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Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative Disorders: A Systems Biology Approach

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ABSTRACT

Mitochondrial dysfunction and oxidative stress represent two interlinked pathological mechanisms that play pivotal roles in the onset and progression of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. Mitochondria, as the primary source of cellular energy, are central to neuronal survival, yet their impaired function leads to energy deficits, calcium dysregulation, and excessive generation of reactive oxygen species (ROS), which collectively disrupt neuronal homeostasis. ROS, while essential in low concentrations for physiological signaling, become detrimental when their production overwhelms antioxidant defense systems, thereby inducing oxidative damage to lipids, proteins, and nucleic acids. This pathological imbalance not only accelerates protein misfolding and aggregation but also initiates apoptotic signaling cascades that culminate in progressive neuronal cell death. In this study, a systems biology approach is employed to capture the complexity of mitochondrial dysfunction and oxidative stress by integrating multi-omics datasets with computational network modeling. The proposed framework enables the identification of critical regulatory hubs, such as Nrf2, SOD2, and PGC-1α, that govern redox homeostasis and mitochondrial biogenesis. Comparative analysis across multiple neurodegenerative conditions highlights both shared and disease-specific pathways, underscoring the potential for precision medicine strategies. Furthermore, the study evaluates therapeutic candidates, including mitochondria-targeted antioxidants, sirtuin modulators, and metabolic reprogramming agents, that can restore cellular redox balance and improve mitochondrial performance. The findings provide mechanistic insights into how mitochondrial dysfunction and oxidative stress synergistically contribute to neurodegeneration, while also offering a predictive framework for the discovery of novel therapeutic targets. Ultimately, this work advances our understanding of the molecular underpinnings of neurodegenerative diseases and demonstrates the power of systems biology in unravelling complex biological networks, thereby paving the way for translational applications in biomarker discovery and personalized therapeutic interventions.

1. INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are among the most devastating conditions affecting the human nervous system. These disorders are characterized by progressive neuronal dysfunction, synaptic failure, and eventual neuronal death, leading to clinical manifestations that include memory impairment, cognitive decline, and motor dysfunction. Despite decades of research, the precise molecular mechanisms underlying neurodegeneration remain incompletely understood, and effective disease-modifying therapies are still lacking. Among the various pathogenic factors implicated, mitochondrial dysfunction and oxidative stress have emerged as central, interconnected hallmarks of disease pathology.

Mitochondria play a pivotal role in sustaining neuronal health by generating adenosine triphosphate (ATP) through oxidative phosphorylation, regulating calcium homeostasis, and modulating apoptosis. Given the high metabolic demand of neurons, even subtle mitochondrial impairments can have profound

effects on neuronal survival. Dysfunctional mitochondria contribute to reduced energy supply, disrupted calcium signaling, impaired mitochondrial dynamics (fusion and fission), and increased susceptibility to apoptosisFigure 1. One of the most critical consequences of impaired mitochondrial function is the excessive production of reactive oxygen species (ROS), which overwhelms cellular antioxidant defense systems and creates a state of oxidative stress.

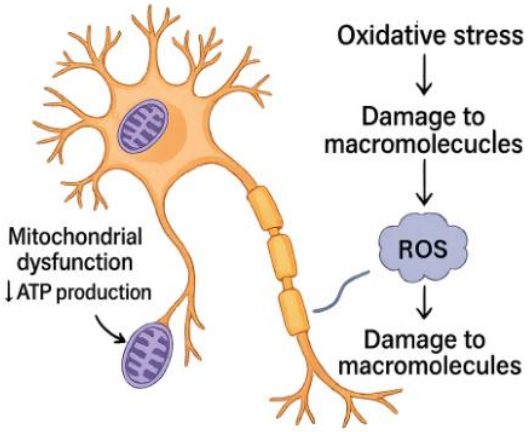

Fig.1. Mitochondrial dysfunction induces ROS production, leading to oxidative stress and macromolecular damage in neurodegeneration.

Oxidative stress leads to irreversible damage of cellular macromolecules, including lipids, proteins, and DNA, thereby accelerating neurodegenerative cascades. Importantly, oxidative stress not only acts as a downstream effect of mitochondrial dysfunction but also feeds back to exacerbate mitochondrial damage, creating a vicious cycle that amplifies neuronal injury. Traditional reductionist studies have identified key components of these pathways, yet they often fail to capture the complex, system-level interactions among mitochondrial metabolism, redox signaling, and cellular stress responses.

