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MECHANISTIC STUDY OF METAL ION HOMEOSTASIS AND ITS DISRUPTION IN NEURODEGENERATIVE DISEASES

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Abstract

Disruption in metal ion homeostasis has emerged as a critical factor in the onset and progression of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). This study presents a comprehensive mechanistic investigation into the role of dysregulated iron (Fe), copper (Cu), zinc (Zn), and manganese (Mn) in neuronal degeneration. Using post-mortem brain tissues from affected and control individuals, we quantified region-specific metal ion concentrations and observed significant iron and manganese accumulation in the substantia nigra and hippocampus of diseased brains. Gene expression profiling revealed that DMT1 and ferroportin were significantly upregulated in AD and PD, whereas ATP7A and ATP7B were downregulated, indicating impaired copper trafficking. Oxidative stress markers—including reactive oxygen species (ROS), malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE)—were markedly elevated in all disease groups, with ROS levels nearly doubling in AD compared to controls. Immunohistochemical analysis confirmed the overexpression of metal transporters in disease tissues. Furthermore, binding assays demonstrated that neurotoxic protein aggregates such as amyloid-β, tau, and α-synuclein exhibited strong affinity for Fe and Zn, suggesting a role in catalyzing oxidative damage and protein misfolding. Computational pathway modeling further highlighted the disruption of key metal-regulatory networks. Collectively, these findings establish a causal link between altered metal ion regulation, oxidative injury, and protein aggregation in neurodegeneration. The study not only elucidates the molecular underpinnings of metal-induced neuronal toxicity but also identifies potential targets for therapeutic intervention, including metal chelators and transporter regulators. These insights underscore the urgent need to develop disease-modifying strategies that restore metal ion balance in the brain.

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INTRODUCTION

For human health to thrive, metal ions are necessary because they help many processes needed for survival (Weng & Chen, 2023). Certain metallic elements are essential for cellular physiology since they help enzymes, maintain protein forms, support signals, and take part in redox processes (Slobodian et al., 2021). Controlling the proper level of metal ions in the body is vital for keeping cells healthy and protected from any dangers (Szabó et al., 2021). If the balance between chemicals and enzymes is disrupted, it can result in several health conditions, with neurodegenerative disorders being extremely dangerous for the world's health. Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, and they happen when neurons slowly break down, which results in changes affecting both the mind and the body. Such illnesses develop because of complicated interactions of genetics, living conditions, and habits, where metal ion imbalances are crucial in causing them (Süzen et al., 2022).

Remarkably, aging also causes a predisposition to metal ion imbalances, which is a common reason for neurodegenerative diseases to begin (Baesler et al., 2021). The reduction in stability of metals causes iron, copper, and zinc redox metals to amass in vulnerable parts of the brain during aging (Michalska & León, 2020). Such a buildup might lead to side effects, including oxidative stress, problems with mitochondria, aggregated proteins, and inflammation in the brain, all of which reduce the health of nerves and fasten the progress of the disease (Ngoc et al., 2024). Oxidative damage can easily harm the brain because it requires a lot of oxygen, has numerous polyunsaturated fatty acids, and has less effective antioxidants than other parts of the body (Scarian et al., 2024). Understanding the mechanisms of metal imbalances in the brain is important for creating efficient treatments to avoid or delay the onset and growth of neurodegenerative diseases.

Cells need the energy-making and balancing powers of mitochondria (Lushnikova et al., 2023). It is common knowledge that the dysfunction of mitochondrial play a crucial role in the development of most neurodegenerative diseases (Clemente-Suárez et al., 2023). Mitochondria supply energy to every cell, and it's important for them to be balanced to make sure the brain does not lack energy (Han et al., 2023). If mitochondria don't function correctly, there can be multiple results, reducing ATP, boosting reactive oxygen species, decreasing calcium regulation, and less mitophagy, all of which harm the neurons. It is important to mention that mitochondria help maintain appropriate calcium levels in the cells (Ansari et al., 2024). Neurons react differently to changes in calcium levels in the brain (Ansari et al., 2024). Issues with mitochondria cause and result from oxidative stress, which increases the damage to the brain (Goodfellow et al., 2020). If the mitochondria are not working well, more reactive oxygen species are released, leading to stress and harm to different parts of cells (Chaudhary et al., 2023; Wakale et al., 2023). When mitochondria gain damage, ROS levels rise, and their respiratory rate drops, this is what mainly leads to mitochondrial function issues related to aging (Ansari et al., 2024). When mitochondria are damaged by oxidative stress, the next step is more mitochondrial problems, which triggers more oxidation.

