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Anatomical and Functional Distribution of Brain Metalloproteins: Roles of Iron, Copper, Zinc, and Selenium and Their Implications in Some Neurological Disorders

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ABSTRACT

Background: Metalloproteins play crucial roles in brain physiology by mediating redox balance, neurotransmission, and cellular metabolism through interactions with trace metals. Understanding their regional distribution and functional relevance enhances insight into neurodegenerative disease mechanisms.
Objective: This systematic and comparative review examines the anatomical distribution, physiological functions, and neuropathological significance of iron-, copper-, zinc-, and selenium-dependent metalloproteins in the human brain.
Methods: Following the PRISMA framework, literature published between 2010 and 2025 was systematically reviewed. Sixty studies met the inclusion criteria and were analysed for patterns of metalloprotein localisation and function across major brain regions.
Results: Iron-related proteins (ferritin, transferrin, DMT1) are predominant in the substantia nigra and basal ganglia, supporting oxygen transport and dopamine metabolism. Copper-binding enzymes (ceruloplasmin, SOD1, cytochrome c oxidase) are enriched in the cerebellum and hippocampus, promoting mitochondrial function. Zinc-associated proteins (ZnT3, metallothionein-III, MMP-9) dominate in the hippocampus and cortex, facilitating synaptic plasticity, while selenium-based selenoproteins (GPX4, SELENOP, TrxR) are concentrated in the cerebellum and hypothalamus, regulating oxidative defence.
Conclusion: Overlapping expression zones such as the substantia nigra (iron and copper) and hippocampus (zinc and selenium) indicate shared redox and signalling roles. Metalloproteins are essential for maintaining neuroanatomical integrity, and their dysregulation contributes to region-specific neurodegenerative disorders, highlighting their potential as diagnostic and therapeutic biomarkers.

BACKGROUND

Metalloproteins account for over a third of the human proteome, exhibiting a wide range of physiological functions and implications for disease, influenced by the specific metals involved and the tissue environment. Their roles encompass catalysis, bioenergetics, redox reactions, DNA repair, cell growth, signalling, the transport of essential elements, and immune responses [1]. Many of the enzymes that depend on trace elements for their activity are not exclusive to the brain; however, certain metalloproteins are brain-specific and play crucial roles in maintaining neuronal homeostasis, particularly in processes such as neurotransmitter metabolism[2]. Trace elements such as iron, copper, zinc, and selenium are indispensable for the proper functioning of the human brain, despite being required in only minute quantities. These metals serve as cofactors for a vast array of enzymes and structural proteins, giving rise to a class of macromolecules known as metalloproteins. Each metal contributes uniquely to the functioning of the nervous system. Iron plays a critical role in oxygen transport and mitochondrial respiration[3,] Copper participates in redox reactions and neurotransmitter biosynthesis[4], zinc is pivotal for synaptic transmission and gene regulation[5], and selenium is central to antioxidant defence and redox homeostasis. The brain's dependence on these metals is shown by their tightly-regulated transport, storage, and utilisation systems, which ensure both availability and protection against toxicity[6.] Metalloproteins incorporating these trace elements are not only fundamental to brain development and function but are also implicated in a range of neurological diseases when their homeostasis is disrupted[7]. Given their biochemical versatility and region-specific localisation within the central nervous system, Iron, copper, zinc, and selenium are essential focal areas for understanding the molecular structure and vulnerability of the brain. These elements serve three primary functions in the brain: regulating signalling pathways, catalysing activity, and providing structural support. Enzymes such as cytochromes and monoamine oxidase, which are essential for mitochondrial respiration and neurotransmitter metabolism, use iron integrated into heme and iron–sulfur clusters as a redox-active core[3]. According to Hare et al. (2013), copper facilitates oxidative metabolism and iron export when it is bound within ceruloplasmin or cytochrome c oxidase[4]. Zinc plays both neuromodulatory and transcriptional regulatory functions through its coordination in synaptic vesicles and zinc finger motif, which serve these roles[5]. The detoxification of reactive oxygen species and preservation of cellular redox equilibrium are made possible by selenium's incorporation into the active sites of selenoproteins, specifically glutathione peroxidase and thioredoxin reductase[8]. Under physiological conditions, these metal-protein interactions are highly selective and thermodynamically stable, ensuring that metal ions remain bioavailable while preventing cytotoxic buildup.

The distribution of metal-dependent proteins in the brain is highly region-specific, reflecting the localised physiological functions and vulnerabilities of distinct neural structures. For example, iron concentrations are notably highest in motor-related regions, including the substantia nigra, globus pallidus, putamen, and caudate nucleus, which are also among the first to exhibit pathology in movement disorders such as Parkinson's disease. Similarly, copper levels are particularly elevated in the substantia nigra, dentate nucleus, and olivary region of the medulla, suggesting its significant role in redox activity and neurotransmitter synthesis in these motor-regulatory centres. In contrast, zinc is more abundant in the white matter due to its structural role in myelin, and it also exhibits a high concentration in the hippocampus and amygdala, where it participates in neuromodulation through zincergic neurons. These anatomical "hotspots" of metal concentration correspond to distinct complements of metalloproteins such as tyrosine hydroxylase in dopamine-rich areas (iron-dependent), Cu/Zn-superoxide dismutase in antioxidant pathways, and zinc-binding myelin-associated proteins, demonstrating that metal homeostasis is tightly interwoven with regional brain function and disease susceptibility[9.] Because they promote neurotransmitter production, antioxidant defence, and synaptic plasticity, metal–protein complexes are essential to brain function. Zinc regulates glutamatergic signalling, especially in the hippocampus, through vesicular transporters such as ZnT3[5.] Copper proteins, such as dopamine β-hydroxylase, aid in norepinephrine synthesis[4], and iron-dependent enzymes, such as tyrosine hydroxylase, facilitate the synthesis of dopamine[3]. Cu/Zn-superoxide dismutase (SOD1) and selenium-based enzymes such as glutathione peroxidase (GPX4) mediate antioxidant defence[8]. By regulating synaptic plasticity and maintaining redox equilibrium, these metalloproteins also promote brain flexibility.