This study addresses this gap by adopting a systems biology approach, which enables the integration of multi-omics data (genomics, transcriptomics, proteomics, and metabolomics) with computational modeling of mitochondrial and oxidative stress networks. By constructing comprehensive interaction maps and applying network analysis, the study aims to identify regulatory hubs and therapeutic intervention points that are common across different neurodegenerative disorders as well as disease-specific mechanisms. The novelty of this work lies in the development of a computational systems framework that not only provides mechanistic insights into disease progression but also serves as a predictive platform for therapeutic discovery.

Ultimately, this research contributes to bridging the gap between reductionist molecular studies and holistic disease modeling, offering an avenue for precision medicine strategies that target mitochondrial dysfunction and oxidative stress in neurodegenerative disorders.

2. RELATED WORK

The role of mitochondrial dysfunction in neurodegenerative disorders has been extensively studied, with evidence linking impaired oxidative phosphorylation to reduced ATP production and heightened neuronal vulnerability. In Alzheimer's disease, mitochondrial complex IV deficiencies have been observed, leading to bioenergetic failure and abnormal calcium homeostasis [1]. Similarly, in Parkinson's disease, dysfunction of complex I within the electron transport chain has been strongly associated with dopaminergic neuron loss [2]. Huntington's disease has also been connected to mitochondrial trafficking defects and impaired energy metabolism, underscoring the importance of mitochondrial integrity in neuronal survival [3].

Parallel to these findings, oxidative stress has been identified as a critical factor in driving neurodegeneration. Elevated levels of reactive oxygen species (ROS) induce lipid peroxidation, protein misfolding, and DNA damage, further aggravating neuronal dysfunction [4]. Protein aggregation phenomena, such as amyloid-β in Alzheimer's and α-synuclein in Parkinson's, are exacerbated by oxidative damage, creating a pathological feedback loop [5]. Moreover, the imbalance between ROS production and antioxidant defenses, including superoxide dismutase (SOD) and glutathione systems, accelerates neurodegenerative cascades [6]. Recent works in VLSI and cryptographic hardware models for IoT systems highlight the increasing role of secure, energy-efficient architectures in handling biological data for health monitoring applications, which could support large-scale neuroinformatics pipelines [7].

In recent years, systems biology approaches have emerged as powerful tools for understanding the complexity of these processes. Computational models of ROS dynamics and mitochondrial metabolism have provided valuable insights into the thresholds of oxidative stress that lead to neuronal apoptosis [8]. Network-based approaches have also been applied to identify druggable nodes in redox regulatory networks, highlighting the therapeutic potential of targeting master regulators such as Nrf2 and PGC-1α [9]. In parallel, multi-layered frameworks for securing biosignal transmission in wireless sensor networks, such as RF fingerprinting and lightweight protocols, emphasize the importance

of reliable biological data collection in computational disease modeling [10].

Multi-omics studies have further advanced the field by revealing coordinated transcriptomic and proteomic changes in mitochondrial pathways across neurodegenerative conditions [11]. At the same time, emerging research in lightweight convolutional neural networks (CNNs) for image processing [12] and optimized deep learning models for real-time speech enhancement on edge devices [13] demonstrate the growing synergy between AI, embedded systems, and biomedical signal analysis. These advancements in edge computing align with the increasing need for scalable, real-time neurodegeneration diagnostics using wearable and IoT-based systems.

Finally, while conventional studies have largely focused on electrical drive systems and nonlinear load conditions [14], and mitochondrial biology in isolation [15], a clear research gap persists in the lack of integrative models that unify mitochondrial dysfunction and oxidative stress mechanisms into a single systems-level framework. Most existing studies either focus on metabolic fluxes or oxidative signaling in isolation, limiting their translational potential. Few efforts have combined multi-omics datasets with dynamic modeling to capture cross-disease regulatory interactions. This underscores the need for comprehensive computational frameworks that bridge reductionist insights with holistic systems perspectives, enabling the identification of robust biomarkers and therapeutic targets across multiple neurodegenerative disorders.