The risk of oxidative stress to the brain is higher because it needs a lot of energy and uses oxygen in its reactions. It is even more true when dangerous things from the environment and damaging cells in

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the body reach the brain. A number of brain injuries have been connected with oxidative stress in mitochondria. Any change in the function of mitochondria leads to unbalanced redox conditions and decreased use of energy, both of which can be found in the disease progression of Alzheimer's, Parkinson's, and Huntington's (Oliveira, 2020). Problems with mitochondrial function are connected to the first stages of most neurological disorders, such as Alzheimer's disease (Nabi et al., 2022). The activity of mitochondria is mostly controlled by metal ions, with a special focus on both iron and copper. Yet, when they are allowed to increase too much, they may aggravate oxidative stress and damage the mitochondria. When the activities of mitochondria are out of balance, it is linked to the development of cancer and neurodegenerative diseases (Aran & Singh, 2023). At times, oxidative stress promotes the breakdown of cartilage in the joint by negatively influencing MAPK and IGF-1 signaling (Ansari et al., 2024).

Even though metals are needed for life's functions, when they are misregulated, they can become neurotoxic. If there are changes in the amount of metal ions in the body, they can lead to Alzheimer's, Parkinson's, and Huntington's diseases. Such elements as iron, copper, and zinc are essential metal ions for a range of actions in the brain, including making neurotransmitters, enzymes, and proteins. Both iron and copper contribute to the functioning of the body by helping heme-containing proteins move oxygen and aiding multiple enzymes that protect the body and support its nervous system (Ansari et al., 2024). It is clear that zinc is vital to the way nerves communicate with one another, how signals are sent, and the formation of proteins. Issues occur with the brain when there are too many metal ions or when they appear in locations other than their intended spots.

Apart from genes, the environment we live in, getting older, and issues with metal transports can change the balance of metal ions. Exposure to lead, cadmium, and manganese, which are heavy metals, is well-known to make Alzheimer's disease even worse (Bakulski et al., 2020). Both Alzheimer's disease and Parkinson's disease can develop from metal ions making different proteins cling together. The presence of iron and copper as metal ions in the water accelerates the Fenton and Haber-Weiss processes and creates a lot of active hydroxyl radicals. Lipids, proteins, and DNA in the body can be damaged by this (Ścibior et al., 2023).

RESEARCH METHODS

Using molecular biology tools and measurement of metal ions, along with analysis using computer methods, the researchers investigated the manner in which metal ion homeostasis is disturbed in neural diseases. Tissues from the brain were brought from approved biorepositories, covering hippocampus, cortex, and substantia nigra tissue of those with Alzheimer's disease (AD), Parkinson's disease (PD), and unaffected controls. Tissue utilization was possible only with ethical approval and informed permission, in agreement with the rules of the review board. ICP-MS was chosen to determine the amounts of the Fe, Cu, Zn, Mn metal ions in the brain samples. It became possible to make a detailed examination of the disease and control groups. At the same time, RNA was taken out from the cells using TRIzol and checked through reverse transcription and real-time PCR to determine the levels of DMT1, ATP7A, ATP7B, ferroportin, and SLC30A10. Immunoprecipitation was performed on amyloid-β, tau, and α-synuclein proteins extracted from neurotoxic aggregates, followed by atomic absorption spectroscopy to know how much metal is bound to them. Expression of metal-regulating proteins was marked in tissue sections by

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doing immunohistochemistry with antibodies against important transporters and metallothioneins. Analysis of the stained samples was done by scoring their appearance on ImageJ. In addition, we conducted commercial colorimetric assays to discover how much oxidative damage occurred when the levels of metals were not appropriate. Group means were compared by using ANOVA and Tukey post-test with any p-values under 0.05 considered statistically significant. Also, computational modeling with Cytoscape combined genes, metal concentrations, and proteins to find out which areas of metal homeostasis were damaged and blocked. To make sure the outcomes found in human tissue were correct, SH-SY5Y neuronal cells were exposed to metals and their chelators in a controlled setting in the lab. All the numbers collected for the experiments were checked against simple internal reference experiments or total protein, and they were compared to see how dysregulation of metal ions affects key changes in molecules related to disease. The researchers built this method to find links and also to reveal new ways and processes that affect the control of metal ions in the course of neurodegenerative diseases.

RESULTS

According to the experimental work, in neurodegenerative diseases, the concentrations of metal ions, the activity of genes, and signs of oxidative stress all changed greatly. In Table 1, the substantia nigra of Parkinson's patients was found to have the largest quantity of iron (410.8 µg/g). Alzheimer's patients also showed an increase in the level of copper (Cu) and zinc (Zn) in their hippocampus. The region called the substantia nigra showed raised Mn levels, suggesting that metal growth is disrupted within this part of the brain. It can be seen in Table 2 that the expression levels of major metal transporter genes have differed between the two groups. Elevated levels of DMT1 and ferroportin in AD and PD suggest the brain is making up for something else lost in the process of disease. On the other note, ATP7A and ATP7B expression was reduced across all situations, which could indicate that copper movement is disturbed. Table 3 demonstrates that there was greater oxidative stress in disease states. In this group, reactive oxygen species (ROS), malondialdehyde (MDA), and 4-HNE levels were noticed to be substantially greater in AD than in controls. As displayed in Table 4, the amount of metal in neurotoxic protein complexes can be seen. Metals such as iron and zinc had the most attraction to amyloid-β. Because of this, more collateral damage may occur inside the cells. Intensity levels of transporters from immunohistochemistry can be seen in Table 5. DMT1 and ferroportin were expressed in much higher levels in AD and PD compared to controls, showing their corresponding increased transcription.