Region-specific brain diseases are associated with disturbances in metal homeostasis. Oxidative damage in Parkinson's disease is exacerbated by iron excess in the substantia nigra[6]. Wilson's illness is characterised by copper buildup in the basal ganglia, which results in symptoms related to cognition and movement[10]. Due to its impact on excitatory neurotransmission, zinc dysregulation in the hippocampus is associated with epileptic seizures[11], whereas a selenium deficiency impairs cognition and development in the cerebellum and hippocampus[12].

Comparing iron, copper, zinc, and selenium-based metalloproteins in terms of their anatomical localisation, physiological functions, and pathological associations within the human brain is the primary goal of this review. The review aims to determine the distinct and overlapping functions that these four vital trace metals play in preserving brain integrity and influencing disease processes. A region-specific explanation of the expression patterns of each metal and its accompanying metalloproteins throughout brain regions, including the hippocampus, cerebellum, Substantia Nigra, and basal ganglia, follows an introduction to the molecular characteristics of each metal. The following sections will examine how each metal-protein complex is involved in crucial brain processes, including oxidative regulation, neurotransmitter metabolism, and synaptic plasticity. It will also explore how these processes relate to neurological conditions such as Wilson's disease, Parkinson's disease, Alzheimer's disease, and epilepsy. The comparative perspective also highlights cross-metal interactions and possible compensating mechanisms.

METHODOLOGY

This study used a qualitative systematic review to compare the distribution, physiological functions, and pathological importance of metalloproteins containing iron, copper, zinc, and selenium in the brain. The review aimed to look at peer-reviewed evidence from 2005 to 2025, with a specific focus on how each metal contributes to neurological function and disease. The protocol followed PRISMA 2020 guidelines to ensure transparency and rigour throughout the review process. Literature searches were conducted across four major databases: PubMed, Scopus, ScienceDirect, and Google Scholar. Search terms combined MeSH headings and Boolean operators targeting specific metalloproteins (e.g., ferritin, ZnT3, ceruloplasmin, GPX4) and neuroanatomical regions (e.g., hippocampus, cerebellum, Substantia Nigra and basal ganglia). Filters were applied to include only peer-reviewed English-language publications within the specified timeframe. Studies were included if they investigated the role of the target metals in brain function or disease. Articles unrelated to brain tissue, non-English texts, and those involving non-relevant metals were excluded.

The study selection process involved two independent reviewers who screened titles and abstracts before assessing the full texts. A standardised data extraction sheet was used to collect details on protein type, metal involved, anatomical localisation, function, disease association, and experimental model (human, animal, or in vitro). Studies were categorised by metal for comparative synthesis. The quality of each included article was assessed using the Mixed Methods Appraisal Tool (MMAT, 2018 version), while systematic reviews were evaluated with the AMSTAR 2 framework to ensure methodological validity.
A narrative synthesis approach was used due to the heterogeneity of the included studies. Findings were grouped and compared by metal type, brain region, biological function, and associated pathology. A structured comparative table was created to highlight similarities and differences among the four metals, supported by visual tools such as brain maps and bar charts. Since the study was based entirely on secondary data, ethical approval was not required; however, all literature was properly cited to maintain academic integrity.

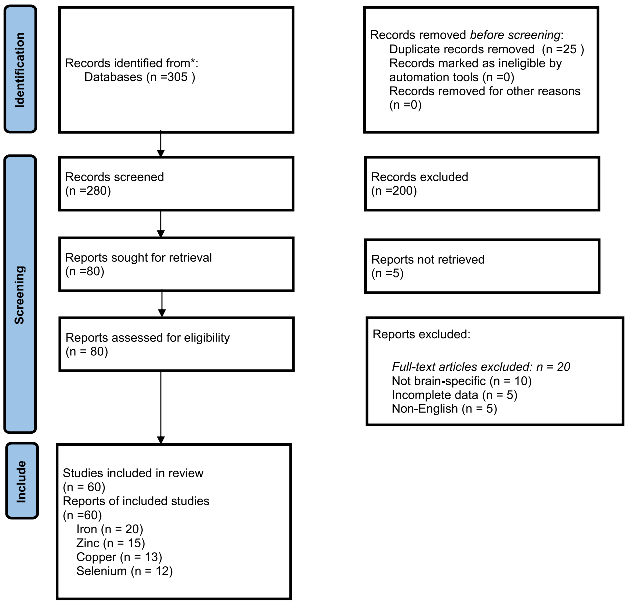

Fig 1: PRISMA flow diagram showing study selection. Flow diagram obtained from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (13). It illustrates the literature search and literature selection process used in the present review.

RESULTS

A total of over 300 articles on metalloproteins involving iron, copper, zinc, and selenium in the brain, published between January 2010 and June 2025, were initially identified. After applying PRISMA-guided screening and strict inclusion criteria, 60 studies were selected for detailed analysis: 20 on iron, 15 on zinc, 13 on copper, and 12 on selenium. The collection includes a variety of methodologies, such as in vitro and proteomics research (e.g., copper nanoparticle response in macrophage proteomics), animal models (rodent models examining synaptic zinc via ZnT3 knockouts and selenium supplementation effects), human studies (post-mortem tissue analysis and epidemiological cohorts, e.g., selenium meta-analysis in Alzheimer's CSF, n=12 studies) (14), and neuroimaging investigations such as quantitative susceptibility mapping (QSM) for iron distribution in neurodegeneration[15.]

