

Ionic-network dysregulation in the brain: Mechanisms, diseases, and therapeutic strategies

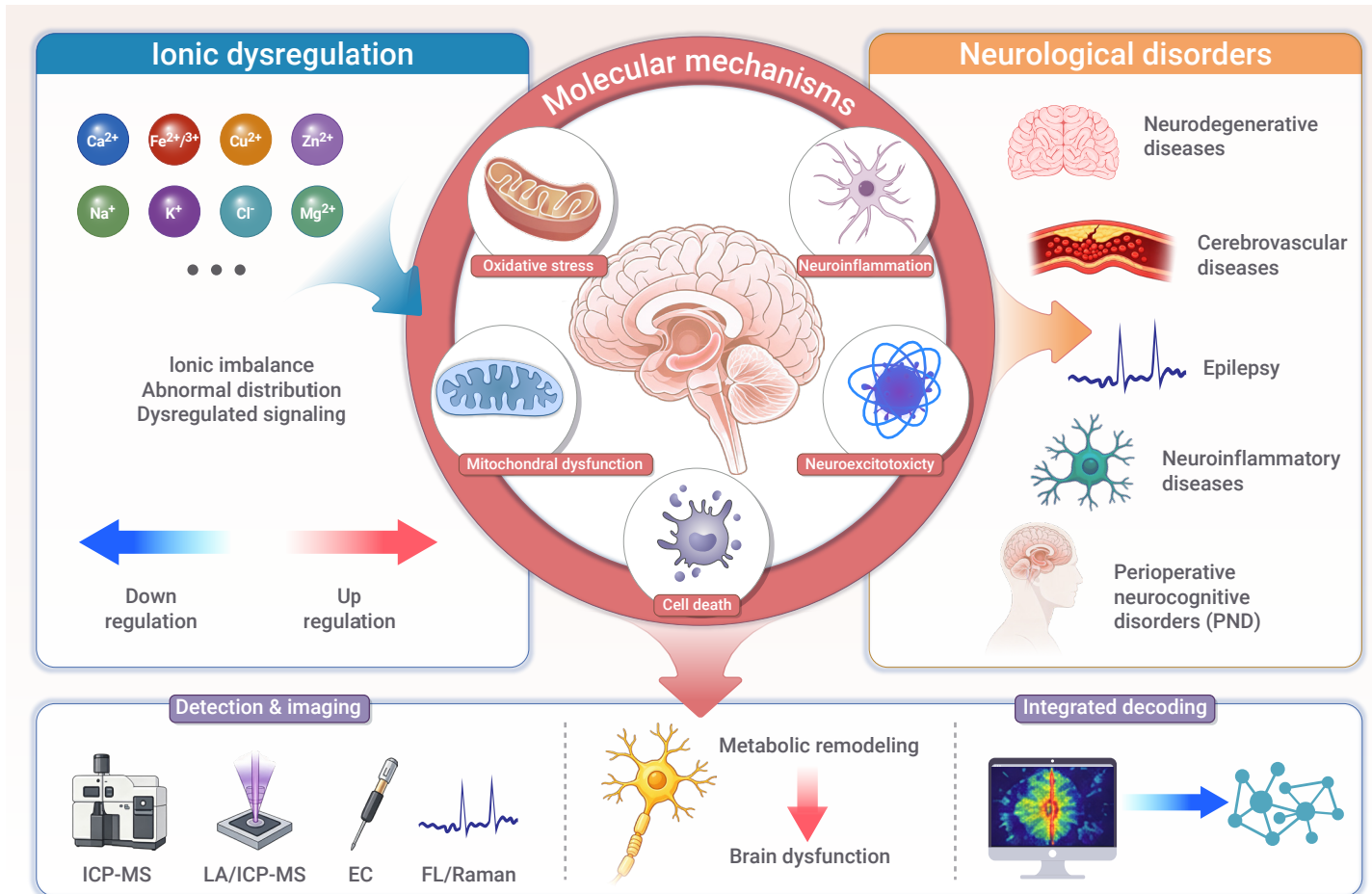
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Ion imbalance is a key molecular event in many neurological disorders.
- Altered Ca²⁺, Fe^{2+/3+}, Cu^{+/2+}, Zn²⁺, Na⁺, K⁺, Cl⁻, and Mg²⁺ disrupt brain function.
- Shared ionic mechanisms link neurodegeneration, stroke, epilepsy and perioperative cognitive disorders.
- Artificial intelligence may help decode multidimensional ion networks in brain diseases.
- Existing therapies target parts of ionic network, but ionomics-guided strategies remain emerging frontiers.

Ionic-network dysregulation in the brain: Mechanisms, diseases, and therapeutic strategies

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Ionic homeostasis is a fundamental organizing principle of brain function, supporting electrical signaling, metabolic coupling, cellular communication, and neurovascular stability. Ionic-network dysregulation has emerged as an important mechanism of neurological diseases. Herein, we review the physiological architecture of brain ionic homeostasis and its dynamic organization across spatial and temporal scales. We then discuss the involvement of ionic network dysregulation in pathological cascades, including excitability imbalance, mitochondrial injury, redox stress, metal-dependent cell death, protein misfolding, neuroinflammation and barrier dysfunction and their involvement in representative neurological diseases. Furthermore, we discuss the potential role of multimodal chemical analysis and artificial intelligence in decoding ionic characteristics in neurological diseases. Finally, we review established and experimental therapies targeting ion channels, redox pathways, metal dyshomeostasis and chloride transport. This review provides an integrated framework for understanding ionic-network dysregulation as both a driver of neurological disease and a promising target for precision diagnosis, risk stratification, and mechanism-guided intervention.

INTRODUCTION

The brain depends on ionic gradients more intensely than most organs. Major inorganic ions, including calcium (Ca^{2+}), sodium (Na^+), potassium (K^+), chloride (Cl^-), magnesium (Mg^{2+}), iron ($\text{Fe}^{2+/3+}$), copper ($\text{Cu}^+/\text{Cu}^{2+}$), and zinc (Zn^{2+}) are essential for maintaining membrane potential, action potential propagation, synaptic transmission, and neuronal excitability in the brain.^{1–3} Specifically, millisecond Na^+ influx and K^+ efflux generate action potentials; Ca^{2+} microdomains couple electrical activity to neurotransmitter release and gene transcription; Cl^- gradients determine whether GABAergic transmission is inhibitory or depolarizing; Mg^{2+} gates NMDA receptor activity and supports ATP-dependent metabolism, and $\text{Fe}^{2+/3+}$, Cu^{2+} and Zn^{2+} act as redox-active or coordination-active cofactors in mitochondrial respiration, antioxidant defense, neurotransmitter synthesis and protein folding.⁴ These ions are not independent biochemical variables. They are coupled by membrane transporters, electrochemical gradients, intracellular organelles, glial buffering and vascular exchange. The neural ionic network can therefore be viewed as a multiscale system that maintains and dynamically redistributes inorganic ions among synapses, the cytosol, intracellular organelles, the extracellular space, glial compartments, and cerebrospinal fluid, as well as across the blood-brain barrier (BBB).⁵

Ionic-network dysregulation is increasingly recognized as impaired spatial, temporal or cell-specific ion regulation, rather than an isolated change in the absolute concentration of a single ion. Accumulating evidence indicates that ionic-network dysregulation is a key and multifaceted contributor to downstream neuropathological processes. Examples include mitochondrial Ca^{2+} overload leading to neuronal injury,⁶ copper dyshomeostasis associated with oxidative and proteotoxic stress,⁷ dysregulated Zn^{2+} signaling affecting protein homeostasis and neuroinflammation,⁸ and altered Na^+ , K^+ , or Cl^- transport disrupting neuronal excitability and network synchronization. These ionic dysregulations may be an initiating lesion in channelopathies and acute ischemic energy failure, an amplifying mechanism in protein aggregation, mitochondrial dysfunction, and neuroinflammation, and a downstream consequence in substantial cellular damage.

In clinical settings, however, conventional biochemical assays and bulk

elemental analyses generally provide average measurements. They therefore offer limited information about ion distributions within brain regions, cellular and subcellular microenvironments⁹. Recent advances in analytical and imaging technologies have provided new opportunities for spatial ionomics and dynamic molecular sensing in the central nervous system.^{10,11} In parallel, therapeutic strategies targeting ionic dysregulation are increasingly being explored, ranging from modulation of ion channels, transporters and exchangers to regulation of metal accumulation, mitochondrial Ca^{2+} overload, and oxidative stress. Together, mechanistic dissection of ionic regulation and the development of ion-targeted interventions may provide new opportunities for understanding, monitoring and treating neurological diseases.