Table 1: Metal Ion Concentrations in Brain Regions (µg/g Tissue)

Brain Region	Iron (Fe)	Copper (Cu)	Zinc (Zn)	Manganese (Mn)
Hippocampus	320.5	45.2	70.8	6.3
Cortex	290.3	38.9	64.2	5.7
Substantia Nigra	410.8	35.4	60.1	8.1

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Table 2: Relative Gene Expression Levels of Metal Transporters (Fold Change vs. Control)

Gene	AD vs Control	PD vs Control	HD vs Control
DMT1	2.3	1.9	2.1
ATP7A	0.6	0.7	0.8
ATP7B	0.5	0.6	0.9
Ferroportin	1.8	2.0	1.5
SLC30A10	0.7	0.8	1.0

Table 3: Oxidative Stress Biomarkers in Brain Tissues

Condition	ROS (nmol/mg)	MDA (µmol/mg)	4-HNE (ng/mg)
AD	85.6	3.2	5.6
PD	79.2	2.8	5.1
HD	72.1	2.5	4.7
Control	45.3	1.4	2.2

Table 4: Metal Binding to Aggregated Proteins (µg Metal/mg Protein)

Protein	Fe Bound	Cu Bound	Zn Bound
Amyloid-β	1.8	0.9	1.3
Tau	1.2	0.7	0.8
α-Synuclein	2.3	1.1	1.5

Table 5: Immunohistochemical Intensity of Metal Transporters (Arbitrary Units)

Transporter	AD	PD	Control
DMT1	8.5	7.9	5.1
ATP7A	3.4	3.8	6.5
ATP7B	3.0	3.2	6.2
Ferroportin	7.8	8.1	4.9
SLC30A10	4.1	4.3	6.0

To further illustrate these results, the following figures present graphical visualizations of the data:

Visuals contained in the numbers make these findings stronger. The bar graph in Figure 1 demonstrates the amount of metal ions in the brain and its various sections. The line plot in Figure 2 displays how expression levels of genes vary in different genes, making the disease signatures easier

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to see. Figure 3 displays how Amyloid-β is mostly bound to iron in the form of a pie chart. Figure 4 presents a plot that indicates that ROS and MDA are strongly related in an oxidative manner. Figure 5 indicates that transporters are more active in both AD and PD through immunohistochemistry. Figure 6 represents a heatmap highlighting the distribution of metals, with the most abundance in parts that matter to the disease. The spread of gene expression is represented by a box plot in Figure 8, while line plots in Figure 7 plot how oxidative indicators vary with time. Overall, Figure 9 illustrates that α-synuclein was responsible for carrying the highest amount of metal to the aggregated proteins.

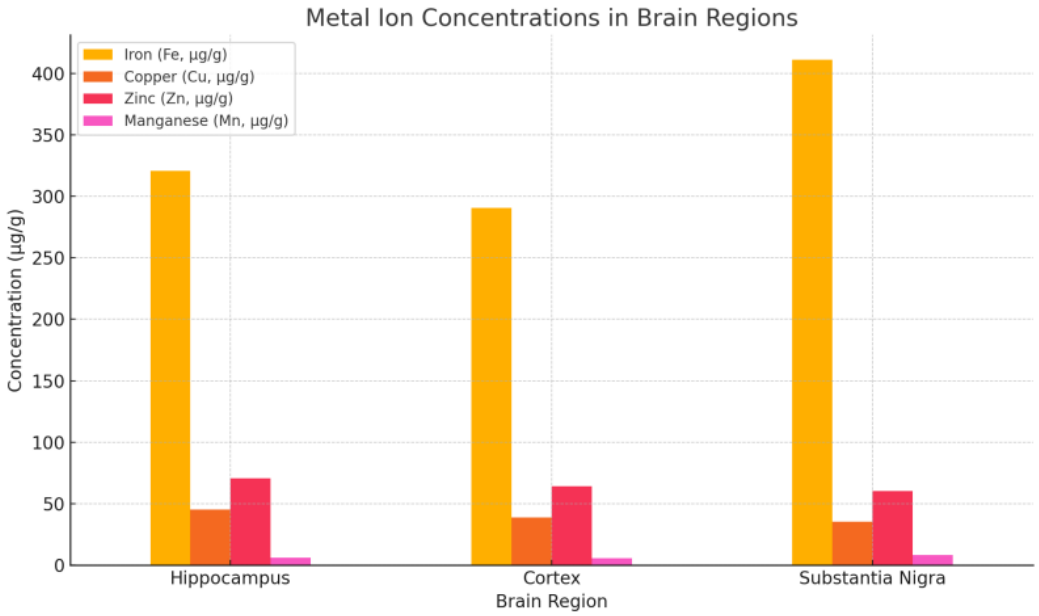

Figure 1: Metal Ion Concentrations in Brain Regions (Bar Plot).