Iron metalloproteins

As a component of proteins involved in cellular activities such as DNA synthesis, oxygen transport, and mitochondrial respiration, iron is essential for numerous physiological processes, including brain metabolism. Additionally, it is crucial for brain functions, including myelination and neurotransmission[16]. Reactive oxygen species (ROS) formation and protein aggregation are linked to the disruption of neuronal iron homeostasis, resulting in cell death and neural degeneration in the affected brain areas[17].

Iron enters the endothelial cells of the blood–brain barrier as a low-molecular-weight complex through transferrin receptor-1-mediated endocytosis of transferrin or independently as non-transferrin-bound iron. Iron accumulation is a metabolic lesion that may occur due to genetic factors, age-related fatigue of the iron transport system, and brain inflammation[18]. Regional expression studies have shown high concentrations of these proteins in the substantia nigra, basal ganglia, hippocampus, and cortex. These areas are notably vulnerable in neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, and ferroptosis-related injury[6,19,20.]

Research indicates that brain endothelial cells play a vital role in maintaining brain iron homeostasis by signalling from within the brain, thus regulating the trafficking of transferrin receptors and iron cycling, rather than simply serving as a conduit for iron transport[21.]

The primary iron transporter in the body is the 80 kDa glycoprotein transferrin (Tf). Each bi-lobed molecule, with two globular units at the N- and C-termini, contains two iron-binding sites. These sites create a tetradentate ligand with four atoms, involving histidine, aspartate, and two tyrosine residues (4). There are many types of Tf since it contains two iron-binding sites. Apo-Tf is non-iron-bound Tf, mono-ferric Tf is Tf that has just one iron atom connected to it, and di-ferric Tf, or just holo-Tf, is Tf that has two irons attached to it. The blood–brain barrier (BBB) effectively prevents excess iron accumulation in cases of hemochromatosis, making the brain uniquely protected among organs from elevated circulating levels of non-transferrin-bound iron (NTBI)[22–24].

Ferritin is a protein that accumulates iron in the brain's glial cells, which include oligodendrocytes and astrocytes. Ferritin comes in three distinct isoforms: mitochondrial ferritin (MtF), heavy chain ferritin (FTH), and light chain ferritin (FTL). A crucial component of cellular iron absorption, the transferrin receptor must pass through the endosomal membrane to be released into the cytosol[25]. Because ferritin accumulates and sequesters iron, it shields cells from harm caused by iron-mediated free radicals. Nevertheless, nothing is known about the process by which iron leaves the ferritin cage and is subsequently used again in the brain. The brain expresses all three ferritin isoforms (FTL, FTH, and MtF), which are crucial for early brain development. FTL is primarily present in microglia, and as previously documented, soluble proteins can enter via blood vessels and be absorbed by astrocyte end feet[26].

Divalent Metal Transporter 1 (DMT1), the first known mammalian divalent metal transporter, primarily maintains non-transferrin-bound iron (NTBI) transport by mediating the movement of ferrous iron and heavy metals from the plasma membrane or endosomes to the intracellular labile iron pool in systemic iron homeostasis[27]. ZIP14 is one of several transporters responsible for NTBI uptake, alongside DMT1. The expression and function of DMT1 are entirely dependent on this complex structure, which produces four distinct isoforms through two alternative splicing scenarios[28].

Copper metalloproteins

Approximately 9% of the body's copper is found in the brain, making it the organ with the third-highest copper content[29, 30.] It is one of the most essential trace elements in the brain, and its distribution is not uniform across different regions. Evidence from Inductively Coupled Plasma–Mass Spectrometry (ICP-MS), usually used in the detection of trace metals and histochemical analyses, reveals that the substantia nigra exhibits some of the highest concentrations of copper in the human brain, nearly twice that of other regions, highlighting its importance in dopaminergic metabolism and neuroprotection[31.] Similarly, the cerebellum demonstrates high copper content. It shows significantly elevated expression of the copper transporter ATP7A, which is essential for copper efflux and homeostasis in Purkinje cells and surrounding glial structures[31.] Beyond the cerebellum and substantia nigra, other copper-rich regions include the hippocampus and brainstem, where copper plays vital roles in mitochondrial function, neurotransmitter synthesis, and redox regulation (32). In the hippocampus, elevated copper levels are associated with enhanced synaptic plasticity and modulation of NMDA receptor activity. Neurones in the locus coeruleus (LC) of the brainstem are the main producers of norepinephrine (NE), the neurotransmitter with the highest concentration of copper in the brain. For vital autonomic and sensory processes, this area and other brainstem regions, such as the medulla, depend on copper-dependent enzymes, highlighting the critical role that copper plays in neurotransmitter synthesis and neural regulation[33].

Disruptions in copper homeostasis in these regions have been implicated in neurodegenerative diseases, underscoring the importance of precise copper transport mechanisms, such as CTR1, DMT1, ATP7A, and ATP7B, in maintaining regional neural integrity[31,34]. Since the brain has a high respiratory rate and is vulnerable to oxidative stress, copper is necessary for a wide range of cell metabolic processes[35.] Accordingly, the redox capacity of copper-dependent proteins is critical for one of their most vital physiological processes. As a cofactor in Cu/Zn-SOD, copper helps quench reactive oxygen species. It also serves as a component of cytochrome C's electron transport chain, which moves electrons between Complexes III (Coenzyme Q-Cyt C reductase) and IV (Cyt C oxidase) at the mitochondria's inner membrane[36].

