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Metals in Neurological Disorders: From Essential Functions to Toxicity, Epidemiology, and Therapeutic Prospects for Brain Health

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ABSTRACT

This review examines the intricate interplay between metals and neurological disorders, highlighting their essential biological roles while addressing toxicity risks. It explores macro-minerals and micronutrients, emphasizing the "exposome" concept, which encompasses lifelong metal exposure. A significant focus is on manganese (Mn), which exemplifies the dual nature of metals as both essential and neurotoxic. The review discusses recent advancements in understanding Mn-induced neurotoxicity, supported by epidemiological and clinical evidence linking Mn exposure to neurodevelopmental and neurodegenerative disorders, including Alzheimer's, ALS, autism, schizophrenia, and ADHD. Challenges in studying metal alterations in neurological diseases are highlighted, underscoring the need for advanced imaging techniques to elucidate brain metal biochemistry. The review calls for multidisciplinary research integrating artificial intelligence and emerging technologies to bridge knowledge gaps on chronic low-dose metal exposures and long-term neurological effects. Ultimately, it advocates for stringent monitoring and targeted interventions to mitigate metal-associated neurotoxicity.

Keywords: Manganese exposure, Neurological disorders, Environmental exposome, Neurodegenerative diseases, Metals and neurotoxicity.

INTRODUCTION

Metals are ubiquitous in the Earth's crust, forming an integral part of rocks, soils, minerals, and water systems. While natural processes contribute to their presence in the environment, human activities such as mining, industrial operations, agriculture, and urbanization have significantly amplified metal emissions, leading to widespread environmental contamination[1]. Due to their non-degradable nature, metals persist in ecosystems and accumulate in living organisms via ingestion, inhalation, or dermal contact-a process known as bioaccumulation[2]. The biomagnification process makes some metals much more dangerous to humans and other animals because their concentrations increase as they go up

the food chain[3]. The toxicological effects of metals such as lead, mercury, cadmium, and arsenic make their long-term exposure to humans particularly risky. When exposed to certain metals, the nervous system, kidneys, and other vital organs are at increased risk of damage.

Metals are just one of many environmental elements that make up an individual's or a population's "exposome" throughout the course of a lifetime[4,5]. The metal exposome reflects exposure from diverse sources such as air pollution, contaminated drinking water, dietary intake, and occupational hazards. Recognizing the health and ecological risks posed by metal pollution, it is imperative to monitor and regulate environmental metal concentrations effectively[6,7]. Environmental policies and monitoring initiatives play a crucial role in mitigating the adverse effects of metal contamination and promoting a safer, more sustainable environment. Emphasizing sustainable practices, along with efficient waste management and pollution control measures, is essential for reducing the burden of metal exposure[8]. In biological systems, metals serve indispensable roles, classified as either essential or non-essential based on their physiological importance. Essential metals are fundamental for maintaining life, supporting various biochemical and physiological processes crucial for survival[9,10].

Essential metals in biological systems are classified as macronutrients or micronutrients. Macronutrients like Na, K, Mg, and Ca are needed in high amounts for nerve signaling, muscle contraction, bone formation, and electrolyte balance[11]. Micronutrients, including Cu, Zn, Fe, Mn, and Mo, are required in trace amounts for redox control, immunity, neurotransmitter function, and enzymatic reactions[12]. Non-essential metals like Cd, Hg, Al, Pb, and As have toxic effects, even in small amounts, leading to neurolotgical damage, kidney failure, and cancer[13,14]. Prolonged exposure to these toxic metals poses serious health risks shown in Table 1. Metal toxicity has dual effects: essential for physiological functions but harmful in excess. Overexposure occurs through contaminated food, water, inhalation, or skin absorption. Many metals accumulate in the brain, making the CNS highly vulnerable to toxicity.