In this review, we describe the physiological functions and spatial and temporal dynamics of ionic homeostasis across brain regions, neural cell types and subcellular structures. We then examine the major pathophysiological processes through which ionic-network dysregulation damages the brain and apply this framework to four clinically important disease groups: neurodegenerative diseases, cerebrovascular disorders, epilepsy, and perioperative neurocognitive disorders (PND). Finally, we discuss the role of multimodal chemical analysis and artificial intelligence in advancing the study of disease-associated ionic regulation and therapeutic strategies that already target ionic mechanisms and those that remain preclinical or experimental.

PHYSIOLOGICAL IONIC HOMEOSTASIS IN THE CENTRAL NERVOUS SYSTEM

Physiological functions of major ionic modules in the brain

The electrical module is built primarily from Na^+ , K^+ , Cl^- and signaling Ca^{2+} . Voltage-gated Na^+ and K^+ channels initiate and shape action potentials. Voltage-gated Ca^{2+} channels trigger neurotransmitter release, and Cl^- transporters determine the polarity of GABAergic currents. The energy-dependent Na^+/K^+ -ATPase restores Na^+ and K^+ gradients after neuronal firing, and NKCC1 and KCC2 are essential chloride co-transporters for the maintenance of Cl^- homeostasis in neural cells.¹²

The metabolic and redox module is governed largely by Ca^{2+} , Mg^{2+} , $\text{Fe}^{2+/3+}$, Cu^{2+} and Zn^{2+} .¹³ Mitochondrial Ca^{2+} uptake couples neuronal activity to ATP production, but sustained loading promotes mitochondrial dysfunction and cell death.¹⁴ Mg^{2+} stabilizes ATP and nucleic acids and modulates NMDA receptor gating. Fe supports mitochondrial oxidative metabolism and oligodendrocyte-dependent myelination, but can become toxic when labile iron drives Fenton chemistry and lipid peroxidation.¹⁵ Cu supports cytochrome c oxidase, superoxide dismutase and dopamine beta-hydroxylase, yet excess or mislocalized Cu can promote oxidative stress, mitochondrial proteotoxicity and cuproptosis-like mechanisms.¹⁶ Similarly, synaptic Zn^{2+} modulates glutamatergic transmission and supports metalloenzymes and transcriptional regulation, whereas dysregulated Zn^{2+} signaling contributes to synaptic dysfunction and protein aggregation.⁸

These two modules are closely interconnected under pathological conditions. For example, during ischemic energy failure, ATP depletion impairs the Na^+/K^+ -ATPase, disrupts Na^+ and K^+ gradients, and promotes depolarization and Ca^{2+} influx. Subsequent mitochondrial Ca^{2+} overload further reduces ATP production and increases oxidative stress, which may be amplified by labile Fe, mislocalized Cu, and Zn^{2+} redistribution. The resulting oxidative damage to channels, transporters, and membranes then further destabilizes neuronal electrical activity. Thus, Ca^{2+} can act as a major interface between electrical signaling and metabolic regulation.¹⁷

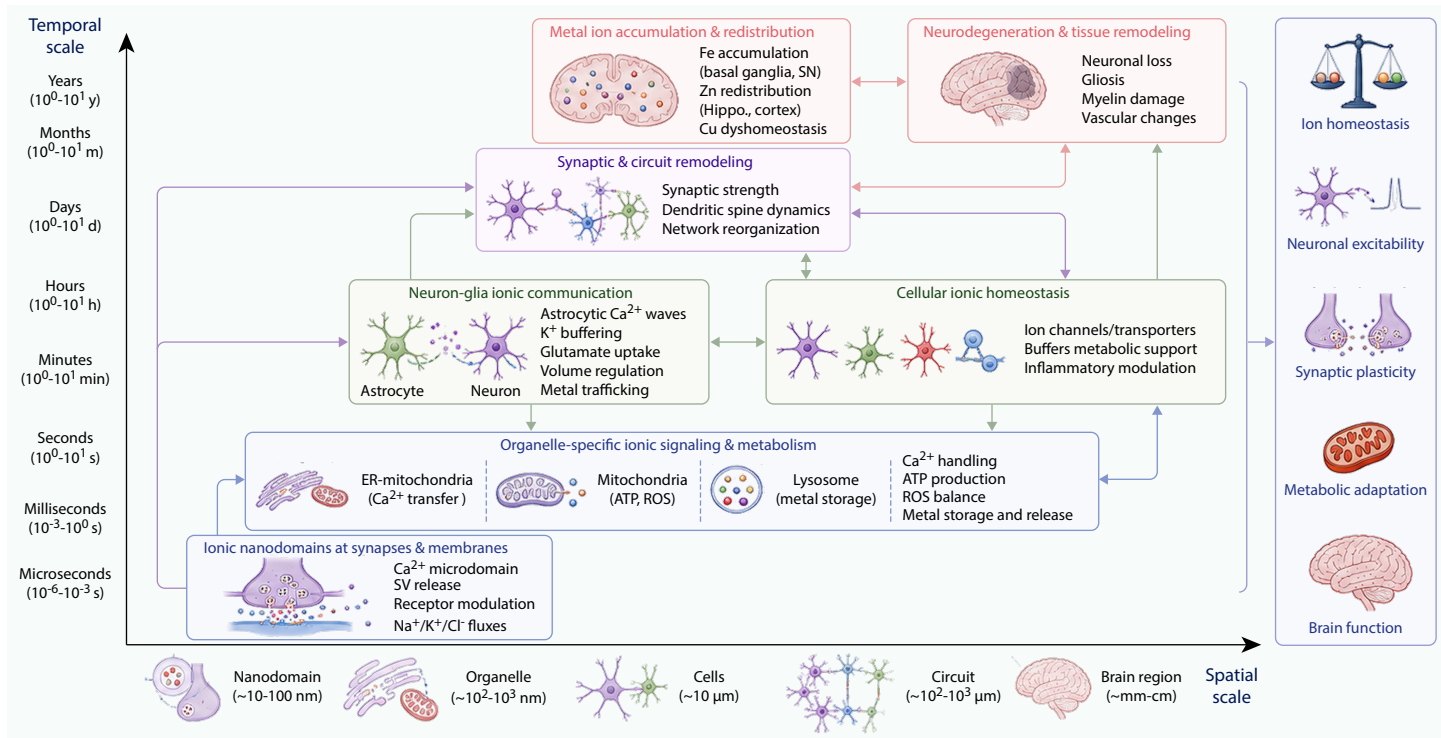


Figure 1. Multiscale organization of ionic homeostasis in the brain

Spatial and temporal dynamics of ionic homeostasis in the brain

Ionic homeostasis in the brain is spatially compartmentalized and temporally organized, linking synaptic nanodomains, organelles, cells, circuits, and brain regions (Figure 1). At the smallest scale, local Ca^{2+} nanodomains near voltage-gated Ca^{2+} channels, NMDA receptors and intracellular release sites couple electrical activity to vesicle fusion, receptor modulation, dendritic integration and activity-dependent gene expression.¹⁸ These spatially restricted signals allow neighboring synapses or organelles to carry different ionic states even within the same neuron.

Ionic regulation at the organelle level provides another layer of spatial control. The endoplasmic reticulum (ER) acts as a major Ca^{2+} store, whereas mitochondria convert Ca^{2+} uptake into changes in ATP production, redox balance and cell-death thresholds.¹⁹ ER-mitochondria contact sites, often referred to as mitochondria-associated membranes (MAMs), form local Ca^{2+} transfer hubs that connect neuronal activity with bioenergetic demand.²⁰ Lysosomes provide an additional compartment for Ca^{2+} and metal handling, linking ionic homeostasis to autophagy, endolysosomal trafficking, and interorganelle communication.²¹

At the cellular and regional scales, ionic homeostasis varies among cell types and brain regions. Neurons generate rapid Na^+ , K^+ , Ca^{2+} and Cl^- fluxes, whereas astrocytes buffer extracellular K^+ , clear glutamate, regulate water movement and shape local Ca^{2+} and cAMP signaling. Microglia, oligodendrocytes and vascular cells further contribute to local ionic and metabolic states.²² Essential metals also show regional organization: $\text{Fe}^{2+/3+}$ is enriched in metabolically active regions such as the basal ganglia and substantia nigra, while Zn-rich glutamatergic terminals are abundant in the hippocampus and cortex.²³ This heterogeneity may contribute to the selective vulnerability of brain regions to systemic or molecular stress in neurodegenerative and cerebrovascular disorders.

The temporal dynamics of ionic homeostasis span microseconds to years. Millisecond-scale ion fluxes initiate action potential and neurotransmitter release. Changes occurring over seconds to minutes regulate synaptic gain, astrocytic buffering, vascular responses, and metabolic support.²⁴ Over hours to days, altered transporter expression, mitochondrial Ca^{2+} handling, ER stress, and metal storage can remodel neuronal and glial phenotypes after seizures, ischemia, inflammation, or anesthetic stress. Over months to years, persistent redistribution of Fe, Cu and Zn, together with altered Ca^{2+} , K^+ or Cl^- handling, may reinforce protein aggregation, myelin damage, gliosis and

vascular remodelling.²⁵ Thus, ionic disturbance becomes pathological when local signals escape their normal spatial and temporal boundaries.