Ceruloplasmin (CP) is a ferroxidase enzyme essential for regulating iron metabolism in the brain. According to the study done by Liu et al. (2019), CP "oxidises ferrous iron (Fe^{2+}) to less toxic ferric iron (Fe^{3+})" and helps protect the brain from iron-induced injury following events such as intracerebral haemorrhage. Cheli et al. (2023) further emphasised that CP expressed in astrocytes is "essential for both early oligodendrocyte maturation and myelin integrity in the mature brain," and its loss leads to hypomyelination, oxidative stress, and iron accumulation during ageing[37.] These findings show the crucial neuroprotective functions of CP, particularly through maintaining iron homeostasis and preventing neurodegenerative damage associated with iron overload.

In parallel, other copper-dependent enzymes play vital roles in brain function and pathology. According to Rowlands et al. (2025), in Parkinson's disease, wild-type superoxide dismutase 1 (SOD1) becomes misfolded and inactive due to deficient copper binding, which contributes to neuronal death. They showed that copper supplementation "mitigates the formation of Parkinson-like wild-type SOD1 pathology" and preserves dopamine neurons[38]. Opačić et al. (2021) found that in epilepsy patients, cytochrome c oxidase (CCO) activity was "significantly reduced" in brain regions with low copper levels, suggesting that "copper deficiency comes before CCO activity reduction and neuronal loss"[39.] Similarly, Gonzalez-Lopez and Vrana (2019) highlighted that dopamine β-hydroxylase (DbH), which synthesises norepinephrine from dopamine, contains "two copper catalytic cores" that are essential for enzymatic function, and its activity is compromised under copper-deficient conditions, potentially leading to neurological symptoms[40.] The enzyme cytochrome c oxidase (Complex IV), which has two copper redox-active centres and catalyses the final electron transfer to oxygen, is essential for mitochondrial respiration because it supports the proton gradient required for ATP production. Additionally, copper imbalance has been linked in recent studies to mitochondrial dysfunction, a key factor in neurodegenerative disorders, characterised by increased mitophagy and decreased energy metabolism[41.]

Electron activity, neurotransmitter production, mitochondrial respiration, and antioxidant defence are among the many vital brain processes that depend on copper, an important trace metal. The creation of cellular energy, redox balance, and neurotransmitter modulation all depend on copper-dependent enzymes such as cytochrome c oxidase (COX), superoxide dismutase (SOD1), and dopamine β-hydroxylase (DBH)[42.] The brain is susceptible to oxidative stress, compromised neurotransmission, and neurodegeneration when copper levels are disturbed. According to a case study by Benkirane et al. (2023), a patient with a symptomatic copper deficit developed a motor neuron disease phenotype mimicking Amyotrophic Lateral Sclerosis (ALS), highlighting the fact that even an acquired copper imbalance can cause progressive and permanent neurological damage[43]. Wilson's disease (WD) and Menkes disease (MD), two inherited disorders affecting copper metabolism, show the vital role copper plays in brain function. Wilson's disease is caused by mutations in the ATP7B gene, which leads to the accumulation of toxic copper, primarily in the brain and liver, particularly in the basal ganglia[44]. Because of copper-induced oxidative damage and apoptosis, this accumulation results in tremors, dysarthria, cognitive impairment, and psychiatric problems.

On the other hand, ATP7A mutations that produce systemic copper deficiency are the aetiology of Menkes disease. Because copper-dependent enzymes such as SOD1 and DBH are essential for maintaining neurotransmitter balance and protecting neurons from oxidative stress, individuals affected by these conditions exhibit severe neurological symptoms early in life, including developmental delays, seizures, and hypotonia[44]. The precise balance needed for copper homeostasis is demonstrated by both conditions, where either an excess or a deficit can have serious neurological effects[44].

The brain's copper and iron homeostasis are closely related, particularly in the context of neurological conditions such as Wilson's disease (WD) and Menkes disease (MD). Multicopper ferroxidases, such as ceruloplasmin (CP) and hephaestin (HEPH), which oxidise ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) and export it via ferroportin (FPN1), require copper for their action. In Cp knockout (KO) astrocytes and Heph KO oligodendrocytes, "iron efflux was impaired and was associated with increased oxidative stress," according to Chen et al. (2019). This suggests that a deficiency in either copper-binding protein can lead to iron accumulation and oxidative damage in glial cell types[45]. Their co-expression in brain areas, such as the blood-brain barrier, where CP, HEPH, and FPN1 are co-localised and interdependent for appropriate iron trafficking, further supports the functional overlap between copper and iron pathways[46]. Their overlapping responsibilities are highlighted by the fact that secondary iron dysregulation results from disturbance of copper metabolism in neurogenetic diseases. Defective ATP7A causes systemic copper deficit and neurological deterioration in Menkes disease by preventing copper from reaching enzymes such as CP and dopamine β-hydroxylase. Because the CP function depends on copper, when it is deactivated, iron accumulates in oligodendrocytes and astrocytes, exacerbating neurodegeneration.

On the other hand, ATP7B mutations in Wilson's disease lead to copper overload and disruption of iron control because oxidative stress from copper buildup impairs ferroxidase activity and mitochondrial iron-sulfur cluster formation. According to research by McCarthy and Kosman (2014), "glial-secreted ceruloplasmin and hepcidin differentially regulate iron efflux from brain microvascular endothelial cells," demonstrating how CP directly affects iron management at the blood-brain barrier as a result of copper metabolism[47.] Because of this, brain disorders are tightly linked to both copper and iron malfunction, both through molecular processes and by geographical co-localisation.