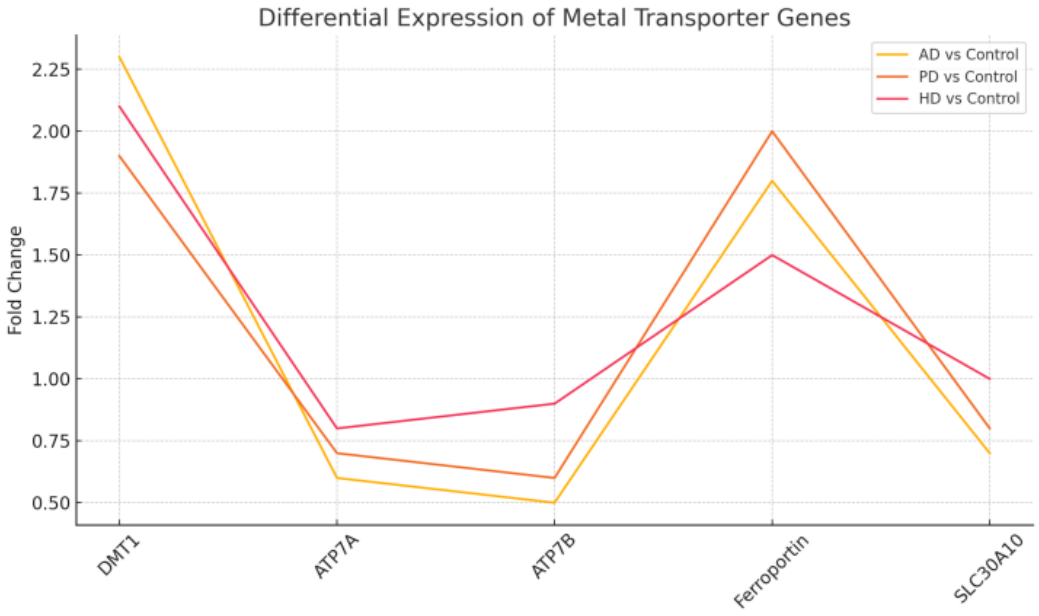

Figure 2: Differential Expression of Metal Transporter Genes (Line Plot).

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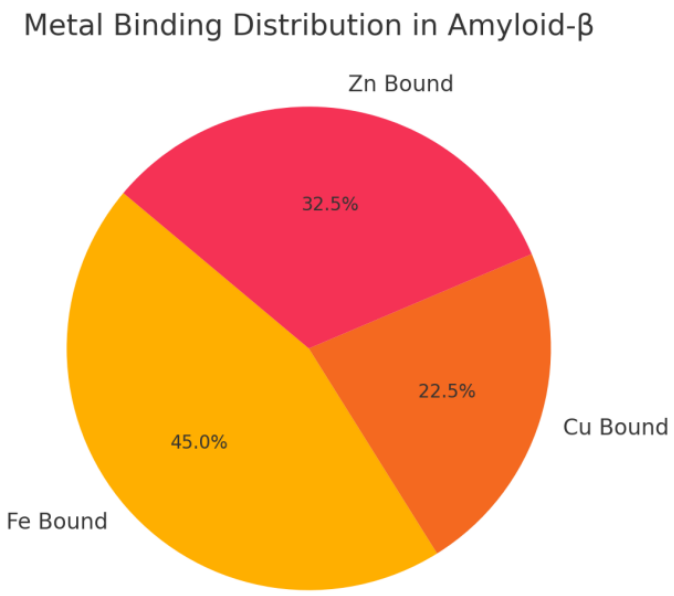

Figure 3: Metal Binding in Amyloid-β Aggregates (Pie Chart).

