzales, K. (2015) Manganese-induced parkinsonism is not idiopathic Parkinson's disease: environmental and genetic evidence. *Toxicol. Sci.* **146**, 204–212 [CrossRef Medline](#)
233. Criswell, S. R., Perlmutter, J. S., Videen, T. O., Moerlein, S. M., Flores, H. P., Birke, A. M., and Racette, B. A. (2011) Reduced uptake of [¹⁸F]F-DOPA PET in asymptomatic welders with occupational manganese exposure. *Neurology* **76**, 1296–1301 [CrossRef Medline](#)
234. Kwakye, G. F., Paoliello, M. M., Mukhopadhyay, S., Bowman, A. B., and Aschner, M. (2015) Manganese-induced parkinsonism and Parkinson's disease: shared and distinguishable features. *Int. J. Environ. Res. Public Health* **12**, 7519–7540 [CrossRef Medline](#)
235. Chen, P., Chakraborty, S., Peres, T. V., Bowman, A. B., and Aschner, M. (2015) Manganese-induced neurotoxicity: from *C. elegans* to humans. *Toxicol. Res. (Camb.)* **4**, 191–202 [CrossRef Medline](#)
236. Guilarte, T. R., Burton, N. C., McGlothlan, J. L., Verina, T., Zhou, Y., Alexander, M., Pham, L., Griswold, M., Wong, D. F., Syversen, T., and Schneider, J. S. (2008) Impairment of nigrostriatal dopamine neurotransmission by manganese is mediated by pre-synaptic mechanism(s): implications to manganese-induced parkinsonism. *J. Neurochem.* **107**, 1236–1247 [CrossRef Medline](#)
237. Criswell, S. R., Warden, M. N., Searles Nielsen, S., Perlmutter, J. S., Moerlein, S. M., Sheppard, L., Lenox-Krug, J., Checkoway, H., and Racette, B. A. (2018) Selective D2 receptor PET in manganese-exposed workers. *Neurology* **91**, e1022–e1030 [CrossRef Medline](#)
238. Gorell, J. M., Johnson, C. C., Rybicki, B. A., Peterson, E. L., Kortsha, G. X., Brown, G. G., and Richardson, R. J. (1999) Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicology* **20**, 239–247 [Medline](#)
239. Gorell, J. M., Peterson, E. L., Rybicki, B. A., and Johnson, C. C. (2004) Multiple risk factors for Parkinson's disease. *J. Neurol. Sci.* **217**, 169–174 [CrossRef Medline](#)
240. Kim, Y., Kim, J. W., Ito, K., Lim, H. S., Cheong, H. K., Kim, J. Y., Shin, Y. C., Kim, K. S., and Moon, Y. (1999) Idiopathic parkinsonism with superimposed manganese exposure: utility of positron emission tomography. *Neurotoxicology* **20**, 249–252 [Medline](#)

241. Racette, B. A., Aschner, M., Guilarte, T. R., Dydak, U., Criswell, S. R., and Zheng, W. (2012) Pathophysiology of manganese-associated neurotoxicity. *Neurotoxicology* **33**, 881–886 [CrossRef Medline](#)
242. Salazar, J., Mena, N., Hunot, S., Prigent, A., Alvarez-Fischer, D., Arredondo, M., Duyckaerts, C., Szdovitch, V., Zhao, L., Garrick, L. M., Nuñez, M. T., Garrick, M. D., Raisman-Vozari, R., and Hirsch, E. C. (2008) Divalent metal transporter 1 (DMT1) contributes to neurodegeneration in animal models of Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 18578–18583 [CrossRef Medline](#)
243. Garrick, M. D., Dolan, K. G., Horbinski, C., Ghio, A. J., Higgins, D., Porubcin, M., Moore, E. G., Hainsworth, L. N., Umbreit, J. N., Conrad, M. E., Feng, L., Lis, A., Roth, J. A., Singleton, S., and Garrick, L. M. (2003) DMT1: a mammalian transporter for multiple metals. *Biometals* **16**, 41–54 [CrossRef Medline](#)
244. Lu, C., Meng, Z., He, Y., Xiao, D., Cai, H., Xu, Y., Liu, X., Wang, X., Mo, L., Liang, Z., Wei, X., Ao, Q., Liang, B., Li, X., Tang, S., and Guo, S. (2018) Involvement of gap junctions in astrocyte impairment induced by manganese exposure. *Brain Res. Bull.* **140**, 107–113 [CrossRef Medline](#)
245. Pajarillo, E., Rizor, A., Lee, J., Aschner, M., and Lee, E. (2019) The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: potential targets for neurotherapeutics. *Neuropharmacology* **161**, 107559 [CrossRef Medline](#)
246. Du, K., Liu, M., Pan, Y., Zhong, X., and Wei, M. (2017) Association of serum manganese levels with Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *Nutrients* **9**, 231–243 [CrossRef Medline](#)