Zinc Metalloproteins – Synaptic and Structural Functions

The hippocampus, amygdala, cerebral cortex, and white matter tracts are among the critical anatomical regions of the brain where zinc is essential. Social memory, object identification, and spatial learning all depend on the zinc transporter ZnT3 in the perirhinal cortex and hippocampal regions. Even though ZnT3 knockout (KO) mice exhibit adequate motor and sensory abilities, they display deficiencies in recognising new items and familiar social partners. In the water maze, a task that primarily relies on the hippocampus, these mice also exhibit difficulty with reversal learning. These results suggest that by modifying synaptic plasticity and potentially functioning as a neuromodulator, vesicular zinc, which is regulated by ZnT3, plays a significant role in hippocampus- and perirhinal cortex-dependent memory activities[48,49.]

Synaptic zinc has a crucial role in associative fear memory and subsequent extinction in the cerebral cortex and amygdala. ZnT3 is significantly expressed in afferent cortical areas that transmit auditory and contextual information, as well as in the lateral, basal, and basomedial nuclei of the amygdala. In fear conditioning paradigms, ZnT3 KO mice exhibit decreased freezing responses, particularly in situations that require complex processing, such as trace conditioning or discontinuous auditory signals. This lends credence to zinc's function in regulating amygdalo-cortical circuit plasticity (50). Zinc's regulatory role in oligodendrocyte activity and myelination further emphasises its participation in white matter pathways; disturbances in zinc homeostasis can lead to white matter damage, as shown in multiple sclerosis and prenatal brain injury[50].

Zinc loading into glutamatergic neuron synaptic vesicles, especially in the hippocampus, amygdala, and cerebral cortex, is primarily the function of ZnT3. Zn^{2+} is co-released into the synaptic cleft with glutamate upon neuronal activity (51). There, it modulates the function of NMDA receptors (NMDARs), particularly those containing the GluN2A subunit[51]. Zn^{2+} binds to high-affinity sites on GluN2A NMDARs, mediating allosteric inhibition and thereby controlling excitatory synaptic transmission and LTP. It also influences dendritic spine shape and neuronal excitability by activating the TrkB/BDNF pathway and metabotropic Zn^{2+} sensing receptors (ZnRs) [52]. In AD brains and during ageing, ZnT3 levels decline. The release of zinc at synapses promotes the aggregation of amyloid-β (Aβ), a fundamental aspect of AD pathogenesis. Accelerated cognitive decline in ZnT3 knockout mice suggests that ZnT3 has a protective role[51]. In neurons, ZIP transporters (such as ZIP1, ZIP3, ZIP4, ZIP8, and ZIP12) are crucial in regulating intracellular zinc homeostasis and facilitating zinc influx into the cytosol. ZIP1 and ZIP3 influence zinc uptake in hippocampal neurons. Postsynaptic structure and glutamate receptor modulation are also affected by ZIP4's interactions with scaffolding proteins, such as SHANK3[51].

The GWAS, ZIP8 mutations are strongly linked to schizophrenia; they impair glutamate receptor function and increase neuroinflammation. For ZIP8-linked schizophrenia, improving glutamatergic signalling or addressing inflammation may be helpful. Overexpression of ZIP12 is also associated with an increased risk of schizophrenia; it promotes neurite outgrowth and tubulin polymerisation (51). Zinc-dependent extracellular metalloproteinase MMP-9 is secreted at excitatory synapses in an activity-dependent manner.

Under oxidative stress, Matellothionein III (MT-III), which is primarily produced in the central nervous system, serves as a buffer and zinc reservoir by binding Zn2+ with a moderate affinity. It regulates the availability of free zinc, which has a neuroprotective effect[51]. By indirectly modifying NMDA receptor activation, MT-III can affect synaptic zinc levels both after injury and in oxidative environments [53]. Increased Aβ aggregation in Alzheimer's disease is correlated with decreased MT-III levels in astrocytes because of unbuffered Zn^{2+}. MTs serve as zinc chaperones for apo-SOD1. In SOD1-G93A ALS mice, MT1/2 impairment lowers lifespan, establishing a connection between MT function and SOD1-mediated toxicity[51].

Zinc-dependent extracellular metalloproteinase MMP-9 is secreted at excitatory synapses in an activity-dependent manner. It affects NMDA receptor mobility and dendritic spine morphology by modulating extracellular matrix components and synaptic adhesion molecules (e.g., neuroligin-1, ICAM-5)[53.] AMPA receptor trafficking, late-phase LTP, and structural alterations, such as spine expansion, all depend on MMP-9 activity. MMP-9 contributes to synaptic remodelling and is elevated during epileptogenesis, particularly in temporal lobe epilepsy. Defects in connection observed in mental disorders may be caused by dysregulated MMP-9 expression, which also affects synaptic stability[54.]

Selenium Metalloprotein

The hippocampus and cerebellum are frequently identified as selenium-rich areas with elevated expression of selenoproteins. While radiotracer studies in rats identified the dentate gyrus and CA3 areas of the hippocampus as hotspots for selenium absorption, post-mortem human Inductively Coupled Plasma–Mass Spectrometry (ICP-MS) analysis has indicated modest Se concentrations in the cerebellum, primarily within grey matter[55,56.] SelP and GPX4 levels in the hippocampus, especially in the CA3 and dentate gyrus, were markedly elevated by selenium supplementation in a mouse model of neuroinflammation, exhibiting potent neuroprotective benefits[57.] Selenoprotein P deficiency in mice causes cerebellar hypoplasia, Purkinje cell death, and significant impairments in hippocampus-based synaptic plasticity, highlighting the importance of Se for maintaining structural and functional integrity in these areas[58].

Se buildup and strong selenoprotein gene expression are also seen in the cerebral cortex and hypothalamus[59]. Multiple selenoprotein mRNAs, such as GPX4, SelM, SelW, and SelP, are highly expressed in the cortex, hippocampus, and cerebellar cortex of adult mice, according to investigations utilising the Allen Brain Atlas[59].The hypothalamus has high levels of selenium P mRNA and protein expression, indicating that selenium is actively transported to and used by neuroendocrine regulatory networks. The complicated role of selenium in neuronal and endocrine function has been echoed by autoradiography investigations that have similarly shown substantial ~75Se uptake in cortical and cerebellar areas[55].