Table 1. Heavy metals toxicity mechanisms, and their health impacts

Heavy Metal	Source of Exposure	Toxicity Mechanism	Health Effects
Lead (Pb)	Paint, batteries, contaminated water,	Disrupts neurotransmitter function, interferes with calcium metabolism, oxidative stress	Neurological disorders, cognitive impairment, kidney damage, anemia, cardiovascular issues
Mercury (Hg)	Fish consumption, industrial waste, dental amalgams, thermometers	Binds to sulfhydryl groups, disrupts protein and enzyme function, induces oxidative stress	Neurotoxicity, developmental defects, tremors, memory loss, renal damage
Cadmium (Cd)	Industrial emissions, cigarette smoke, contaminated food, batteries	Disrupts calcium metabolism, induces oxidative stress, inhibits DNA repair	Kidney damage, osteoporosis, lung cancer, immune dysfunction
Arsenic (As)	Contaminated water, pesticides, industrial waste, mining	Inhibits cellular respiration, induces DNA damage, oxidative stress	Skin lesions, cancer (lung, skin, bladder), cardiovascular diseases, neurological effects
Aluminum (Al)	Food packaging, antacids, cookware, cosmetics	Disrupts iron metabolism, interferes with synaptic activity	Neurotoxicity, Alzheimer's disease risk, bone disorders, anemia
Chromium (Cr VI)	Industrial waste, stainless steel production, contaminated water	Generates reactive oxygen species (ROS), DNA damage, carcinogenic	Lung cancer, dermatitis, kidney and liver toxicity
Nickel (Ni)	Jewelry, batteries, industrial emissions, contaminated water	Induces immune hypersensitivity, DNA damage, oxidative stress	Respiratory issues, skin allergies, lung cancer, kidney dysfunction
Manganese (Mn)	Mining, welding fumes, contaminated water, industrial emissions	Accumulates in basal ganglia, interferes with dopamine function	Neurotoxicity, Parkinson-like symptoms, cognitive decline
Zinc (Zn) (Excess Exposure)	Overuse of supplements, industrial exposure	Disrupts copper absorption, interferes with immune function	Nausea, vomiting, immune suppression, neurological effects

Metals in the brain can disrupt cellular and chemical processes, linking metal toxicity to neurodevelopmental and neurodegenerative diseases. Acute and sub-acute exposures show similarities to neurological illness mechanisms. Chronic low-dose exposure also causes serious effects, but its molecular impact remains unclear. Toxicity may persist after exposure ends (persistent toxicity) or emerge later (latent toxicity). Understanding these effects is crucial for developing preventive and therapeutic strategies. Further research is needed on long-term metal neurotoxicity, alongside environmental monitoring and exposure reduction measures to mitigate risks and safeguard neurological health. This review explores the role of metals in neurological disorders, focusing on Mn's dual nature as an essential nutrient and neurotoxin[15]. It highlights metal-induced neurotoxicity, research gaps, and future directions[16]. Emphasizing the need for deeper understanding, it advocates for translational research to improve diagnosis, prevention, and treatment.

Effects of Mn on neurological disorders

Concern about Mn's neurotoxic effects was first voiced in the context of occupational exposure to high concentrations of the metal. However, it has become evident that non-occupational environmental exposures can also lead to Mn toxicity[17]. Individuals chronically exposed to elevated Mn levels, regardless of the source of exposure, may experience abnormal neurological symptoms, and the impact can vary across different ages and between sexes. Interestingly, research has shown that the mutation responsible for Huntington's disease (HD) can alter brain Mn homeostasis and reduce the availability of Mn. Further research into the interplay between Mn and HD has demonstrated that age, gender, and neuronal lineage can all alter the results. Patients with chronic hepatic dysfunction are another group at risk for Mn-related neurotoxicity, and mutations in Mn transporter genes can also put individuals at risk[18,19]. Mn's harmful effects are modulated by a variety of biological variables, resulting in varying clinicopathological phenotypes throughout life.

Alzheimer's disease (AD)

The findings of recent studies indicate that Mn may be involved in neurodegenerative processes, such as Alzheimer's disease. The findings are inconsistent, which makes it difficult to establish an exact link between Mn and AD[20-22]. This is the case despite the fact that various investigations have been conducted to analyze altered blood Mn levels in Alzheimer's disease in comparison to control groups. Significant results, such as the aggregation of plaque formation, phosphorylation and aggregation of tau protein, impairment of the blood-brain barrier, neuroinflammation, oxidative stress, apoptosis, and necrosis of neurons, are illustrated in Fig. 2 in animal studies that have been conducted on the effects of Mn exposure. In non-human primates that were given a prolonged intravenous infusion of Mn, the development of amyloid beta (Aβ) plaques and neurodegeneration in the frontal cortex was seen. Furthermore, mice that were exposed to Mn displayed cognitive abnormalities, which suggests that the frontal brain is particularly susceptible to Mn and that this may have a potential importance in Alzheimer's disease[23,24].