Intercellular and subcellular ionic communication networks in the brain

The multiscale pattern shown in Figure 1 depends on communication among neurons, glia, organelles and the neurovascular unit. This section focuses on two interfaces that organize ionic homeostasis: neuron-glia communication and neurovascular exchange. These interfaces prevent physiological ionic signaling from spreading into excitotoxic, inflammatory or metabolic stress.

Neuron-glia ionic communication. Astrocytes are key regulators of the extracellular ionic environment. During neuronal firing, they take up extracellular K^+ through channels including Kir4.1, remove glutamate through excitatory amino acid transporters and coordinate water movement through aquaporin-dependent pathways.²⁶ These functions keep neuronal membranes within a narrow excitability range and limit spillover excitation. Astrocytic Ca^{2+} and cAMP signals further allow astrocytes to integrate local synaptic activity and modulate synaptic efficacy, although the timing and functional meaning of astrocytic Ca^{2+} signals remain context dependent.^{27,28}

Microglia add an immune-sensing layer to this network. Extracellular ATP, K^+ efflux, Ca^{2+} signals, protons and redox-active metals can influence microglial motility, phagocytosis and inflammasome activation.²⁹ Ionic dyshomeostasis can therefore function as a tissue-level signal that recruits innate immune responses and alters the extracellular environment surrounding neurons and astrocytes. Cell-specific vulnerability depends on intrinsic ion-handling capacity and reliance on glial support. Neurons with sustained firing, extensive axons, high Ca^{2+} and metabolic demands may be more vulnerable to cell death when astrocytic K^+ and glutamate clearance is impaired and microglial inflammatory signaling is increased.^{30,31}

Neurovascular ionic coupling and blood-brain barrier regulation. The BBB and neurovascular unit form the interface between systemic physiology and the ionic microenvironment of the brain. Endothelial cells, pericytes, astrocytic endfeet and basement membrane components regulate water, pH, Na^+ , K^+ , Cl^- , Ca^{2+} and metal movement across the vascular interface.³² In vivo evidence indicates that astrocytic Ca^{2+} signaling amplifies functional hyperemia and neurovascular coupling during sustained neuronal activation.³³ This mechanism links activity-dependent ionic and glial signaling to local blood flow and metabolic support.

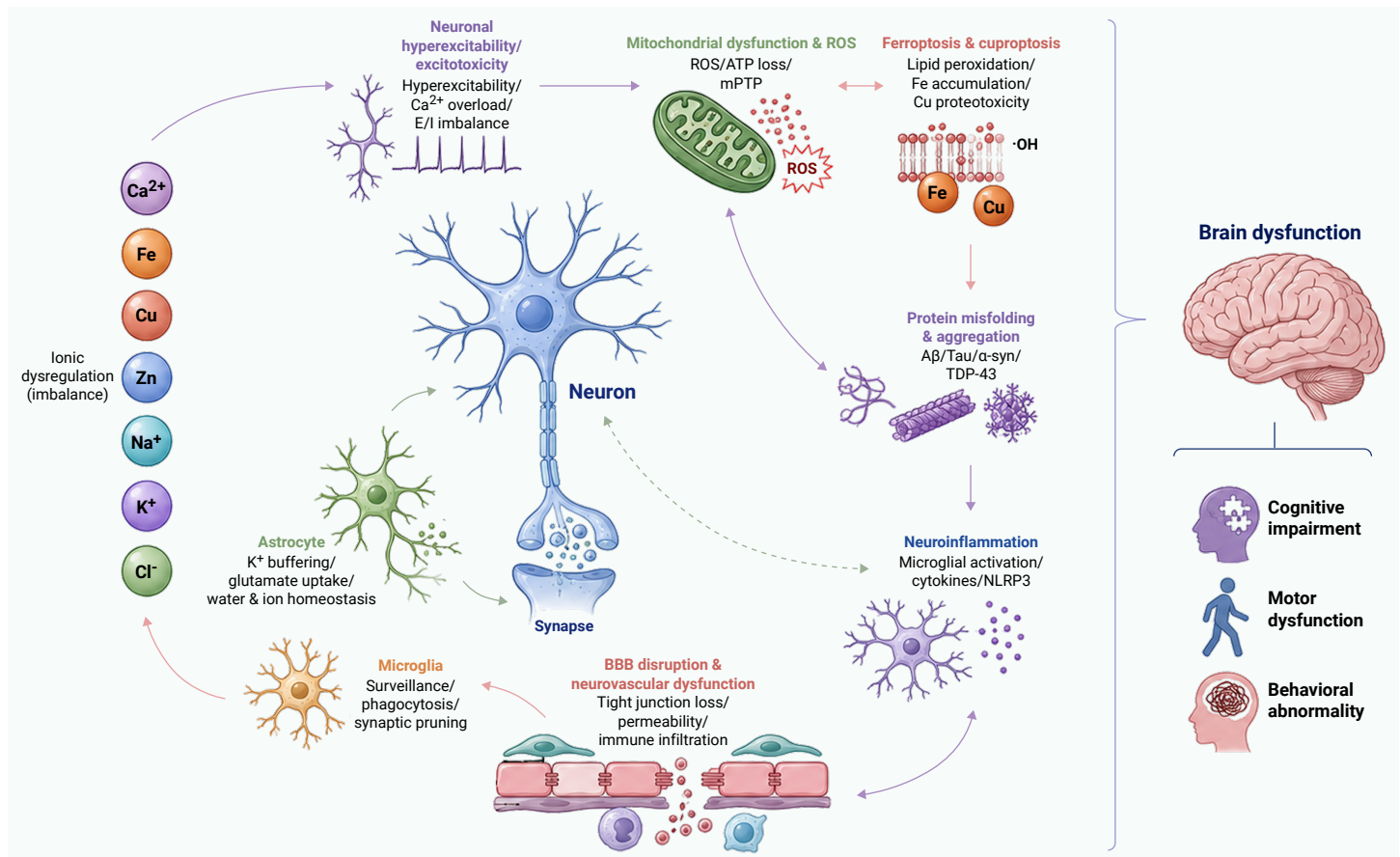


Figure 2. Molecular and cellular mechanisms linking ionic dysregulation to brain dysfunction

BBB-mediated ionic regulation is clinically relevant because the barrier helps maintain ionic, fluid, and metabolic homeostasis in the central nervous system. Disruption of BBB endothelial transport and junctional integrity has been associated with Alzheimer's disease (AD) and vascular cognitive impairment, and may increase the vulnerability of neural tissue to edema, inflammatory mediators and altered metal handling after vascular injury.^{34–36} Thus, BBB dysfunction is not merely a downstream consequence of ionic-network dysregulation but may serve as a permissive interface through which vascular disturbances exacerbate neuronal and glial stress.

IONIC-NETWORK DYSREGULATION AND MOLECULAR MECHANISMS OF BRAIN DYSFUNCTION

Neuronal hyperexcitability and excitotoxicity

Neuronal excitability is one of the earliest functional readouts of ionic-network dysregulation (Figure 2). Under physiological conditions, Na⁺ influx, K⁺ efflux, Ca²⁺ entry and Cl[−] gradients cooperate to generate action potentials while preserving excitation-inhibition balance. Disruption of these gradients promotes neuronal hyperexcitability, excessive glutamatergic signaling and aberrant network synchronization, thereby increasing seizure susceptibility and excitotoxic injury.³⁷

Ca²⁺-dependent excitotoxicity provides a well-characterized mechanistic link between ionic-network dysregulation and neuronal injury. Excessive activation of NMDA receptors, Ca²⁺-permeable AMPA receptors or voltage-gated Ca²⁺ channels drives protease activation, nitric oxide production, mitochondrial stress and synaptic impairment.³⁸ Recent studies have further implicated excitotoxicity as a key driver of amyotrophic lateral sclerosis (ALS) and age-related neurodegeneration, especially when combined with mitochondrial dysfunction and ferroptosis-like oxidative injury.^{39,40}

Dysregulation of Na⁺, K⁺, and Cl[−] reinforces these processes. Na⁺/K⁺-ATPase disruption during ischemia raises extracellular K⁺ and lowers the threshold for neuronal firing.⁴¹ Impaired astrocytic K⁺ buffering further amplifies extracellular K⁺ accumulation and sustained depolarization.⁴² At inhibitory

synapses, KCC2 downregulation or NKCC1 upregulation increases intracellular Cl[−], weakening hyperpolarizing GABA signaling and shifting networks toward excitation.⁴³ This places Cl[−] transport as an important modulator of circuit instability in epilepsy and other forms of neurological injury.