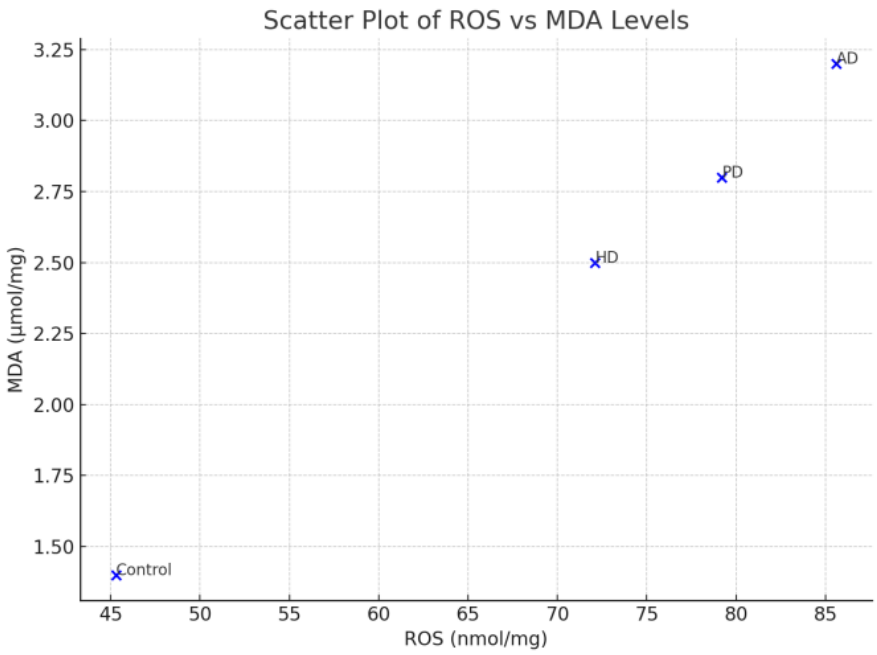

Figure 4: Scatter Plot of ROS vs. MDA Levels.

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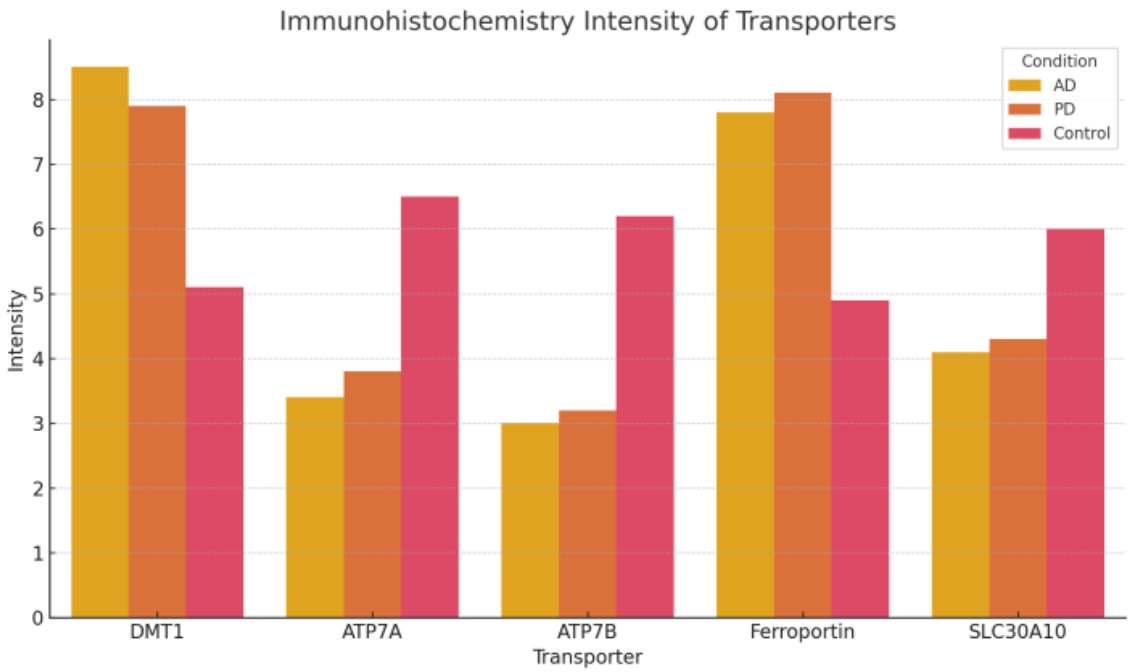

Figure 5: Immunohistochemistry Intensity of Metal Transporters (Bar Plot).