Human studies have also shown links between Mn exposure and neuropathological alterations associated with AD. Increased cortical Mn and neuropathological alterations, such as hyperphosphorylated tau and diffuse A plaques, were linked to high levels of pollution in Mexico City in young people. In a similar vein, people living in South African regions with high levels of airborne Mn pollution had worse cognitive function, and the longer they were exposed to these levels, the worse their scores got. The hypothesis that Mn exposure could lead to neuropathological alterations similar to AD was supported by the increased levels of Mn and Aβin the cortex and hippocampus observed in AD model mice when exposed to Mn by drinking water[25-27].

Amyotrophic Lateral Sclerosis (ALS)

Many people have been interested in the possibility of a connection between Mn exposure and ALS for a long time. An early discovery that may indicate to a link between exposure to Mn and bulbar ALS was discovered nearly a century ago when a German labourer contracted the disease while working at a Mn smelter. Although studies investigating metal homeostasis dysregulation in ALS have shown Mn as a possible pathogenic component, our understanding of the precise function of Mn in this disease is limited. Multiple studies have compared Mn levels in CSF and blood between ALS patients and controls, but the findings

have been contradictory[28-31]. The amounts of Mn in the two fluids were shown to be higher in ALS patients in some investigations, but not in others. A new study evaluated the absorption of metals, including Mn, in ALS patients and control subjects by dental indicators. The research indicated that metal concentrations varied across the childhood exposure period, implying that early-life metal exposure may have a role in the onset of ALS. Further evidence of a possible relationship between Mn and ALS was found in the spinal cords of affected animals in a mouse model of frontotemporal lobar degeneration and amyotrophic lateral sclerosis (ALS) compared to control animals. This finding adds to the existing body of evidence[32,33]. Interestingly, one person who had ALS after a conventional medical operation that involved inserting potassium permanganate into their lower back was documented in a case study. Case study shows that Mn exposure may have contributed to the development of amyotrophic lateral sclerosis (ALS), and potassium permanganate is a substance that includes Mn[34].

Disorder of Attention Deficit Hyperactivity

The evidence that early-life Mn exposure may affect dopaminergic neurons in the striatum suggests that it may have a role in the genesis of attention deficit hyperactivity disorder (ADHD). Mn can build up in neurons due to a malfunction in the dopamine transporter (DAT), which has been demonstrated to occur in ADHD. Researchers discovered that children with ADHD had lower serum Mn levels than controls after taking methylphenidate, a DAT inhibitor and common treatment for the illness[35-37]. Furthermore, exposure to Mn in drinking water has been associated with reduced cognitive function, including attention, memory, and intelligence quotient (IQ), throughout a variety of developmental stages, even at levels believed to be non-toxic. There is evidence from animal research that developmental exposure to Mn can have negative effects. Adult rats that were given Mn orally when they were newborns showed persistent behavioral abnormalities related to anxiety and attention. Furthermore, consistent neuroinflammation and a decrease in medial prefrontal cortex catecholaminergic system proteins were both brought about by the identical exposure paradigm. These results are intriguing, but more research is needed to clarify the association between Mn exposure in childhood and ADHD[38-41]. Understanding this potential link is essential to improve our knowledge of the etiology of ADHD and how early-life exposures to Mn might contribute to the development of this neurodevelopmental disorder. It is also crucial to explore whether the effects of early-life Mn exposure persist into adulthood and how they may influence long-term brain function and behavior.