Neuronal hyperexcitability is increasingly recognized as one mechanism by which ionic-network dysregulation may contribute to brain dysfunction. In early AD, dysfunctional inhibitory microcircuits in the neocortex have been found to mediate progressive retrograde amnesia, whereas ALS involves cortical and motor-neuron hyperexcitability.⁴⁴ In stroke and traumatic brain injury, acute pump failure and extracellular K⁺ accumulation accelerate spreading depolarization.⁴⁵ In PND, systemic inflammation and anesthetic stress may lower the threshold at which vulnerable circuits lose excitation-inhibition balance.⁴⁶

Oxidative stress and mitochondrial dysfunction

Mitochondria translate ionic stress into cellular metabolic dysfunction. Physiological mitochondrial Ca²⁺ uptake supports tricarboxylic acid-cycle activity and ATP production. Sustained Ca²⁺ loading, however, can cause membrane depolarization, permeability transition, respiratory-chain impairment, and excessive production of reactive oxygen species (ROS).⁴⁷ Postsynaptic mitochondria are particularly important because they couple local Ca²⁺ transients to the energetic demands of synaptic transmission and plasticity.⁴⁸

Transition metals can modify mitochondrial vulnerability, although their effects depend on concentration, localization, and cellular context. Fe is required for iron-sulfur clusters and electron transport, whereas excess labile Fe can promote oxidative and lipid damage.⁴⁹ Cu supports cytochrome c oxidase and antioxidant enzymes, but Cu dyshomeostasis can impair respiratory proteins and mitochondrial quality control. Zn regulates synaptic and antioxidant pathways, whereas excessive Zn accumulation can impair respiration, promote mitochondrial depolarization, and contribute to neurodegeneration.⁵⁰ These convergent effects explain why oxidative stress is not merely a downstream consequence of ionic dysregulation, but a feedback amplifier

of channel dysfunction, ATP depletion and glial activation. The pathogenic significance of this feedback loop is broad. AD, Parkinson's disease (PD), stroke, epilepsy, and perioperative neurocognitive disorders all show different combinations of Ca^{2+} overload, mitochondrial stress, redox imbalance and metal redistribution. The shared pattern supports a network view in which mitochondria act as a convergence point for multiple ionic insults rather than as a single downstream organelle.

A current frontier is the compartment-specific nature of mitochondrial stress. Ca^{2+} entry at synapses, ER-mitochondria contact sites and axonal mitochondria may have different consequences for ATP supply, ROS production and cell survival.⁴⁷ This distinction matters because a global measurement of mitochondrial dysfunction can obscure the local failure that destabilizes synapses or axons first. Future studies that combine organelle-resolved Ca^{2+} imaging, redox sensors and spatial metal mapping may help distinguish reversible adaptation from progression toward irreversible injury.

Ferroptosis and iron-dependent lipid peroxidation

Ferroptosis is a regulated form of cell death driven by iron-dependent lipid peroxidation, marked by massive iron-induced lipid oxidation, enhanced oxidative stress, and depletion of antioxidant defenses (Figure 3).⁵¹ Neural tissue may be particularly susceptible because it combines high oxygen consumption, abundant polyunsaturated membrane lipids, and region-specific iron enrichment. The core pathway involves an expanded labile $\text{Fe}^{2+/3+}$ pool, Fenton chemistry, and peroxidation of phospholipids containing polyunsaturated fatty acids. The accumulation of lipid peroxides in the cellular membrane can increase its permeability and ultimately lead to cell rupture.⁴⁹ The system Xc^- -glutathione-GPX4 axis remains the canonical protective pathway. Reduced cystine uptake, glutathione depletion or GPX4 inactivation allows lipid hydroperoxides to accumulate.⁵² More recent work has also expanded this framework by identifying GPX4-independent antioxidant systems, including FSP1-CoQ10 and mitochondrial dihydroorotate dehydrogenase pathways.^{53,54}

In neurological disease, ferroptosis links metal dyshomeostasis to excitotoxicity, mitochondrial injury and inflammation. During ischemic stroke, ATP depletion and mitochondrial dysfunction promote ionic collapse and oxidative stress, whereas hemorrhage adds a direct source of hemoglobin-derived iron that can drive lipid peroxidation and ferroptosis-related secondary injury.⁵⁵ In parallel, abnormal regional distributions and concentrations of iron are also common features of chronic neurodegenerative diseases.⁵⁶ Emerging experimental evidence also suggests that anesthetic and perioperative stress can disturb brain iron handling and activate ferroptosis-related pathways in vulnerable hippocampal circuits.⁵⁷

Translating these mechanisms into therapy will require greater cellular and mechanistic specificity. Iron chelation, radical trapping and lipid-peroxidation blockade can be protective in experimental models, but neurons, oligodendrocytes, astrocytes and endothelial cells may not share the same ferroptotic threshold. Moreover, ferroptosis can overlap with excitotoxicity, mitochondrial permeability transition, inflammatory pyroptosis and necroptosis. It may therefore be more informative to assess ferroptosis as a measurable lipid-redox component of a broader ionic pathology network than as an isolated cell-death label.

Cuproptosis and copper-dependent cell death

Copper (Cu) is an essential micronutrient and catalytic cofactor for cytochrome c oxidase, superoxide dismutase, dopamine β -hydroxylase, and ceruloplasmin.⁵⁸ The same redox and coordination chemistry that makes Cu useful also makes it hazardous when transport, chaperoning or storage fails. Copper dyshomeostasis can promote oxidative stress, disturb mitochondrial respiration and alter protein folding and superoxide dismutase 1 (SOD1) function (Figure 3).

Cuproptosis provides a more specific mitochondrial model of copper toxicity. In the canonical pathway, excess intracellular Cu binds lipoylated tricarboxylic-acid-cycle proteins, promotes their aggregation and destabilizes iron-sulfur cluster proteins, leading to proteotoxic stress and cell death.⁵⁹ This mechanism is conceptually relevant to the nervous system because neurons and glia depend heavily on oxidative metabolism. However, the contribution of canonical cuproptosis to common neurological disorders remains less

established *in vivo* than that of ferroptosis. Cu dyshomeostasis has a well-established role in Wilson disease and has also been implicated in neurodegenerative disorders and stroke.⁶⁰ Further studies must distinguish canonical cuproptosis from broader forms of Cu-mediated oxidative injury, mitochondrial dysfunction, and proteinopathy. Spatial Cu imaging, markers of lipoylated protein aggregation, and cell-type-specific models could help determine whether and where canonical cuproptosis occurs *in vivo*.⁷

Protein misfolding

Protein misfolding and aggregation are defining pathological features of many neurodegenerative disorders.⁶¹ Disrupted metal ion homeostasis and abnormal metal-protein interactions linked to protein aggregation are characteristic features of multiple neurodegenerative disorders. Metal ions can reshape protein conformation, redox state, oligomer formation and clearance. In tauopathies and synucleinopathies, studies showed that metal ions such as Fe, Cu and Zn can significantly accelerate tau and α -synuclein aggregation via different binding modes, and promote the formation of amyloid fibrils with distinct morphologies.⁶² Dysregulated Fe, Cu and Zn in the brain has been recognized as a precursor event for amyloid- β plaques aggregation.⁶³ These processes place metal dyshomeostasis upstream of classical protein misfolding.⁶⁴ Moreover, the relationship is bidirectional. Amyloid-beta oligomers can disturb Ca^{2+} handling and synaptic function, α -synuclein aggregates can compromise mitochondria and lysosomes, and impaired lysosomal acidification can reduce aggregate clearance.⁶⁵ In PD, recent work has emphasized the interaction between α -synuclein and iron import, export and speciation, linking protein aggregation to local metal chemistry and oxidative stress.⁶⁶ This section therefore frames protein aggregation as an active participant in the ionic pathology network. Aggregates alter membranes, organelles and glial responses, while ionic and metal stress accelerates the formation of toxic oligomers. This feedback helps connect excitotoxicity, mitochondrial dysfunction, ferroptosis, cuproptosis-like stress and neuroinflammation.

The most important pathological species may also differ by disease and stage. Soluble amyloid-beta oligomers are strongly linked to synaptic Ca^{2+} dysregulation, while fibrillar deposits may act as longer lasting inflammatory and metal-binding reservoirs. Tau pathology can destabilize microtubules and axonal transport, indirectly impairing mitochondrial and lysosomal ion handling.⁶⁷ Nuclear magnetic resonance (NMR)-based studies show that α -synuclein interacts weakly but specifically with several metal ions, including Ca^{2+} , $\text{Cu}^+/\text{Cu}^{2+}$, Mn^{2+} and Zn^{2+} , and that these interactions induce metal-specific conformational perturbations in distinct regions of the protein, providing a plausible structural basis by which local metal chemistry may modulate α -synuclein self-assembly and aggregation propensity.⁶⁸ These differences argue against a single metal-protein mechanism for all neurodegenerative disorders.