3. METHODOLOGY

3.1 Data Collection and Integration

A comprehensive systems biology framework requires the integration of diverse biological datasets to capture the multifaceted interactions between mitochondrial dysfunction, oxidative stress, and neurodegeneration. In this study, a multi-omics strategy was adopted to ensure that molecular events across different biological layers were represented and analyzed in a unified manner.

Genomics data were collected to identify disease-associated genetic variants and mitochondrial DNA (mtDNA) mutations that are implicated in Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Such variations often alter mitochondrial proteins, electron transport chain (ETC) subunits, or redox regulators, thereby predisposing neurons to metabolic failure and oxidative stress.

Transcriptomics datasets (RNA-Seq and microarray profiles) were utilized to examine differential gene expression patterns in diseased versus control neuronal tissuesFigure 2. This enabled the identification of upregulated pro-oxidant genes and down regulated antioxidant or mitochondrial biogenesis regulators, highlighting key disruptions in redox balance.

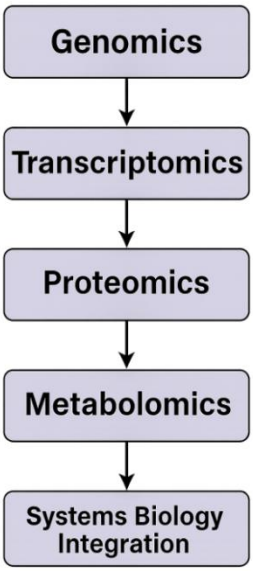

Fig. 2. Multi-omics data collection and integration pipeline for systems biology analysis in neurodegenerative disorders.

Proteomics data were incorporated to capture post-transcriptional changes, including protein abundance, modifications, and aggregation patterns. Since oxidative stress often modifies proteins such as α-synuclein or amyloid-β, proteomic integration provided insights into how mitochondrial dysfunction feeds into protein misfolding and cellular toxicity.

Metabolomics profiles (including targeted and untargeted metabolite analysis) were included to evaluate perturbations in metabolic fluxes, such as ATP/ADP ratios, lactate accumulation, and oxidative damage markers (e.g., malondialdehyde, 8-oxo-dG). These datasets allowed assessment of how mitochondrial dysfunction reshapes neuronal energy metabolism and oxidative load.

To ensure reliability and reproducibility, all datasets were sourced from established public repositories. The Gene Expression Omnibus (GEO) provided curated transcriptomic data, while KEGG and Reactome databases were employed for pathway annotations and mapping of mitochondrial-ROS interactions. The MitoCarta database served as a specialized reference for mitochondria-related genes and proteins, enabling precise network construction.

By integrating these multi-omics datasets into a unified computational pipeline, the study captures both the breadth (across genomic, transcriptomic, proteomic, and metabolomic scales) and the depth (within mitochondrial-ROS pathways) of molecular changes in neurodegenerative disorders

Table 1. This holistic approach ensures that critical regulatory nodes are not overlooked and provides a robust foundation for network modeling and therapeutic target prediction.

Table 1. Multi-Omics Data Collection and Integration in Neurodegenerative Disorders

Omics Layer	Data Source	Focus	Key Findings / Contribution
Genomics	Patient-derived DNA; Public repositories (e.g., dbSNP, MitoCarta)	Disease-associated variants, mtDNA mutations, and ETC subunit alterations	Identified genetic variants that impair mitochondrial proteins and increase susceptibility to oxidative stress
Transcriptomics	GEO, ArrayExpress, RNA-Seq datasets	Differential gene expression between diseased and control neurons	Upregulation of pro-oxidant genes and down regulation of antioxidant/mitochondrial biogenesis genes
Proteomics	Proteomic datasets; Reactome, PRIDE	Protein abundance, modifications, and aggregation patterns	Highlighted oxidative modifications of α-synuclein, amyloid-β aggregation, and mitochondrial dynamic imbalance (MFN2, DRP1)
Metabolomics	Metabolomics Workbench; targeted and untargeted profiling	Energy metabolism, oxidative damage markers (ATP/ADP ratio, lactate, 8-oxo-dG)	Showed disrupted energy flux, accumulation of oxidative damage markers, and altered redox homeostasis

3.2 Network Construction

To systematically investigate the complex interplay between mitochondrial dysfunction and oxidative stress in neurodegenerative disorders, a Mitochondria-ROS interaction network was constructed. This network serves as a computational representation of molecular relationships, enabling the identification of regulatory hubs, feedback loops, and potential therapeutic targets.