Autism Spectrum Disorder (ASD)

Anxieties related to metal exposure in childhood has also been investigated. Researchers have looked into the correlation between Mn and ASD in the past by analyzing biomarkers such blood, urine, hair, teeth, and airborne Mn concentrations. Nonetheless, there has been conflicting evidence; some researches have shown reduced Mn levels in ASD youngsters, while others have failed to detect a correlation. There was a strong correlation between elevated blood Mn levels and increased neuroinflammatory markers[42] in a study of 78 children with ASD. Be wary of drawing any firm conclusions from this study because it did not include a control group. To validate and comprehend the possible association between Mn exposure and ASD, more research with appropriate control groups is required. There may be some overlap in the pathogenic pathways between ADHD and ASD, which is an intriguing finding[43,44]. Because of this overlap, further research examining the possible connection between Mn exposure and both ADHD and ASD may shed light on the role of Mn in neuro-developmental disorders. Understanding the relationship between Mn and neuro-developmental disorders like ASD is complex, and more research is needed to elucidate the underlying mechanisms and potential contributions of Mn exposure to the development of these conditions. Such research could have a significant impact on detecting environmental risk factors and establishing tailored therapies for neurodevelopmental disorders[45-47].

Schizophrenia

Intriguingly, there has been little research on the possible link between Mn and schizophrenia. In a matched case analysis, researchers discovered that serum Mn levels were higher in those with schizophrenia than in healthy controls. This discovery, which may point to a link between Mn and schizophrenia, was made using inductively coupled plasma-mass spectrometry. Furthermore, schizophrenia is one of several metabolic, inflammatory, and neurological

diseases linked to a particular single nucleotide polymorphism (rs13107325) in the SLC39A8 (ZIP8) gene. Prevalence estimates for this SNP range from 5-10% in some populations[48]. The fact that this SNP is associated with multiple diseases, including schizophrenia, suggests that Mn dysregulation may play a role in the development of schizophrenia49. Additional research is needed to fully comprehend the mechanics and implications of this link between Mn and schizophrenia, however this evidence does point to a possible linkage. Additional research is required to fully understand the function of Mn in the aetiology of schizophrenia and to identify the specific pathways by which this multifaceted mental illness may be impacted. The potential link between Mn and schizophrenia could open new avenues for research and potential interventions to improve the diagnosis and treatment of schizophrenia. However, it is essential to approach this area of investigation with caution and conduct robust studies to establish a clearer picture of the association between Mn and schizophrenia[50].

Brain manganese homeostasis

Mn plays an important part in many biological processes, and it is a trace element that all prokaryotes and eukaryotic organisms need to survive. Numerous enzymes, including glycosylation enzymes, signalling kinases, and glutamine synthetase, rely on it as a cofactor[51]. Both the immune system and the body's reaction to oxidative stress rely heavily on Mn. Water and foods high in Mn, such as nuts, soybeans, and rice, are the main oral sources of Mn, although other dietary sources also contribute. A major route of exposure can also be inhalation, particularly in work environments. Despite the minimal quantity of orally ingested Mn that reaches the brain, the central nervous system is particularly vulnerable to Mn-induced damage. Specific regions of the brain, including the frontal cortex, substantia nigra, striatum, and globus pallidus, exhibit a propensity to accumulate Mn. Even trace amounts of Mn are essential for some cerebral functions[52,53]. The brain keeps this balance delicately. One of Mn's twin roles as a neurotoxic metal and an essential nutrient is due to its restricted dose range. Disruptions to this homeostatic equilibrium, even in the smallest changes to Mn influx and outflow, can cause a host of neuropathological consequences, such as motor, cognitive, and behavioural impairments. In order to benefit from Mn's nutritional properties without causing neurotoxicity, efficient uptake and removal of excess Mn are essential. Eliminating the source of exposure, improving excretion, and implementing chelation therapy are the main therapeutic strategies for acute Mn overexposure. There is a great need to comprehend the subcellular distribution of Mn after transporter-mediated entry and efflux in different intracellular compartments. Both physiological and overload situations point to the Golgi apparatus as a key player in Mn storage[54-56]. Some neurological diseases may be impacted by Mn buildup in the Golgi apparatus, which has been linked to SLC30A10 gene mutations[57]. To better understand the possible interaction between altered subcellular Mn dynamics and neuropathology, as well as the translational implications of our findings, additional *in vivo* investigations are required[58,59].