Selenoprotein levels in the brainstem are nonetheless functionally relevant despite being comparatively lower than in the forebrain areas. Studies using autoradiography and regional quantification reveal detectable selenium uptake in brainstem nuclei, such as the medulla and inferior colliculus, linking these areas to activities that depend on selenium[55]. Even in cases of selenium shortage, radiotracer tests demonstrate that selenium is preserved in the grey matter of the brainstem, highlighting the critical role that selenoproteins, such as SelP and GPX4, play in maintaining redox equilibrium and neuronal survival across various neuroanatomical locations[55]. The hippocampus's CA3 area and dentate gyrus were the primary sites of expression for selenium protein P and GPX4. Notably, selenium supplementation reduced the oxidative and neuroinflammatory damage brought on by LPS and enhanced the expression of these selenoproteins[57].

SELENOW is a neuronally enriched selenoprotein that is abundantly expressed in the cortex, hippocampus, and cerebellum. It has been linked to tau protein homeostasis, redox control, and synaptic maintenance[60]. SELENOW regulates tau ubiquitination by controlling acetylation, leading to its degradation via the proteasome pathway. Loss of SELENOW function leads to tau aggregation, which is strongly associated with Alzheimer's pathology, particularly in the hippocampus and other parts of the cerebral cortex[61].

Redox homeostasis in the brain depends on the thioredoxin reductase (TrxR) family of mitochondrial and cytosolic enzymes, particularly TrxR1 and TrxR2. These selenoproteins are widely distributed in white matter tracts, hippocampus neurons, and Purkinje cells of the cerebellum, where they regenerate decreased thioredoxin to prevent oxidative damage (62). The brain's astrocytes and endothelial cells produce the majority of SELENOP, which is also highly expressed in areas including the cortex, hippocampus, and cerebellum. Utilising the ApoER2 receptor-mediated endocytosis pathway, it promotes selenium absorption and transport to neurons[63]. Se supplementation can alleviate the lower brain Se content, seizures, and aberrant EEGs that result from genetic ablation of the selenium transport protein, selenoprotein P (Selenop), in rats[64]. There is strong evidence that idiopathic generalised epilepsy (IGE) is linked to selenium insufficiency, according to a new case-control study carried out in Karachi, Pakistan.

In contrast to 30 healthy age- and gender-matched controls, the researchers assessed blood selenium levels and the expression of three essential selenoproteins in 30 drug-naïve epileptic patients: GPx1, TrxR1, and SEPW1. With a p-value of 0.031, they found that the mean selenium levels in epileptic patients were considerably lower (37.6 ± 2.0 μmol/ml) than in controls (38.9 ± 2.7 μmol/ml). Additionally, gene expression profiling showed modest overexpression of SEPW1 and downregulation of GPx1 and TrxR1, indicating compromised antioxidant defence systems in patients. These results support the notion that selenium has a neuroprotective function and that a deficiency may exacerbate oxidative stress in the brain, potentially leading to seizure pathogenesis[65]. Additionally, research has found that erythrocyte Se levels decline in tandem with cognitive performance. The findings highlight the significance of the relationship between Se exposure and cognitive performance, as erythrocytes are a reliable indicator of long-term nutritional status. Erythrocyte Se has been found to decline in tandem with cognitive performance. The findings highlight the significance of the relationship between Se exposure and cognitive performance, as erythrocytes are a reliable indicator of long-term nutritional status[66]. A study also showed that supplementing 3 × Tg-AD mice with selenium can enhance their memory deficits and spatial learning. In the brain tissue of 3 × Tg-AD mice, selenium treatment raised selenium and GSH-Px levels and markedly improved neuronal conditions. Moreover, selenium administration resulted in a significant increase in the expression levels of proteins associated with the BDNF/TrkB pathway[67].

Comparative Table 1: Brain Metalloproteins by Region, Function, and Disorder

	Primary Brain Regions	Key Proteins	Main Functions	Associated Disorders	Key References
Iron	Substantia nigra, hippocampus, cortex, basal ganglia	Ferritin, Transferrin (Tf), TfR1, DMT1, Cytochromes	Oxygen transport, mitochondrial respiration, dopamine synthesis	Parkinson's disease, Alzheimer's disease, ferroptosis	(17,18,18,20,22,22,26,28,28,45–47,67)
Copper	Substantia nigra, cerebellum, brainstem, hippocampus	Ceruloplasmin, SOD1, Cytochrome c oxidase, Dopamine β-hydroxylase	Redox regulation, mitochondrial ATP production, neurotransmitter synthesis	Menkes disease, Wilson's disease, ALS	(31,34,34,36,38,39,41–43,45,54)

Zinc	Hippocampus, amygdala, cerebral cortex, white matter tracts	ZnT3, ZIPs, MT-III, SOD1, MMP-9	Synaptic vesicle signaling, antioxidant defense, gene expression modulation	Epilepsy, cognitive decline	(5,5,49,49,49,50,52,54,68–70)
Selenium	Hippocampus, cerebellum, hypothalamus, brainstem	GPX4, SELENOP, SELENOW, TrxR	Redox defense, selenium transport, ferroptosis regulation	Seizures, neurodevelopmental delay, Alzheimer's disease	(12,14,55,55–57,57–59,63–68)