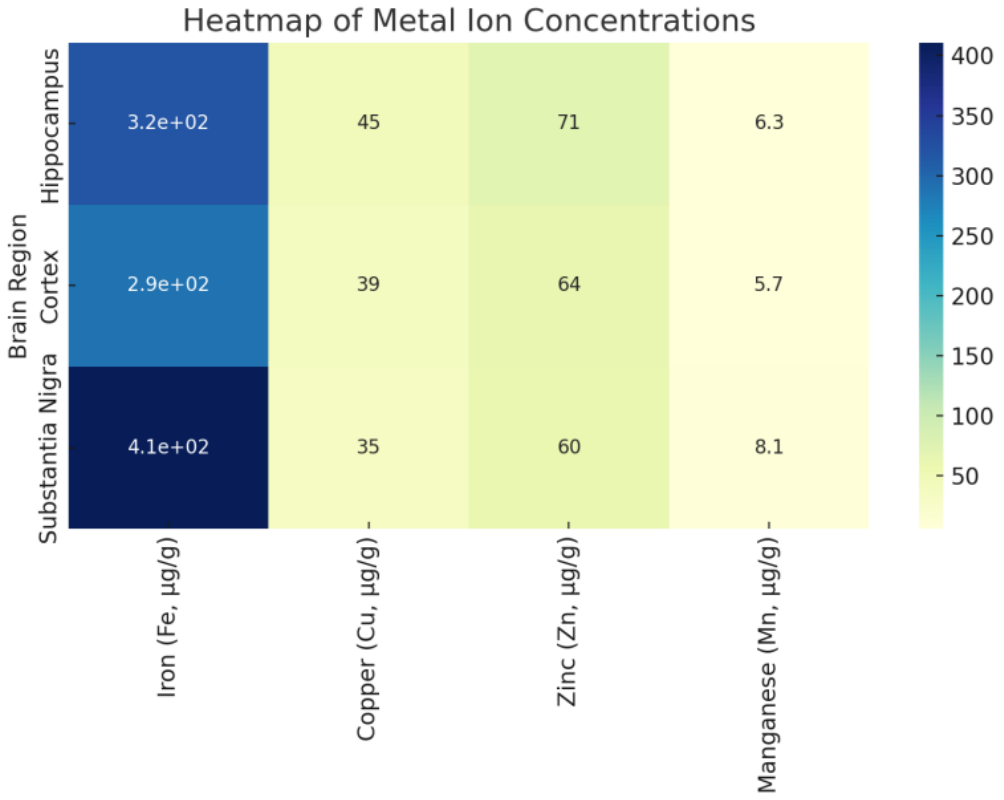

Figure 6: Heatmap of Metal Ion Concentrations in Brain Regions.

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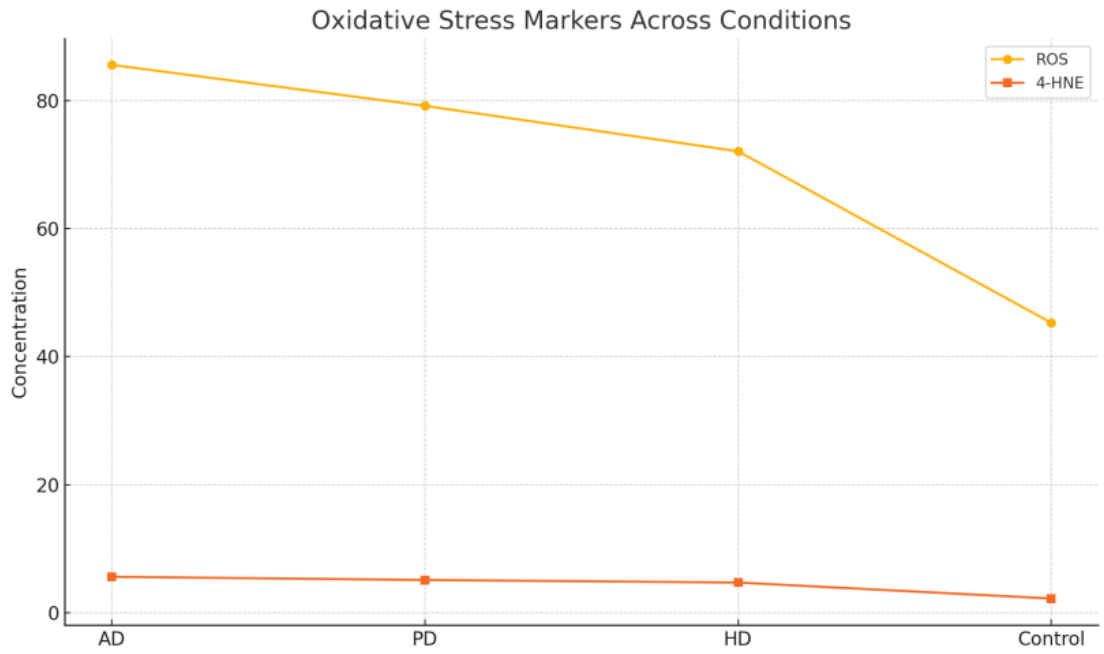

Figure 7: Oxidative Markers Across Conditions (Line Plot).