Neuroinflammation

Neuroinflammation can propagate local ionic stress into tissue-level pathology.⁶⁹ Microglia and astrocytes sense extracellular ATP, K^+ efflux, Ca^{2+} signals, protons, ROS, oxidized lipids, protein aggregates and metal redistribution (Figure 4). These cues alter surveillance, phagocytosis, cytokine release and synaptic pruning. For example, exposure to uremic conditions impairs calcium homeostasis in microglia, enhances microglial potassium efflux via the calcium-dependent channel $\text{K}_{\text{Ca}3.1}$, and induces p38-MAPK associated IL-1 β maturation in microglia.⁷⁰ Thus, ionic disturbance functions as a damage signal, not merely as a neuronal electrophysiological event. K^+ efflux is especially important because it is a convergent trigger for NLRP3 inflammasome activation.^{71,72} Ca^{2+} overload, mitochondrial ROS and oxidized lipids further lower the threshold for inflammasome assembly and cytokine maturation.⁷³ Although specific inflammasome pathways vary by cell type and disease, ionic disturbances can initiate and sustain inflammatory amplification.

Inflammatory signaling can in turn modulate ionic homeostasis. Experimental evidence indicates that pro-inflammatory cytokines and oxidative stress can modulate neuronal and glial ion homeostasis by regulating Na^+/K^+ -ATPase activity, potassium channel function, and NMDA receptor excitability, thereby increasing susceptibility to neurological diseases.^{26,74} Reactive astro-

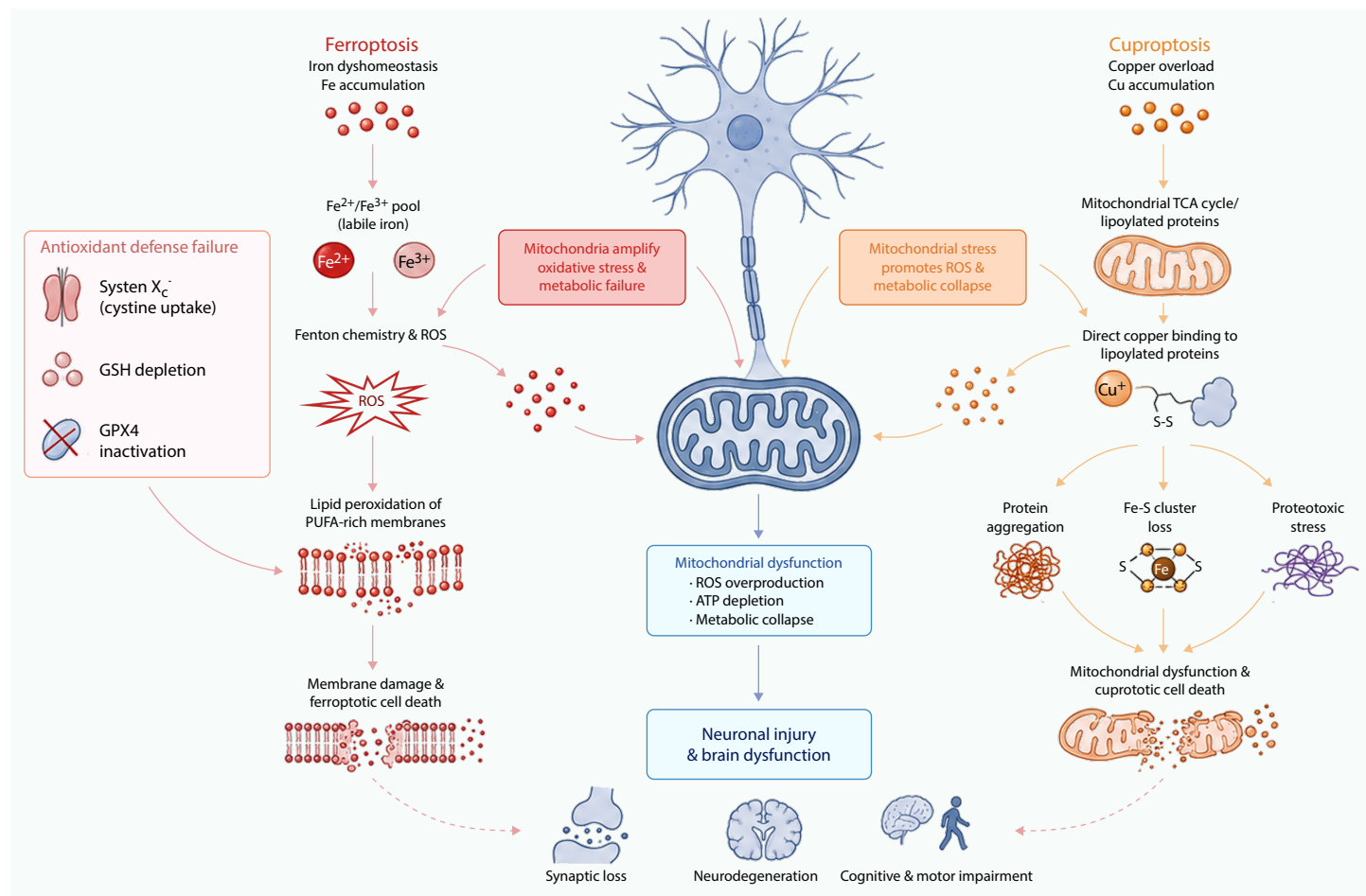


Figure 3. Metal-dependent cell death pathways in neurological disorders

cytes are often associated with impaired K^+ spatial buffering due to reduced Kir channel function and decreased glutamate uptake via downregulation of EAAT transporters.⁷⁵ In parallel, activated microglia can enhance oxidative stress through ROS production and contribute to local metal dyshomeostasis, including iron accumulation and altered redox-active metal handling.⁷⁶ This feedback loop explains why persistent neuroinflammation can maintain disease progression even after the initiating ionic insult has passed. This bidirectional relationship is particularly relevant to aging and perioperative stress. Aging, as a high risk factor for neurodegenerative disease, reduces mitochondrial reserve, weakens proteostatic clearance and increases basal inflammatory tone.⁷⁷ In perioperative and systemic inflammatory conditions, these pre-existing vulnerabilities may facilitate maladaptive glial activation and prolong neuroimmune responses.^{78,79} In this setting, suppressing cytokines alone may be insufficient when extracellular K^+ , glutamate, ATP, lipid-peroxide and metal environment continue to drive immune signaling.

Blood-brain barrier disruption and neurovascular ionic dysfunction

The BBB is often described as a selective physical barrier and regulatory interface for the ionic network (Figure 4).⁸⁰ Brain endothelial cells, pericytes, astrocytic endfeet, basement membrane components, and closely associated immune cells form the neurovascular unit, which continuously adjusts the exchange between the circulation and the central nervous system.⁸¹

BBB disruption also alters the exposure of neural tissue to metals and other blood-derived factors. After hemorrhage or vascular injury, hemoglobin-derived iron and other redox-active blood products can intensify lipid peroxidation and ferroptotic injury.^{82,83} In chronic neurodegeneration and vascular dementia, altered endothelial ion channels and transporters may weaken barrier function, disturb metal handling and impair neurovascular coupling.³⁴ For patients with aging-related barrier fragility, this neurovascular disturbance can lower the threshold for postoperative cognitive decline, which may

explain why peripheral physiological stress becomes translated into cognitive impairment.^{81,84}

BBB dysfunction interacts bidirectionally with ionic and inflammatory pathology. Ionic dyshomeostasis promotes protein aggregation and immune activation, whereas inflammatory mediators and proteases damage the BBB in neurodegenerative diseases.³⁴ Barrier breakdown can then disrupt transport, metal distribution, nutrient supply, and waste clearance. Neurovascular ionic dysfunction may therefore actively propagate cellular injury across brain tissue.

The BBB also provides measurable targets for disease monitoring and treatment.⁸⁴ Dynamic contrast imaging, permeability markers, endothelial transporter profiling and quantitative susceptibility mapping can help connect vascular damage with metal redistribution and tissue vulnerability.⁸⁵ Therapeutically, strategies that stabilize endothelial junctions, restore astrocytic endfoot function or limit iron-driven vascular oxidative injury may complement neuron-centered interventions.^{81,86} Such combined approaches may be particularly relevant to mixed neurodegenerative and vascular pathologies, in which ionic dysfunction spans neurons, glia, and the neurovascular unit.