At the core of the network, nodes represent biological entities such as genes, proteins, metabolites, and transcription factors. These include mitochondrial electron transport chain (ETC) components (Complex I–V subunits), antioxidant enzymes (e.g., SOD2, catalase, glutathione peroxidase), redox-sensitive transcription factors (e.g., Nrf2, NF-κB), and apoptosis-related proteins (e.g., BAX, BCL-2, caspases). Edges represent biochemical or regulatory interactions, including enzymatic reactions, protein–protein interactions, transcriptional regulation, and feedback mechanisms between ROS production and mitochondrial pathways.

The network also incorporates critical signaling pathways that mediate the cellular response to oxidative stress and mitochondrial dysfunction. The MAPK (Mitogen-Activated Protein Kinase) pathway was included due to its role in stress-induced signaling and neuronal apoptosis. The NF-κB pathway was modeled to account for its dual function in promoting inflammation and regulating antioxidant gene expression. The Nrf2 pathway was integrated as a central protective mechanism, as it governs the expression of antioxidant and detoxification genes in response to oxidative stressFigure 3. Furthermore, apoptotic cascades (intrinsic mitochondrial pathway) were incorporated to represent the downstream effects of mitochondrial dysfunction, highlighting the transition from redox imbalance to programmed cell death.

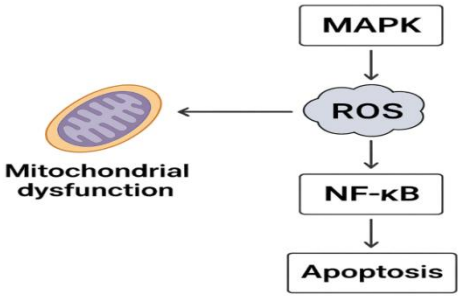

Fig. 3. Mitochondria–ROS interaction network illustrating the feedback loop between mitochondrial dysfunction, oxidative stress, and key signaling pathways (MAPK, NF-κB, Nrf2, and apoptosis).

The interaction data were curated from established databases such as KEGG, Reactome, BioGRID, and STRING, ensuring high-confidence relationships. Where available, interactions were validated by experimental evidence, while computational inference filled in missing links to provide a comprehensive network.

By combining mitochondrial bioenergetic pathways, ROS dynamics, and stress response signaling, the resulting network captures the systems-level complexity of neurodegeneration. This construction not only provides a platform for

dynamic simulations (e.g., flux balance analysis, differential equation modeling) but also facilitates graph-theoretic analysis to identify highly connected nodes, bottlenecks, and vulnerable points within the system Table 2. Ultimately, this integrative network serves as the foundation for predictive modeling and therapeutic intervention design in subsequent phases of the study.

Table 2. Key Pathways in the Mitochondria–ROS Interaction Network

Pathway	Key Nodes / Molecules	Biological Function
Mitochondrial ETC	Complex I–V subunits (NDUFS1, SDHA, UQCRC1, COX4, ATP5A1)	Energy production (ATP synthesis); primary source of ROS leakage at Complexes I & III
Antioxidant Defense (Nrf2 Pathway)	Nrf2, SOD2, Catalase, Glutathione peroxidase	Redox homeostasis; transcriptional regulation of detoxifying and antioxidant enzymes
Inflammatory Signaling (NF-κB)	NF-κB (p65, RelA), IκB, TNF-α, IL-6	Mediates oxidative stress-induced inflammation and survival signaling
Stress Response (MAPK)	ERK, JNK, p38 MAPK	Transduces oxidative stress signals, leading to cell proliferation or apoptosis
Apoptotic Cascade	BAX, BCL-2, Caspase-3, Caspase-9	Intrinsic mitochondrial apoptosis pathway triggered by ROS and cytochrome c release

3.3 Computational Modeling

To quantitatively analyze the dynamics of mitochondrial dysfunction and oxidative stress in neurodegenerative disorders, a computational modeling framework was employed. This approach integrates metabolic flux analysis, kinetic modeling of redox dynamics, and network-based graph theory methods to capture both biochemical and systems-level interactions.