Role of Essential Metals in CNS Function

Essential metals play a vital role in CNS function, influencing metabolism, neurotransmission, and enzymatic activity. Fe, Cu, Zn, and Mn are essential for neural integrity, with distinct regional distributions. Fe is abundant in motor regions, Cu in the cerebellum, Zn in the hippocampus, and Mn in the corpus pineale. Their balance is crucial, as disruptions can contribute to disorders like multiple sclerosis. Advanced imaging techniques such as MRI help analyze metal homeostasis and neurodegenerative disease progression, highlighting the importance of metallomics in understanding CNS health and developing targeted therapies.

Essential metals in the normal brain

The presence of these metals is essential for the proper functioning of biological tissues, and they play crucial roles in numerous physiological processes. The biological systems rely on alkali and alkaline earth metals including Na, K, Mg, and Ca. They play a role in metabolism, redox reactions, protein modification, neurotransmitter production, oxygen and electron transport, and cell adhesion. Ni, Co, Mo, Fe, Zn, Cu, and essential transition metals are all part of this group. In addition to their structural and catalytic roles, transition metals function as cofactors in metabolism. Second messenger pathways and

cell signalling are two more areas where they are involved[60]. Metalloproteins necessitate specific metals, particularly Fe, Cu, and Zn, to operate effectively in the CNS. Several biological functions depend on Fe, including energy metabolism, myelination, oxygen homeostasis, DNA synthesis and repair, and neurotransmission[61-63]. Cu is involved in the synthesis of neurotransmitters, the immune system, connective tissues, synaptic transmission, and antioxidant defence[64]. The reactions of microglia and astrocytes are influenced by Mn, which is linked to the astrocyte-specific enzyme glutamine synthetase. Zn is an essential mineral for enzymes and transcription factors, which in turn aid in antioxidant and immunological responses[65]. These essential metals are integral to the proper functioning of the CNS, impacting various aspects of brain health, neurotransmission, immune response, and oxidative stress regulation. Their roles are multifaceted, and deficiencies or imbalances in these metals can lead to disruptions in physiological processes and potentially contribute to neurological disorders or other health issues.

Regional heterogeneity in brain parenchyma

Fe is mainly found in myelin and oligodendrocytes. Ferritin mostly stores it as ferric (Fe^{3+}) form. The Fe concentration of gray matter structures is typically higher than that of white matter structures. The amount of Fe in brain areas linked to motor functions is two to three times higher than in regions unrelated to motor functions[66,67]. The areas with the highest amounts of Fe include the placenta, substantia nigra, globus pallidus, dentate nucleus, locus coeruleus, caudate nucleus, red nucleus, etc[68-70]. In comparison to the cerebrum, Cu levels are greater in the cerebellar cortex and white matter. A lot of copper is located in the cerebellum, dentate nucleus, locus coeruleus, and substantia nigra. Zn is abundant in myelin and helps stabilize its structure. In comparison to white matter, the Zn content in gray matter structures is typically lower[71]. Zn is abundant in the amygdala and the hippocampus because of neurons that are sensitive to Zn. The *Corpus pineale* has been found to have high amounts of Mn. These metal distributions further highlight the intricate roles of essential metals in different brain regions and their involvement in various physiological processes. The variations in metal concentrations across brain structures underscore the specialized functions of each region and the specific requirements for these essential metals in maintaining their proper function and integrity.