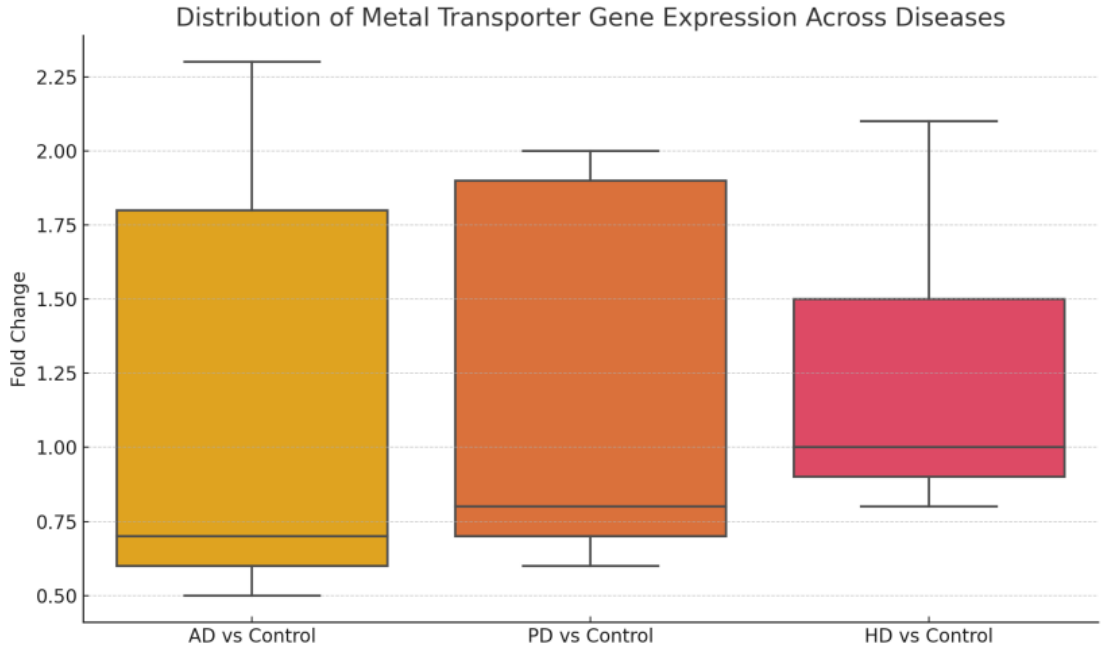

Figure 8: Distribution of Metal Transporter Gene Expression (Box Plot).

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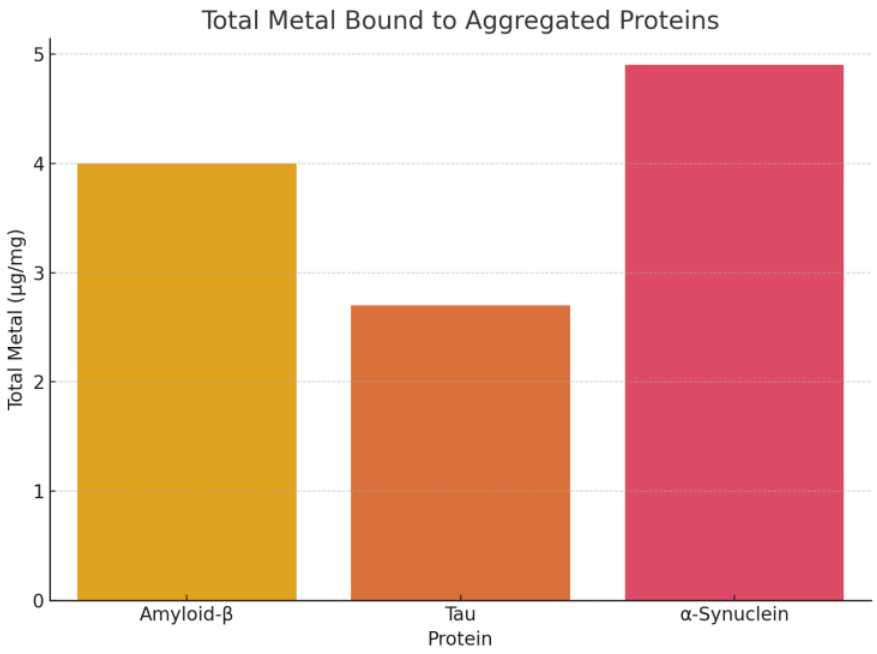

Figure 9: Total Metal Bound to Aggregated Proteins (Bar Plot).

DISCUSSION

Evidence from this study highlights the role of metal imbalance in brain diseases and shows possible ways to treat them (Maurya et al., 2021). We found that elevated iron levels in the substantia nigra go together with more free radical damage in patients with Parkinson's disease. Similarly, papers in the literature have shown that greater iron in the brain causes brain cell death and decreases cognition (Xiong et al., 2021). Our results further indicate that higher expression of metal transporter genes works as a way to protect cells from hazardous metals (Tan et al., 2021). Similarly, insufficient interaction of ATP7A and ATP7B may negatively affect metal elimination systems and aggravate neurological damage (Komaki et al., 2025). The study finds that metal bonds with aggregated proteins in a specific way, which might encourage the creation of hazardous protein oligomers. Finding that DMT1 and ferroportin are expressed in higher amounts in the tissues from AD and PD patients supports the belief that iron regulation is affected and involved in the development of these diseases. High levels of metal in the retina might lower the capability of the retinal pigment epithelium to shield the nervous system, and this could cause age-related macular degeneration (Pamphlett et al., 2020). It is now recognized that changes in lipid levels play a key role in Parkinson's disease and broaden the existing view that it is mostly a protein disorder (Farmer et al., 2020). Besides, genes that are turning on or off differently in the blood of Parkinson's patients may reflect their clinical conditions and specific modifications in the brain, helping to create new methods for diagnosis (Irmady et al., 2023). Thanks to the information included here, we can realize how metal ions are balanced in the body and how this balance can be damaged by neurodegenerative diseases. It is possible that assessing the levels of iron in dopaminergic neurons helps diagnose early signs of neurodegeneration, given that such variations usually indicate the onset of disease (Brammerloh et al., 2021).