Comparative Table 2: Metal Imbalances, Disease Associations, and Mechanisms

Metal	Associated Diseases	Affected Brain Regions	Mechanisms of Pathology	Key Notes
Iron	Parkinson's disease, Alzheimer's disease, Ferroptosis	Substantia nigra, Hippocampus, Cortex	Oxidative stress, ferroptosis, iron accumulation	Iron overload causes dopaminergic neuron loss via ROS and lipid peroxidation; ferroptosis is a key pathway in neurodegeneration.
Copper	Wilson's disease, Menkes disease, ALS	Basal ganglia, Cerebellum, Brainstem	Redox imbalance, mitochondrial dysfunction, excitotoxicity	ATP7B mutations in Wilson's cause toxic copper buildup; ATP7A mutations in Menkes lead to deficiency, both affecting motor control centers.
Zinc	Epilepsy, Cognitive dysfunction, Depression	Hippocampus, Amygdala, Cortex	Synaptic dysfunction excitotoxicity, reduc antioxidant activity	ZnT3 loss leads to zinc dyshomeostasis, promoting hyperexcitability in epilepsy and impaired cognition.
Selenium	Seizures, Neurodevelopmental delay, Alzheimer's	Hippocampus, Brainstem, Cerebellum	Neuroinflammation, impaired redox control, ferroptosis sensitivity	Deficiency in GPX4 and SELENOP leads to oxidative stress and vulnerability to inflammation-driven damage.

DISCUSSIONS

1. Anatomical Patterns and Region-Specific Metal Utilisation.

The anatomical distribution of metalloproteins in the human brain is highly organised, reflecting the regional specialisation of neural networks. Selenium, copper, zinc, and iron are not distributed randomly; instead, they preferentially accumulate in specific regions of the brain, where they play vital physiological roles. The functional requirements of each area, as well as the biological characteristics of each metal, are reflected in this geographical distribution. According to Dexter and Jenner (2013) and Ward et al. (2014), the substantia nigra, basal ganglia, and hippocampus, which are centres for dopamine production, motor coordination, and memory processing, respectively, are especially rich in iron. Iron-dependent enzymes, such as cytochromes and tyrosine hydroxylase, are crucial in these fields[6,19]. A similar geographical specificity is observed with copper. Research employing Inductively Coupled Plasma–Mass Spectrometry (ICP-MS) and histochemical techniques shows that a specific compound is abundant in the brainstem, cerebellum, and substantia nigra, with significant amounts being found in the hippocampus[34,40]. These results are consistent with the functions of copper in catecholamine production, antioxidant defence, and oxidative phosphorylation. Zinc is also widely distributed in the cerebral cortex, amygdala, and hippocampus, where it regulates NMDA receptors and vesicular zinc to promote synaptic plasticity and modify excitatory neurotransmission[5,52].

2. Functional Divergence and Overlap of Metalloproteins

All four metals play crucial roles in redox equilibrium, neural signalling, and brain development despite having different chemical characteristics. Iron forms the catalytic core of proteins that include heme and iron-sulfur, and it is essential for mitochondrial activity, oxygen transport, and neurotransmitter production[3,28].

To minimise oxidative stress and maintain metabolic availability, ferritin, transferrin, DMT1, and ferroportin closely control iron trafficking and sequestration. According to Montes et al. (2014) and Gonzalez-Lopez & Vrana (2020), copper-dependent enzymes such as cytochrome c oxidase, dopamine β-hydroxylase, and SOD1 play roles in the synthesis of mitochondrial ATP, catecholamine synthesis, and ROS detoxification, respectively[37, 47]. Interestingly, the multicopper oxidase ceruloplasmin also has a dual function, promoting the metabolism of iron and copper, especially in astrocytes and the blood-brain barrier[37, 47]. Zinc primarily functions in synaptic compartments, where it modulates NMDA receptor activation and long-term potentiation by co-releasing vesicular Zn^{2+} with glutamate[51]. Metallothionein III buffers zinc availability and guards against oxidative damage, whereas zinc transporters, including ZnT3 and ZIP family members, regulate intracellular zinc fluxes. Ferroptosis resistance and redox control depend on selenium-based proteins, such as GPX4, SELENOP, and TrxR. In neurons, GPX4 inhibits lipid peroxidation, whereas SELENOP serves as an antioxidant effector and a transporter. These roles are vital in areas such as the hippocampus and cerebellum, which are prone to inflammation and metabolic activity[62,63].

3. Pathological Relevance: Disease-Specific Metal Disruption

Neurological disorders are strongly associated with disturbances in metal homeostasis, which frequently present as region-specific illnesses that reflect the anatomical distribution of the metalloproteins in question. Ferroptosis, a type of iron-dependent cell death, oxidative damage, and mitochondrial dysfunction are all exacerbated by excessive iron accumulation in the substantia nigra in Parkinson's disease (PD)[16,18]. Advanced imaging modalities, such as quantitative susceptibility mapping, can identify iron buildup, which occurs before dopaminergic neuron death(15). Additionally, PD models and human tissues have been shown to exhibit altered expression of ferritin, transferrin receptor, and DMT1. Two opposing pathologies, Wilson's disease, caused by ATP7B mutations that lead to copper accumulation and damage to the basal ganglia, and Menkes disease, caused by ATP7A deficiency and impairing copper delivery to the brain, illustrate how copper imbalance contributes to neurodegeneration[10,44]. These disorders highlight how copper dysregulation can impact myelination, oxidative stress, and neurotransmitter production in the basal ganglia, cerebellum, and other parts of the brain. SOD1 misfolding, resulting from inadequate copper incorporation, has also been linked to ALS[38]. On the other hand, synaptic activity and neuroplasticity are primarily impacted by zinc imbalance. Deficits in zinc transporter (e.g., ZnT3 KO models) result in greater vulnerability to seizures and cognitive impairment.