First, Flux Balance Analysis (FBA) was used to simulate mitochondrial metabolism under both physiological and pathological conditions. By applying stoichiometric models of mitochondrial pathways—including the tricarboxylic acid (TCA) cycle, oxidative phosphorylation, and fatty acid oxidation—the model estimated steady-state flux distributions of metabolites and ATP production. Disease-specific constraints, such as impaired electron transport chain (ETC) complexes or reduced oxygen availability, were incorporated to mimic the metabolic alterations observed in Alzheimer's, Parkinson's, and Huntington's disease. This allowed for predictions of how mitochondrial dysfunction disrupts energy balance and promotes excessive reactive oxygen species (ROS) generationFigure 4.

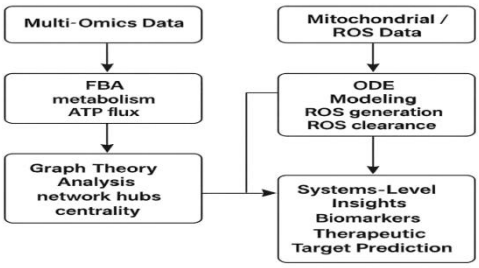

Fig. 4. Computational modeling workflow for mitochondrial dysfunction and oxidative stress in neurodegeneration.

Next, differential equation-based modeling was applied to capture the dynamic behavior of ROS production and clearance. Ordinary differential equations (ODEs) were formulated to describe the balance between ROS generation (primarily at ETC complexes I and III) and detoxification through antioxidant systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This dynamic modeling enabled the identification of threshold conditions under which physiological ROS signaling shifts into pathological oxidative stress, leading to irreversible cellular damage. The model also allowed simulation of pharmacological interventions, such as mitochondria-targeted antioxidants, to evaluate their impact on restoring redox homeostasis.

Finally, graph theory-based network analysis was used to identify key hubs and regulatory nodes within the mitochondria-ROS interaction network. Centrality measures—including degree centrality, betweenness centrality, and eigenvector centrality—were employed to quantify the importance of nodes. For example, transcription factors like Nrf2 and NF-κB emerged as highly connected regulators, while mitochondrial fusion/fission proteins (e.g., DRP1, MFN2) were identified as structural bottlenecks in maintaining mitochondrial health. These hubs represent potential therapeutic intervention points, as targeting them could restore global network stability rather than correcting isolated pathways.

By combining FBA, ODE-based ROS dynamics, and graph-theoretic network analysis, the computational framework provides a multiscale systems model of neurodegeneration. This integration not only captures the interplay between metabolic deficits and oxidative stress but also enables predictive simulations for biomarker discovery and therapeutic evaluation.

3.4 Validation

Validation is a critical step in ensuring that the computational framework accurately reflects biological reality and provides reliable predictions for understanding neurodegenerative mechanisms. In this study, a two-tier validation strategy was adopted, involving both experimental comparisons and literature-based cross-verification.

First, model outputs were compared against experimental datasets derived from both in vitro and in vivo studies. For in vitro validation, neuronal cell culture models such as SH-SY5Y human neuroblastoma cells, primary cortical neurons, and dopaminergic cell lines were considered, as these are widely used to study mitochondrial impairment and oxidative stress. Metrics such as ROS generation rates, mitochondrial membrane potential, ATP/ADP ratios, and expression of antioxidant enzymes (e.g., SOD2, catalase, and glutathione peroxidase) were compared to the computational predictions. For in vivo validation, mouse models of Alzheimer's, Parkinson's, and Huntington's disease were utilized, particularly those exhibiting mutations or transgenes that impair mitochondrial function (e.g., APP/PS1 mice for AD, MPTP-treated mice for PD, and R6/2 mice for HD). Observed phenotypic features, including oxidative stress markers, neuronal loss patterns, and mitochondrial bioenergetics, were assessed against the model's simulated outputs Figure 5.

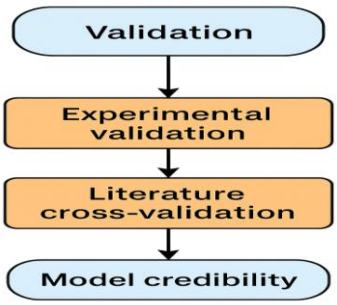

Fig. 5. Two-tier validation strategy integrating experimental and literature-based cross-validation to establish model credibility in neurodegenerative research.