IONIC-NETWORK DYSREGULATION IN NEUROLOGICAL DISORDERS Neurodegenerative diseases

Neurodegenerative diseases are characterized by chronic failure of ionic buffering, metal metabolism and proteostatic clearance. In AD, amyloid-beta and tau pathology interact with Ca^{2+} dysregulation, mitochondrial stress and metal dyshomeostasis. Recent experimental studies further support metal dyshomeostasis as an active contributor of AD progression. Aron et al. reported that endogenous brain lithium is significantly reduced in MCI and AD, and that A β further sequesters lithium.⁸⁷ In AD mouse models, lithium deficiency aggravated A β deposition, tau phosphorylation, microglial inflammation, myelin and synaptic loss, and cognitive decline, suggesting lithium as

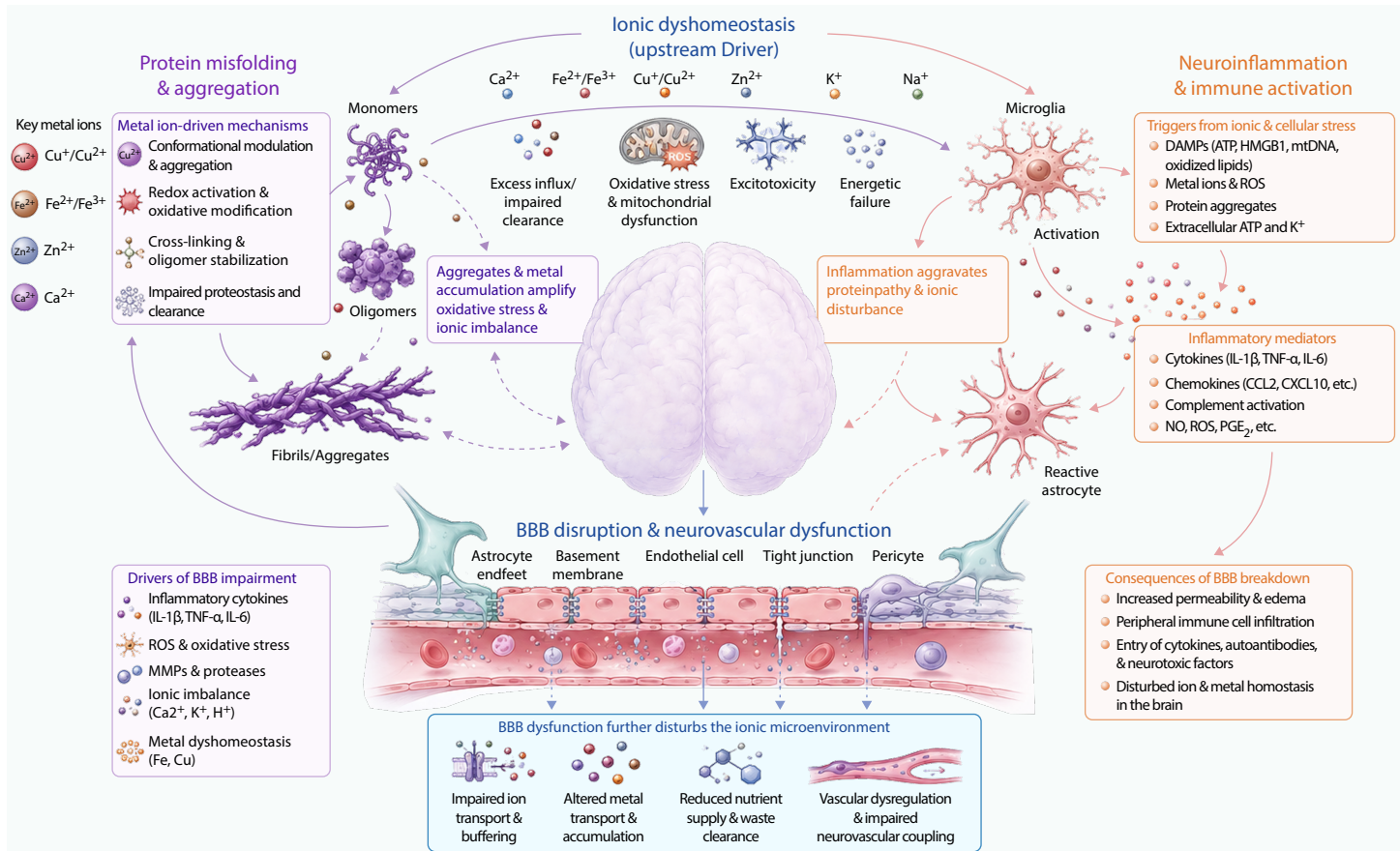


Figure 4. Protein misfolding, neuroinflammation and BBB dysfunction related to ionic-network dysregulation

a newly recognized metal factor linking aging, A β pathology and cognitive resilience.⁸⁷ Fe deposition can promote lipid peroxidation and ferroptosis, which are pathological features of AD and are closely linked to the onset of cognitive dysfunction.^{25,64} Deng et al. demonstrated that artemisinin inhibited neuronal ferroptosis in AD models by targeting KEAP1 and activating the Nrf2-SLC7A11-GPX4 axis, highlighting iron-dependent lipid peroxidation as a metal-related injury pathway with translational potential in AD.⁸⁸ Therefore, maintaining trace element homeostasis represents a promising strategy for both prevention and treatment of AD, although achieving precise and safe modulation of metal levels remains a key translational challenge.

In PD, iron enrichment in the substantia nigra and related basal ganglia circuits is a prominent ionic abnormality. Quantitative susceptibility mapping has become an important imaging approach for studying iron-sensitive changes in PD, although it remains a biomarker of tissue susceptibility rather than a direct readout of labile iron toxicity.⁸⁹ Recent experimental studies have reinforced a central role of iron dysregulation in PD. Nigrostriatal iron accumulation has been shown in human and primate models and correlates with dopaminergic neuron loss and disease severity.⁹⁰ Iron-loaded microglia exhibit enhanced oxidative stress and increased susceptibility to ferroptosis, thereby amplifying dopaminergic neurotoxicity in experimental models.⁹¹ Genetic manipulation of neuronal iron uptake pathways, such as transferrin receptor deficiency in dopaminergic neurons, induces progressive neurodegeneration and motor deficits in mouse models, indicating that iron bioavailability imbalance itself can drive PD-like pathology.⁹² Consistently, ferroptosis has been identified as a convergent mechanism linking iron accumulation, lipid peroxidation and neuronal death, and pharmacological inhibition of ferroptosis confers neuroprotection in preclinical PD models.⁹³

ALS is characterized by the degeneration of motor neurons in spinal cord, motor cortex and brainstem.⁹⁴ Cortical and motor neuron hyperexcitability, glutamate excitotoxicity, mitochondrial dysfunction and impaired metal handling can converge on selective motor neuron vulnerability. Standing on these premises ionic homeostasis dysregulation has been assumed to repre-

sent one of the main triggers of the pathological cascade that culminates in motor neuron loss.⁹⁵ Clinical data from a Chinese ALS cohort suggest that lower serum Ca²⁺ and higher serum Mg²⁺ levels are associated with worse functional status, and serum Mg²⁺ is related to an extended survival time in sporadic ALS.⁹⁶ At the molecular level, Cu and Zn are directly relevant to SOD1 maturation and antioxidant function, whereas mutant or improperly matured SOD1 can misfold and engage downstream pathways involving mitochondrial dysfunction, excitotoxicity, oxidative stress and neuroinflammation.⁹⁷ In multiple sclerosis (MS) and related demyelinating conditions, ionic-network dysregulation is more closely linked to axonal conduction failure, mitochondrial energy deficit, Ca²⁺-dependent axonal injury and inflammatory demyelination.⁹⁸ Across these diseases, the shared theme is that regional vulnerability reflects a combination of ionic load, energy reserve, glial support and proteostatic capacity.

Cerebrovascular disorders

Cerebrovascular disorders such as stroke provide a classic acute example of disrupted ionic homeostasis. During ischemic stroke, oxygen and glucose deprivation rapidly depletes ATP and weakens Na⁺/K⁺-ATPase-dependent ion gradients. The resulting neuronal and astrocytic depolarization increases extracellular K⁺, glutamate release and Ca²⁺ influx, promoting excitotoxicity, cytotoxic edema and downstream cell death pathways.⁹⁹ In the penumbra, spreading depolarizations further amplify injury by repeatedly increasing ionic and energetic demand in tissue with limited metabolic reserve.^{100,101}

Ca²⁺ overload and mitochondrial dysfunction then lead to acute electrical failure and cell death. Excessive Ca²⁺ entry through NMDA receptors, voltage-gated channels and damaged membranes promotes mitochondrial permeability transition, ROS production and protease activation.¹⁰² Recent reviews emphasize that calcium dysregulation remains central to neuronal death in ischemic stroke, but therapeutic translation requires better timing and cell-type specificity. Metal-dependent injury is especially important after reperfusion and hemorrhage. In ischemic stroke, ferroptosis links iron handling, lipid

peroxidation, mitochondrial stress and BBB injury. In intracerebral hemorrhage, hemoglobin degradation increases local iron burden and drives oxidative lipid damage around the hematoma.¹⁰³ In the hemorrhagic transformation after intravenous thrombolysis, endothelial cell ferroptosis has been shown as a main promoter of BBB breakdown.¹⁰⁴