Elemental imaging to comprehend the complexities of metal biochemistry

Interdependence and intricate interactions are displayed by the fundamental chemical components necessary for optimal brain metabolism, which include Ca, Cu, Zn, and Fe[71]. The antagonistic effects occur when low Zn levels boost copper levels and vice versa, as a result of the competition for binding sites caused by the physicochemical characteristics of Cu and Zn. Elements' interactions, for example with Al, can alter the transit of important metals like Fe, which in turn modifies the metal profile as a whole[72]. Recent studies have explored the complex role of metal homeostasis in multiple sclerosis (MS), particularly focusing on elements like Fe and Zn. Deregulation of these metals has been implicated in the pathogenesis of MS, suggesting that both accumulation and depletion can influence disease progression[73]. Advanced imaging techniques have been instrumental in studying metal distribution in the brain. Magnetic resonance imaging (MRI), especially at higher field strengths like 7 Tesla (7T), offers enhanced sensitivity and specificity in detecting disease activity and severity in MS. These advancements allow for better characterization of brain and spinal cord involvement[74]. Quantitative MRI methods, including relaxometry, myelin imaging, magnetization transfer, and diffusion MRI, have been applied to assess tissue microstructural changes in MS patients. These techniques provide insights into demyelination, neuronal loss, and glial activity, contributing to a more comprehensive understanding of MS pathology[75]. Despite these advancements, challenges remain in fully elucidating metal alterations in MS. Methodological limitations and the need for more extensive studies hinder a comprehensive understanding. However, ongoing research in metallomics and imaging techniques holds promise for unraveling the complexities of metal-related processes in neurological disorders like MS[73].

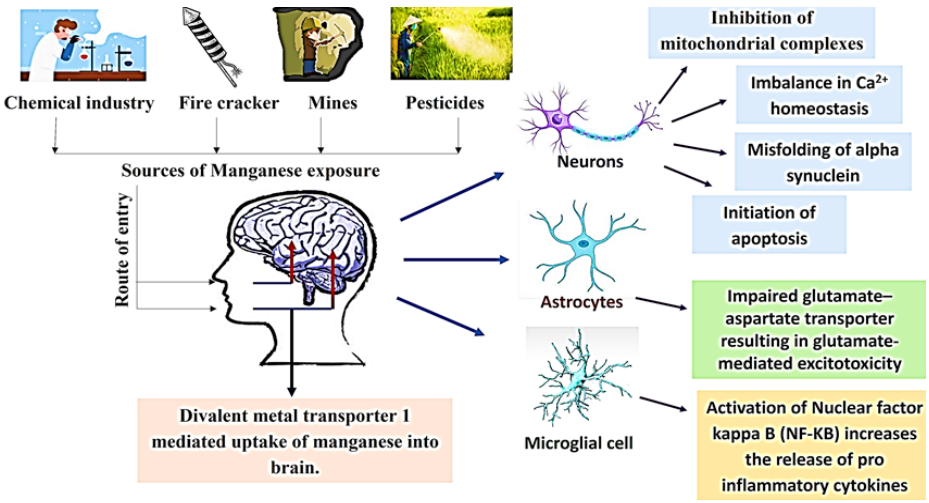

Fig. 1. Manganese induced neurotoxicity and its implications for brain health and disease