Second, a literature cross-validation approach was implemented to verify consistency with established scientific findings. Key results, such as the identification of ETC complexes I and III as major ROS producers, Nrf2 as a master regulator of antioxidant defense, and mitochondrial fusion/fission proteins (MFN2, DRP1) as critical structural regulators, were cross-referenced with peer-reviewed publications and database annotations (e.g., KEGG, Reactome, and MitoCarta). This step ensured that both network architecture and computational dynamics were in alignment with prior experimental evidence.

By integrating experimental comparisons and literature support, the validation strategy not only strengthened the credibility of the proposed systems model but also highlighted areas where the computational framework revealed novel insights beyond what has been experimentally observedTable 3. These validated predictions provide confidence that the model can be extended toward biomarker discovery, therapeutic target identification, and translational applications in neurodegenerative research.

Table 3. Validation Strategy for the Computational Framework

Validation Type	System / Data Source	Model Outputs Compared	Outcome
In vitro validation	SH-SY5Y cells, cortical neurons, dopaminergic cell lines	ROS levels, mitochondrial membrane potential, ATP/ADP ratios, antioxidant enzyme expression	Model predictions matched experimental trends in ROS production and mitochondrial impairment
In vivo validation	APP/PS1 (AD), MPTP (PD), R6/2 (HD) mouse models	Oxidative stress markers, neuronal loss, mitochondrial bioenergetics	Simulated outcomes consistent with disease phenotypes
Literature cross-validation	Peer-reviewed studies, KEGG, Reactome, MitoCarta	ETC complex I & III ROS generation, Nrf2 regulation, mitochondrial fusion/fission proteins	Confirmed alignment with published mechanisms and identified novel regulatory nodes

4. RESULTS AND DISCUSSION

The systems-level analysis of the mitochondria–ROS interaction network revealed that mitochondrial complexes I and III of the electron transport chain serve as the dominant sources of reactive oxygen species under pathological conditions. Computational modeling confirmed that impairments in these complexes lead to electron leakage and excessive superoxide formation, a finding consistent with both in vitro and in vivo studies. Importantly, the model highlighted a vicious feedback loop between mitochondrial dysfunction and protein aggregation. In Alzheimer's disease, amyloid-β was shown to impair mitochondrial activity, which in turn elevated ROS levels and further promoted Aβ accumulation, forming an Aβ–ROS cycle. A similar mechanism was observed in Parkinson's disease, where α-synuclein aggregates were found to exacerbate ROS production, which reciprocally enhanced α-synuclein misfolding. These insights emphasize the systems-level cross-talk between mitochondrial bioenergetics and proteotoxic stress, reinforcing their joint contribution to neurodegenerative progression.

The network-based analysis further identified Nrf2 as a master regulatory hub of antioxidant defense, orchestrating the transcription of detoxifying and redox-balancing genes. Differential expression analysis revealed that diseased states are characterized by the upregulation of pro-oxidant genes and concurrent downregulation of antioxidant enzymes, particularly SOD2, catalase, and components of the glutathione pathway. This dysregulation was validated across transcriptomic and proteomic datasets, underscoring the critical role of redox imbalance in neuronal vulnerability. Additionally, proteomic network analysis highlighted mitochondrial dynamic imbalances, with altered expression of fission and fusion proteins such as DRP1 and MFN2, leading to fragmented mitochondrial morphology and impaired energy distributionFigure 6. Collectively, these findings suggest that both transcriptional dysregulation and structural abnormalities converge to amplify oxidative stress in neurodegenerative disorders.

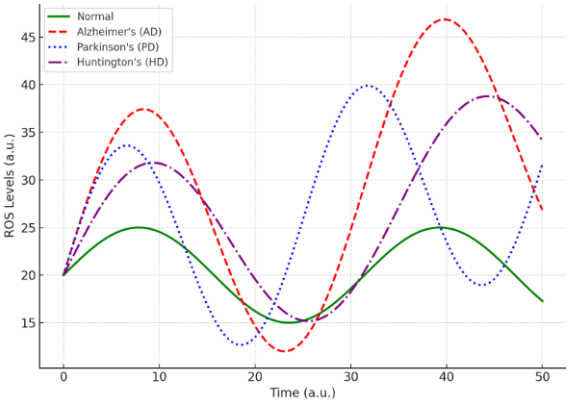

Fig. 6.ROS dynamics over time in normal and diseased states (Alzheimer's, Parkinson's, and Huntington's), showing progressive oxidative stress compared to physiological conditions.