The neurovascular unit determines whether local ionic injury remains restricted or spreads across brain tissue.^{105,106} Endothelial ion channels and transporters regulate water, pH, Na⁺, K⁺, Cl⁻, Ca²⁺ and metal movement across the BBB. Disruption of the BBB allows immune mediators, thrombin, hemoglobin products and redox-active metals to enter parenchyma. Related neurovascular and ionic disturbances also occur in cerebral small-vessel disease, vascular dementia, and mixed vascular-neurodegenerative pathology.¹⁰⁷

Epilepsy

Epilepsy is the disease group in which ionic-network dysregulation most directly appears as circuit dysfunction. Many epilepsies arise from altered Na⁺, K⁺, Ca²⁺ or Cl⁻ channel and transporter function.¹⁰⁸ Voltage-gated Na⁺ channels promote action-potential initiation, Ca²⁺ channels regulate transmitter release and dendritic excitability, and K⁺ channels set repolarization and firing frequency. Genetic or acquired disruption of K⁺ channels can therefore promote repetitive firing and network hypersynchrony.¹⁰⁹

Cl⁻ homeostasis is another core mechanism. KCC2 downregulation, NKCC1 upregulation or local Cl⁻ microdomain dysfunction weakens inhibition and can make GABAergic signaling less effective.¹¹⁰ This mechanism also contributes to acquired epilepsy after injury, inflammation, or prolonged seizures, when transporter expression and neuronal Cl⁻ gradients can be remodeled. Moreover, glial and vascular ionic regulation also participate in shaping seizure threshold.¹¹¹ Studies have found that both astrocyte Kir4.1 channels and gap junctions play important roles in regulating the concentration of extracellular potassium and inducing spontaneous epileptic activity.¹¹² Functional Kir4.1 in astrocytes limits activity-dependent rises in extracellular K⁺ and restricts glutamate diffusion out of synaptic clefts. Loss of Kir4.1 buffering capacity causes concurrent buildup of interstitial K⁺ and glutamate, which acts synergistically to promote pathological synchronized bursting across neuronal circuits.¹¹³ Recurrent seizures can also disrupt BBB integrity, activate microglia and increase cytokine signaling, which further modifies ion channels and promotes synaptic loss.¹¹⁴

Additionally, repeated seizures recruit the downstream mechanisms described in Section 3. Ca²⁺ overload, mitochondrial ROS, Zn redistribution and inflammatory signaling can damage hippocampal and cortical circuits.¹¹⁵ These interacting processes cannot be fully explained by dysfunction of a single ion channel. This may partly explain why antiseizure drugs targeting Na⁺ or Ca²⁺ channels can control seizures but do not always prevent epileptogenesis or associated cognitive impairment.

Perioperative neurocognitive disorders

Perioperative neurocognitive disorders (PNDs) are common complications following surgery, especially in elderly patients.⁷⁸ Surgery, anesthesia, pain, sleep disturbance and systemic inflammation can induce perturbations of ion homeostasis. For example, deep isoflurane anesthesia suppresses Na⁺/K⁺-ATPase activity, slows extracellular potassium clearance and causes its accumulation, implying isoflurane disrupts brain ion homeostasis.¹¹⁶ In young or resilient brains, ATP-dependent transport, organellar sequestration, glial buffering, and neurovascular exchange may contain physiological ionic fluctuations. In the aging brain, however, BBB disruption, mitochondrial dysfunction, impaired cellular stress responses and chronic inflammation reduce this compensatory reserve, allowing ionic disturbances to persist and amplify metabolic and inflammatory stress.¹¹⁷ Consequently, in older patients or those with pre-existing neurodegeneration, the same perioperative challenge may exceed the brain's ionic and metabolic reserve.¹¹⁸

Mitochondrial dysfunction is increasingly recognized as an important contributor to the pathophysiology of PND.¹¹⁹ Anesthetic and surgical stress can alter mitochondrial Ca²⁺ handling, oxidative phosphorylation, mitophagy and ROS production. These changes reduce ATP-dependent ion-pump capacity and impair synaptic plasticity in hippocampal and cortical circuits. For example, Hou et al. found that dexmedetomidine alleviated cognitive

deficits in PND rats by preserving mitochondrial calcium homeostasis and mitigating mitochondrial dysfunction.¹²⁰ Recent reviews therefore frame postoperative cognitive dysfunction as a disorder of neuroinflammation coupled to mitochondrial and metabolic failure, rather than as a direct toxic effect of one anesthetic exposure.¹²¹

Iron homeostasis and ferroptosis provide another potential mechanistic link. General anesthetics such as ketamine and sevoflurane can induce hippocampal iron dyshomeostasis, iron overload and ferroptosis, thereby leading to mitochondrial dysfunction and cognitive decline in PND models.¹²² Moreover, Ge et al. using radiation micro-X-ray fluorescence (μ -XRF) demonstrated that sevoflurane caused iron overload in the brain of 15-month-old mice, which induced oxidative stress and impaired mitochondrial function that further led to glucose metabolism disorder and reduced ATP production.¹²³ These results suggest that iron balance and glucose metabolism homeostasis may play an important role in PND. In parallel, isoflurane-associated PND shows typical features of ferroptosis, including decreased GPx4 and elevated lipid peroxidation. Liproxstatin-1, an inhibitor of lipid peroxidation, can alleviate neuronal injury and inflammatory responses and improve cognitive performance in isoflurane-exposed aged mice.¹²⁴ These changes can interact with Ca²⁺ overload, glutathione depletion and mitochondrial ROS, linking perioperative stress to the same metal-dependent death pathways.⁶⁴

Taken together, disease specificity in ionic-network dysregulation is determined not only by which ions are altered, but also by where, when, and in which cellular context these alterations occur. Iron accumulation in the substantia nigra may be particularly damaging in Parkinson's disease because dopaminergic neurons combine high oxidative burden, dopamine metabolism, and limited resilience to mitochondrial stress. In contrast, calcium dysregulation in Alzheimer's disease strongly interacts with synaptic failure and proteinopathy, whereas acute ionic collapse in stroke rapidly converts energy failure into excitotoxicity and edema. Epilepsy represents a circuit-level manifestation in which Na⁺, K⁺, Ca²⁺, and Cl⁻ disturbances directly reshape excitation-inhibition balance. In PND, aging-related loss of ionic and metabolic reserve may lower the threshold at which systemic stress becomes central cognitive dysfunction. Thus, similar ionic abnormalities generate distinct pathological outcomes through the interaction of regional vulnerability, cell-type-specific ion handling, metabolic demand, and compensatory capacity.

AI-ASSISTED MULTIMODAL NEUROLOGICAL IONIC NETWORK DECODING

Neurological diseases involve coordinated disturbances of Na⁺, K⁺, Ca²⁺, Cl⁻ and metal ions. However, it is still unclear how disturbed homeostasis of these elements is involved in the development and progression of neurological diseases. Ionomics aims to characterize these changes across brain regions, cell types and disease stages.¹²⁵ Advanced analytical techniques such as inductively coupled plasma mass spectrometry (ICP-MS) and XRF imaging are widely used in both clinical and experimental research for multi-element quantification in biological fluids and tissues.²⁹ ICP-MS-based analyses have confirmed alterations in brain metal content in occipital lobe samples following total joint arthroplasty, with increased concentrations of cobalt, titanium, manganese, and molybdenum being associated with higher odds of neuritic and diffuse plaque pathology.¹²⁶ X-ray fluorescence, including synchrotron XRF, provides complementary imaging capabilities with subcellular resolution in some configurations, and is non-destructive, preserving tissue morphology for subsequent histological analysis. Synchrotron μ -XRF studies have demonstrated region-specific and age-related accumulation of iron, copper, and zinc within the basal ganglia in aging brains, revealing that regional metal dyshomeostasis may be highly related to neurodegenerative diseases.¹²⁷ XRF mapping reveals extensive loss of K⁺ accompanied by Na⁺, Ca²⁺ and Cl⁻ accumulation in ischemic brain tissue.¹²⁸ Molecular probes, Raman/surface-enhanced Raman spectroscopy SERS platforms and electrochemical sensors may support more dynamic and minimally invasive measurements, but most remain at the preclinical or early translational stage. For example, nanopipette sensors have enabled *in vivo* monitoring of cerebral Cu²⁺ and Cl⁻ regulation in experimental models.¹²⁹⁻