In Alzheimer's disease, zinc also regulates amyloid-beta aggregation; poorer pathology is associated with reduced ZnT3 expression[51]. Alzheimer's disease, neurodevelopmental problems, and epilepsy are all becoming more closely linked to selenium deficiency. According to recent human research, oxidative susceptibility and epileptogenesis are linked to low serum selenium and decreased GPX4/TrxR expression[65]. In contrast, selenium supplementation improves memory and synaptic plasticity in AD animal models and restores hippocampus selenoprotein expression[67].

4. Cross-Metal Interactions and Convergent Pathways

The overlap and interconnectedness of metal routes, especially those between iron and copper, is a significant result of this review. A copper-containing ferroxidase called cereuloplasmin converts ferrous iron to ferric iron, which is then exported by ferroportin. As observed in both knockout models and neurodegenerative disorders, ceruloplasmin deficiency leads to iron accumulation and oxidative damage in astrocytes and oligodendrocytes (45). This demonstrates how iron homeostasis may be indirectly impacted by copper shortage and vice versa. Similar to this, zinc and selenium interact through antioxidant pathways. For example, SOD1 needs both copper and zinc, while GPX4 and TrxR, which are based on selenium, cooperate with metallothioneins and SOD1 to protect against oxidative stress.

5. Emerging Techniques and Research Gaps

This review highlights critical gaps in the literature despite notable advancements, particularly in the functional characterisation and anatomical mapping of selenium and copper-binding proteins in limbic and cortical areas. Selenoprotein expression remains poorly understood at the cellular level compared to iron and zinc, and most research relies on animal models without direct human validation. Furthermore, there are still disagreements about zinc's dual function as a pro-excitatory modulator and neuroprotectant, especially in conditions such as epilepsy and schizophrenia. Integrated neuroanatomical proteomics, which encompasses in situ hybridisation, single-cell mass spectrometry, and spatial transcriptomics, may fill these gaps by generating high-resolution maps of metalloprotein distribution. By allowing for the dynamic, non-invasive measurement of metals in vivo, multimodal imaging techniques such as MR-based susceptibility imaging and synchrotron-based metal mapping may enhance biochemical investigations. To close the translational gap, post-mortem human tissue should be included in metalomics research, and iPSC-derived brain organoids should be developed.

6. Clinical and Therapeutic Implications

In the central nervous system (CNS), metalloproteins are essential for preserving cellular redox stability, neurochemical balance, and enzymatic control. Many neurological and systemic disorders are caused by dysregulation of their synthesis, transport, or action. New paradigms for diagnosing and treating metal-associated illnesses can be gained by understanding the clinical and therapeutic significance of metalloproteins.

A valuable technique for illness monitoring is the measurement of metalloproteins such as selenoprotein P (SELENOP), transferrin, ceruloplasmin, and superoxide dismutase (SOD1). While increased ferritin and transferrin receptor expression are associated with Parkinson's disease and neurodegeneration with brain iron accumulation (NBIA), altered levels of ceruloplasmin and ferroportin are early markers of Wilson's and Alzheimer's diseases, respectively[71,72].

Modification of metal–protein interactions or metalloprotein activity has great therapeutic potential. In addition to being approved for the treatment of Wilson's disease, iron chelators (deferiprone) and copper chelators (penicillamine, trientine) have demonstrated promise in reducing metal-induced oxidative damage in models of Parkinson's and Alzheimer's disease[73]. Similarly, selenium supplementation increases GPX4 and TrxR activity, providing resistance to neuroinflammation and apoptosis, while zinc supplementation has shown neuroprotective effects in epilepsy and depression through modulation of ZnT3 and MMP-9 signalling pathways[72]. Future pharmaceutical approaches to restore homeostasis without causing secondary deficiencies may involve targeting metallochaperones and metal transporters (such as ATP7A/B, DMT1, and ZIPs)(74).

The goal of new protein replacement and gene editing technologies is to address metalloprotein deficits at the molecular level. Preclinical results have demonstrated that CRISPR-based restoration of SOD1 in ALS and AAV-mediated gene therapy for ATP7A mutations in Menkes disease can restore copper homeostasis and lessen oxidative damage[75]. Similarly, recombinant selenoprotein P delivered via nanocarriers may shield hippocampus neurones from oxidative stress and promote cognitive performance in selenium-deficient environments. With the advent of precision treatments, therapy paradigms have shifted from symptomatic to molecularly focused.

Conclusion

This comparative analysis demonstrates the complex neuroanatomical and biochemical interactions of iron-, copper-, zinc-, and selenium-dependent metalloproteins in sustaining brain structure and function. While the literature clearly shows their distinct and overlapping functions in redox balance, neurotransmission, and cellular metabolism, the next step is to translate this molecular understanding into preventive and therapeutic applications for managing neurological diseases. The presence of metal dyshomeostasis in illnesses such as Parkinson's, Alzheimer's, Wilson's, and epilepsy emphasises the critical need to investigate targeted manipulation of metalloprotein pathways as a means of restoring neuronal homeostasis.

Future Research Recommendation

Future research should go beyond descriptive mapping and into functional integration, using improved neuroimaging, metalloproteomics, and gene-editing methods to identify causative links between metalloprotein dynamics and disease development. Clinical investigations involving metal chelation, supplementation, or metalloprotein stabilisation could lead to new options for early intervention and neuroprotection. Furthermore, personalised medicine approaches based on individual metal metabolism profiles may aid in predicting vulnerability to neurodegenerative diseases and guiding specific therapy regimens.

Closing the gap between molecular anatomy and clinical neuroscience will elevate metalloprotein research from a descriptive framework to a translational model of neural health and disease prevention. The biochemical precision of metalloproteins can enhance the knowledge, diagnosis, and treatment of CNS degenerative illnesses by emphasising integrative processes and therapeutic innovation.

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