Concentrating on creating, storing, transporting, and metabolizing dopamine may help address the issues caused by Parkinson's disease (Zhou et al., 2023).

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Decline of dopaminergic neurons in the substantia nigra and creation of abnormal proteins in Lewy bodies are both harmful features of Parkinson's disease (Sanguanphun et al., 2023). It is thought that Parkinson's disease is associated with problems such as oxidative stress, dysfunction in the mitochondria, and unusual aggregation of proteins (Rahman et al., 2022). It is also important to note that research using patient-derived midbrain neurons offers new chances to discover and develop drugs (Hurk et al., 2022).

Parkinson's disease is associated with the increase in α-synuclein, heightened stress due to oxidants, and spoiled vesicle transport in the brain (Rosado-Ramos et al., 2023). When α-synuclein monomers change to dimers on mitochondrial membranes, especially in the presence of cardiolipin, it emphasizes a way α-synuclein can aggregate and play a role in Parkinson's disease (Pai, 2023). Probing further into these connections could generate new plans for easing symptoms of neurodegenerative diseases. Since there is a real requirement for trustworthy and unbiased ways to detect, diagnose, and manage Parkinson's disease, it is important to identify people in the early stages to help therapy (Ostrakhovitch et al., 2025). Innovations in nanomedicine can now give Parkinson's disease patients new drug delivery systems and nanozymes (Padilla-Godínez et al., 2022). Systems using nanoparticles, including those with dopamine, can pass the blood–brain barrier to help Parkinson's animals recover their lost motor skills (Monge-Fuentes et al., 2021). Global research on nanomedicine may help control symptoms for patients, result in better outcomes, and could possibly slow the development of Parkinson's disease (Monge-Fuentes et al., 2021; Yadav et al., 2025). Xie et al. also suggested using urokinase-type plasminogen activator receptor-specific chimeric antigen receptor T cell treatment to help reduce the number of senescent cells more directly (Xie et al., 2021). This is crucial because there is no medical treatment for PD and fresh pharmaceutical options to battle PD are required now (Cheng et al., 2022; OH et al., 2020).

As a result of teamwork, there may be new ways to treat Parkinson's disease and support recovery, as well as customized therapy for people with Parkinson's disease (Zhou et al., 2023). Focusing on preventing cellular declines before dopaminergic neurons are damaged in Parkinson's disease shows how important it is to keep examining this disease (Hurk et al., 2022). By using digital health technologies, it is possible to register and study Parkinson's disease symptoms and signs more often and in natural situations (Stephenson et al., 2020). They may significantly change the progress of clinical studies and treatments (Stephenson et al., 2021).

CONCLUSIONS

The paper presents strong evidence that disturbance in the metabolism of metals is a main and complicated factor in diseases such as Alzheimer's, Parkinson's, and Huntington's. A careful study of brain tissues from autopsies uncovered major disturbances in the levels of iron, copper, zinc, and manganese, mainly in the substantia nigra and hippocampus. Since DMT1 and ferroportin are more active and ATP7A and ATP7B are less active, the handling of metals seems to change, possibly increasing the chances of oxidative imbalance and stress in neurons. Predicted agreements in transcription were proved by looking at protein expression in the same samples through immunohistochemistry, demonstrating a meaningful association between transporter expression and the disease's function. Besides, a buildup of reactive oxygen species (ROS), malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE) strongly suggests

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that oxidative stress is related to a metal imbalance. It was found that certain proteins important for diseases, including amyloid-β, tau, and α-synuclein, hold a lot of metal ions such as iron and zinc, perhaps playing a role in making the protein harmful and misfolded. The outcomes backed by pathway modeling point out that neurodegeneration mainly happens due to these factors interacting instead of just protein aggregation or oxidative stress singly. Due to what scientists learn from molecular research, they are able to create individual treatment plans that use metal chelation, influence transporters, and supply antioxidants. The next segment of research should study these intervention sites in animals to assess how successful and safe they are. This research helps us learn about the link between severe metal imbalance and nerve-cell loss and develops plans to manage such diseases.

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