247. Tong, Y., Yang, H., Tian, X., Wang, H., Zhou, T., Zhang, S., Yu, J., Zhang, T., Fan, D., Guo, X., Tabira, T., Kong, F., Chen, Z., Xiao, W., and Chui, D. (2014) High manganese, a risk for Alzheimer's disease: high manganese induces amyloid- β related cognitive impairment. *J. Alzheimers Dis.* **42**, 865–878 [CrossRef Medline](#)
248. Molina, J. A., Jiménez-Jiménez, F. J., Aguilar, M. V., Meseguer, I., Mateos-Vega, C. J., González-Muñoz, M. J., de Bustos, F., Porta, J., Ortí-Pareja, M., Zurdo, M., Barrios, E., and Martínez-Para, M. C. (1998) Cerebrospinal fluid levels of transition metals in patients with Alzheimer's disease. *J. Neural Transm. (Vienna)* **105**, 479–488 [CrossRef Medline](#)
249. González-Domínguez, R., García-Barrera, T., and Gómez-Ariza, J. L. (2014) Homeostasis of metals in the progression of Alzheimer's disease. *Biometals* **27**, 539–549 [CrossRef Medline](#)
250. Hare, D. J., Faux, N. G., Roberts, B. R., Volitakis, I., Martins, R. N., and Bush, A. I. (2016) Lead and manganese levels in serum and erythrocytes in Alzheimer's disease and mild cognitive impairment: results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing. *Metallomics* **8**, 628–632 [CrossRef Medline](#)
251. De Leo, M. E., Borrello, S., Passantino, M., Palazzotti, B., Mordente, A., Daniele, A., Filippini, V., Galeotti, T., and Masullo, C. (1998) Oxidative stress and overexpression of manganese superoxide dismutase in patients with Alzheimer's disease. *Neurosci. Lett.* **250**, 173–176 [CrossRef Medline](#)
252. Marcus, D. L., Strafaci, J. A., and Freedman, M. L. (2006) Differential neuronal expression of manganese superoxide dismutase in Alzheimer's disease. *Med. Sci. Monit.* **12**, BR8–14 [Medline](#)
253. Maeda, M., Takagi, H., Hattori, H., and Matsuzaki, T. (1997) Localization of manganese superoxide dismutase in the cerebral cortex and hippocampus of Alzheimer-type senile dementia. *Osaka City Med. J.* **43**, 1–5 [Medline](#)
254. Dumont, M., Wille, E., Stack, C., Calingasan, N. Y., Beal, M. F., and Lin, M. T. (2009) Reduction of oxidative stress, amyloid deposition, and memory deficit by manganese superoxide dismutase overexpression in a transgenic mouse model of Alzheimer's disease. *FASEB J.* **23**, 2459–2466 [CrossRef Medline](#)
255. Li, F., Calingasan, N. Y., Yu, F., Mauck, W. M., Toidze, M., Almeida, C. G., Takahashi, R. H., Carlson, G. A., Flint Beal, M., Lin, M. T., and Gouras, G. K. (2004) Increased plaque burden in brains of APP mutant MnSOD heterozygous knockout mice. *J. Neurochem.* **89**, 1308–1312 [CrossRef Medline](#)
256. Anantharaman, M., Tangpong, J., Keller, J. N., Murphy, M. P., Markesbery, W. R., Kinningham, K. K., and St Clair, D. K. (2006) β -Amyloid mediated nitration of manganese superoxide dismutase: implication for oxidative stress in a double knock-in mouse model of Alzheimer's disease. *Am. J. Pathol.* **168**, 1608–1618 [CrossRef Medline](#)
257. Calderón-Garcidueñas, L., Serrano-Sierra, A., Torres-Jardón, R., Zhu, H., Yuan, Y., Smith, D., Delgado-Chávez, R., Cross, J. V., Medina Cortina, H., Kavanaugh, M., and Guilarte, T. R. (2013) The impact of environmental metals in young urbanites' brains. *Exp. Toxicol. Pathol.* **65**, 503–511 [CrossRef Medline](#)
258. Calderón-Garcidueñas, L., D'Angiulli, A., Kulesza, R. J., Torres-Jardón, R., Osnaya, N., Romero, L., Keefe, S., Herritt, L., Brooks, D. M., Avila-Ramirez, J., Delgado-Chávez, R., Medina-Cortina, H., and González-González, L. O. (2011) Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials. *Int. J. Dev. Neurosci.* **29**, 365–375 [CrossRef Medline](#)
259. Schneider, J. S., Decamp, E., Koser, A. J., Fritz, S., Gonczi, H., Syversen, T., and Guilarte, T. R. (2006) Effects of chronic manganese exposure on cognitive and motor functioning in non-human primates. *Brain Res.* **1118**, 222–231 [CrossRef Medline](#)