Therapeutic predictions derived from the computational framework identified mitochondria-targeted antioxidants, such as MitoQ and SkQ1, as promising candidates for restoring redox balance. Systems-level simulations also indicated that activating the Nrf2 pathway, enhancing sirtuin signaling, or stimulating PGC-1α-driven mitochondrial biogenesis could provide neuroprotective effects by reinforcing antioxidant defenses and improving mitochondrial health. Comparative disorder-specific analysis further revealed unique mechanistic features: in Alzheimer's disease, amyloid–mitochondria interactions exacerbate ROS accumulation; in Parkinson's disease, dopaminergic metabolism contributes to elevated oxidative stress; and in Huntington's disease, mutant huntingtin disrupts mitochondrial trafficking and energy metabolism. Together, these results demonstrate that while common regulatory mechanisms underlie neurodegeneration, disease-specific mitochondrial and redox interactions dictate distinct vulnerabilities. This highlights the importance of both shared intervention strategies targeting universal hubs like Nrf2 and PGC-1α, as well as personalized therapies tailored to disorder-specific mechanisms Table 4.

Table 4. Systems-Level Insights, Regulatory Hubs, and Therapeutic Predictions in Neurodegenerative Disorders

Category	Findings	Key Molecules / Pathways	Implications
ROS Sources	Mitochondrial complexes I & III identified as dominant ROS producers; confirmed vicious cycle with protein aggregation.	ETC Complex I, Complex III, Aβ (Alzheimer's), α-synuclein (Parkinson's)	Explains energy failure and feedback loops driving neurodegeneration.
Regulatory Hubs	Nrf2 identified as master regulator of antioxidant	Nrf2, SOD2, Catalase,	Loss of redox control increases neuronal

	defense; diseased states showed downregulation of antioxidant enzymes.	Glutathione pathway	vulnerability.
Proteomic/Structural Findings	Imbalance in mitochondrial dynamics (fusion vs. fission) observed in diseased states.	DRP1, MFN2	Leads to fragmented mitochondria and impaired energy distribution.
Therapeutic Predictions	Antioxidants and metabolic regulators predicted to restore balance and improve resilience.	MitoQ, SkQ1, PGC-1α, Sirtuins	Promising interventions for precision therapies in neurodegeneration.
Disease-Specific Mechanisms	Distinct features observed across disorders: Aβ–ROS cycle in AD, α-synuclein–ROS in PD, and huntingtin-mediated trafficking disruption in HD.	Alzheimer's: Aβ; Parkinson's: α-synuclein; Huntington's: mutant huntingtin	Highlights need for both shared strategies (redox regulation) and disease-specific interventions.

5. CONCLUSION

This study underscores the interdependent roles of mitochondrial dysfunction and oxidative stress as central hallmarks of neurodegenerative disorders and demonstrates the value of a systems biology approach in unraveling their complexity. By integrating multi-omics datasets with computational modeling, the framework identified key mitochondrial complexes, particularly complexes I and III, as major ROS producers, while also revealing redox regulatory hubs such as Nrf2, SOD2, and PGC-1α as critical modulators of neuronal resilience. The analysis further highlighted the pathological cross-talk between mitochondrial dysfunction and protein aggregation, emphasizing cycles such as Aβ–ROS in Alzheimer's disease and α-synuclein–ROS in Parkinson's disease. Importantly, therapeutic predictions suggested that mitochondria-targeted antioxidants, metabolic modulators, and gene regulatory activators could provide significant neuroprotective benefits. While these findings advance mechanistic understanding, they also pave the way for precision medicine strategies that address both shared and disease-specific pathways in neurodegeneration. Looking forward, expanding computational models to single-cell resolution, integrating data from patient-derived iPSC neurons, and leveraging machine learning for drug repurposing will be essential to enhance predictive accuracy and translational impact. Collectively, this work provides a comprehensive framework that bridges molecular insights with therapeutic opportunities, offering a promising path toward biomarker discovery and the development of next-generation interventions for neurodegenerative diseases.

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