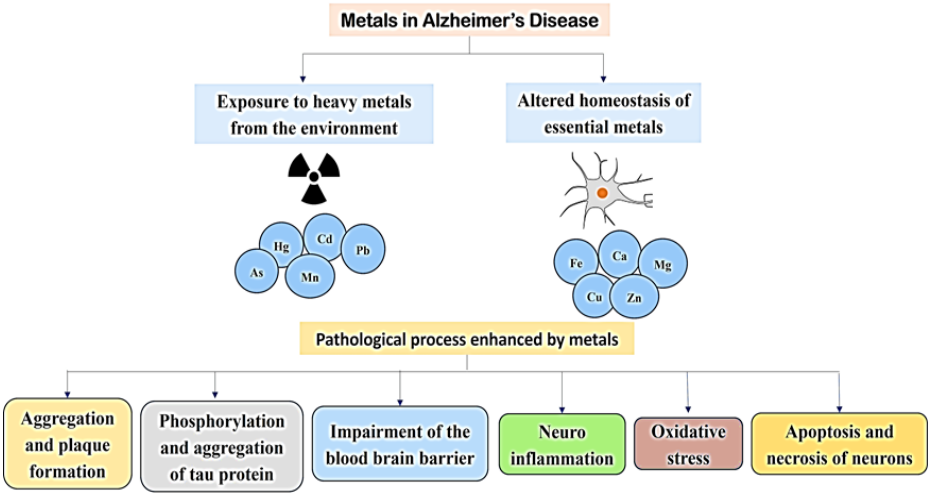

Fig. 2. Pathological process enhanced by metals in Alzheimer's Disease

DISCUSSION

The human body and brain rely on metals in essential ways. Negative impacts on brain health, possibly resulting in neurotoxicity, may result from their changed distribution or substance. Neurodegenerative illnesses and other chronic neurological conditions may have their roots in xenobiotic metal exposure or disruptions in the chemistry of critical metals. In light of these issues, a promising strategy for treating neurodegenerative diseases is the return of metal homeostasis by the use of tailored chelation treatments. While Fe chelation therapies have been identified as a potential avenue for treating neurodegenerative diseases, the intricate complexity of metal homeostasis within the brain remains largely unexplored. Existing clinical trials have examined the safety and therapeutic value of Fe chelation therapies specifically in patients with multiple sclerosis (MS), revealing promising but limited insights. Consequently, there is a pressing need for more comprehensive investigations into broader abnormalities in metal biochemistry within the brain. This exploration aims to uncover new therapeutic strategies for managing neurodegenerative diseases like MS. The ever-changing field of medical research demands the use of cutting-edge imaging techniques and safe, non-invasive analysis tools. These instruments are fundamental for acquiring a full picture of the "metallome," which includes real-time information about metal depletion, accumulation, and distribution in MS brains. For clinical decision-making and individualizing treatment approaches, such data

can be priceless. Prior to conducting intricate, interdisciplinary investigations that probe the function of metals in MS brains, the current overview provides a vital groundwork. Our current knowledge of metals as possible causes or risk factors for neurological illnesses could be drastically altered by these upcoming investigations. Furthermore, they may provide novel insights into disease diagnosis, severity assessment, relapse prediction, and the development of personalized metal-targeted therapeutic interventions. A cautious approach is warranted when targeting specific metals for therapeutic intervention. Thorough evaluation of the metal's specificity and potential toxicity is imperative. The decision to utilize metal chelators should be carefully considered, recognizing that high-affinity chelators might disrupt normal metal-protein pathways. Alternatively, moderate-affinity chelators could offer a more balanced approach, minimizing impact on regular cellular processes. Reducing the likelihood of harmful events while protecting essential metal-dependent pathways is possible through the careful design of molecules that enable the shift of metals from excess to deficiency. In this endeavor, it is highly recommended that compounds with specific roles, including "ionophores," "modulators," "chaperones," or "metal protein attenuating compounds," be developed accordingly. These compounds could hold the key to optimizing metal homeostasis, thereby offering innovative avenues for treating neurodegenerative diseases and improving patient outcomes. As research in this field progresses, a comprehensive and collaborative approach is essential to unlock the full potential of metals' impact on brain health and disease management.

CONCLUSION

Researchers have learned more about Mn's dual nature in relation to human health and disease through epidemiological and pre-clinical investigations. Acute exposures with high cellular Mn levels have been the main focus of mechanistic toxicity studies, although these levels frequently surpass that observed in clinical cases of Mn poisoning associated with environmental exposures. Chronic exposure scenarios, more representative of real-world situations, remain challenging to model due to their extended timeframes. Despite the limitations of high-dose approaches, they have uncovered molecular/cellular toxicity mechanisms, informing our grasp of chronic exposure effects. Future research should capitalize on insights from acute studies, grounded in epidemiological relevance, to explore biological changes occurring in prolonged chronic exposures. Such investigations mirror common human exposures and hold greater real-world significance. New developments in single-cell resolution multi-omics have made it possible to distinguish between main and secondary latent toxic effects, to evaluate compensatory responses, and to identify variations in susceptibility or resilience. Leveraging artificial intelligence (AI) can further elucidate mechanisms of chronic metal toxicity by analyzing comprehensive-omics, imaging, and high-content datasets. AI can bridge acute and chronic exposure insights. Additionally, genome editing tools like CRISPR-Cas9, coupled with diverse model systems, enable exploration of gene-toxicant interactions and their contributions to pathology. This powerful approach promises deeper insights into the intricate relationship between genes and toxicants. In summary, knowledge from acute exposure studies informs a shift towards investigating chronic exposures, closer to real-world conditions. By integrating advanced technologies and AI, we can unravel the intricate mechanisms underpinning chronic metal toxicity, paving the way for enhanced understanding of human health implications and potential interventions.

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Conflict of interest

The authors declare no conflicts of interest

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