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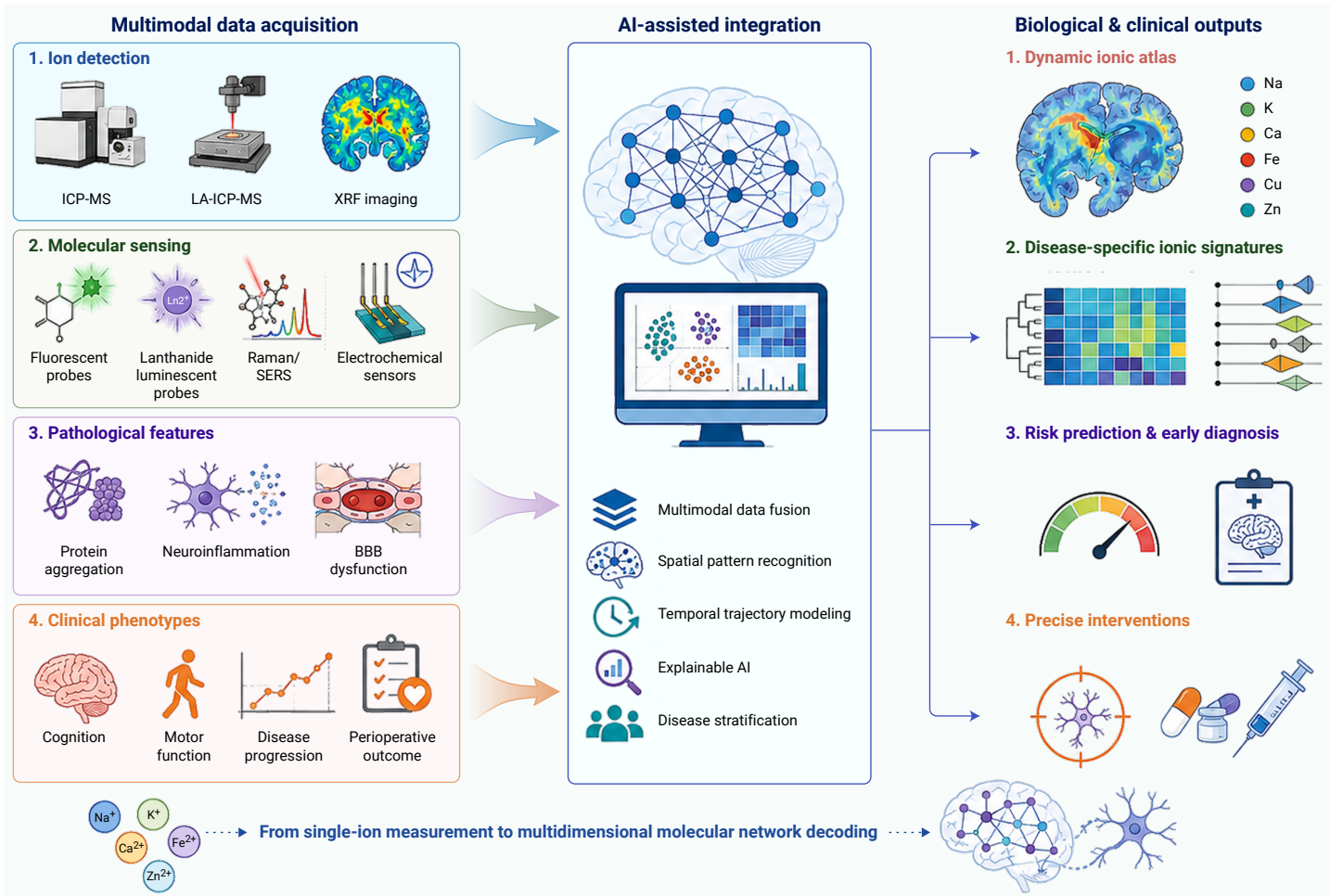


Figure 5. AI-assisted multidimensional decoding of ionic network in neurological disorders

Blood-brain barrier dysfunction, neuroimaging and clinical phenotypes (Figure 5). Self-supervised methods such as DeepION can extract spatial relationships among mass spectrometry ion images without extensive manual annotation.¹³¹ Structure-based deep learning models such as Metal3D can accurately predict metal-binding sites in protein structures, help to decode molecular interaction in diseases.¹³²

Clinically, multimodal integration could extend these approaches beyond single-modality ion analysis. Combining ionic measurements with neuroimaging, electroencephalogram, molecular biomarkers, pathological features, and clinical data may provide a more complete representation of disease progression. For example, multimodal AI models combining clinical, imaging and electroencephalographic data have been explored for seizure prediction.¹³³ Integrating AI with ionomics and multimodal biological data may ultimately enable a more comprehensive framework for understanding ion dysregulation in complex neurological disease.¹²⁵

Nevertheless, AI-assisted neuro-ionomics should currently be regarded as a hypothesis-generating and integrative framework rather than a standalone diagnostic solution. Major barriers include limited cohort size, differences in tissue processing and ion-imaging platforms, inconsistent spatial resolution across modalities, and the lack of standardized reporting for ionic datasets. In addition, deep-learning models trained on one disease cohort or analytical platform may not generalize to independent datasets. Explainable AI and external validation will therefore be essential to determine whether AI-derived ionic signatures reflect reproducible biological mechanisms rather than platform-specific artifacts. Future studies should prioritize harmonized data acquisition, cross-platform calibration, prospective validation, and mechanistic interpretation of model outputs.

THERAPEUTIC STRATEGIES TARGETING IONIC-NETWORK DYSREGU-

LATION

Therapeutic targeting of ionic-network dysregulation is potentially valuable because it contributes to neuronal hyperexcitability, mitochondrial dysfunction, oxidative injury and ferroptosis, yet this same centrality creates risk. Ions are indispensable for normal neuronal signaling and metabolism, so effective therapies must correct pathological ionic states preserving normal physiological functions.

The most clinically established strategy is the modulation of ion channels and neurotransmitter receptors (Table 1). Clinically established antiseizure medications provide representative examples of ionic modulation in neurological disease. Current epilepsy clinical guidelines recommend individualized antiseizure medication treatment strategy, with commonly used agents acting through Na^+ channel blockade carbamazepine, Ca^{2+} channel modulation ethosuximide, GABA_A receptor positive allosteric modulators benzodiazepines or NMDA receptor antagonists felbamate.¹³⁴ For moderate to severe dementia of the Alzheimer's type, memantine acts as a low-affinity NMDA receptor antagonist and is used to dampen pathological glutamatergic Ca^{2+} influx while preserving physiological synaptic transmission.¹³⁵ In aneurysmal subarachnoid hemorrhage, nimodipine remains a guideline-supported L-type calcium channel antagonist that improves functional outcomes and helps prevent delayed cerebral ischemia.¹³⁶ These examples highlight that ion-targeted therapies may act on both neuronal and vascular compartments, and their efficacy depends strongly on disease context and timing.

The second tier contains mitochondrial and redox-directed therapies that act downstream of ionic stress. Edaravone, approved for ALS therapy in several regions, is best viewed as a redox-modulating therapy that may reduce injury propagated by mitochondrial dysfunction and oxidative stress.¹³⁷ Evidence from a recent systematic review supports continued clinical interest, although effect size, patient selection and timing remain impor-

Table 1. Representative therapeutic strategies targeting ionic-network dysregulation in selected neurological diseases

Strategy class	Therapeutic targets	Representative agents	Targeted diseases	Level of evidence, clinical status, and major limitations
Ion-channel and receptor modulation	Voltage-gated Na ⁺ channels	Carbamazepine (Voltage-gated Na ⁺ channels blocker)	Epilepsy	Clinical evidence; guideline-supported therapy. Established antiseizure medicines recommended within individualized treatment strategies ¹³⁴
	T-type Ca ²⁺ channels	Ethosuximide (T-type Ca ²⁺ channels blocker)		
	GABA _A receptors	Benzodiazepines (GABA _A receptors positive allosteric modulators)		
	Pathological NMDA receptor-mediated Ca ²⁺ influx	Memantine (low-affinity, uncompetitive NMDA receptor antagonist)	AD	
	L-type Ca ²⁺ channels	Nimodipine (L-type Ca ²⁺ channels blocker)	Aneurysmal subarachnoid haemorrhage	
Mitochondrial and redox protection	Oxidative injury downstream of Ca ²⁺ overload and mitochondrial dysfunction	Edaravone (free-radical scavenger and redox modulator)	ALS	Clinical evidence; approved symptomatic treatment. Clinical benefit is generally modest, without established disease-modifying efficacy ¹³⁵
Metal-homeostasis modulation	Labile brain iron and iron-dependent oxidative injury	Deferiprone (membrane-permeable iron chelator)	PD and AD	Clinical evidence; guideline-supported therapy. Improves functional outcomes, although hypotension may limit treatment. Clinical evidence; approved in several regions. Reported benefits are heterogeneous and may be limited to selected patients ¹³⁷⁻¹³⁸⁻¹³⁶
Metal-homeostasis modulation	Heme-derived iron after intracerebral hemorrhage	Deferoxamine (high-affinity iron chelator)	Intracerebral hemorrhage	Clinical trials; no established efficacy. Failed to provide clinical benefit and was associated with worse clinical outcomes in PD and AD ¹³⁹⁻¹⁴⁰⁻¹³⁸
Ferroptosis inhibition	Fe-dependent lipid peroxidation and GPX4 failure	Ferrostatin-1 and liproxstatin-1 (radical-trapping antioxidants and ferroptosis inhibitors)	Experimental cerebral ischemia and rtPA-associated hemorrhagic transformation	Preliminary clinical evidence. No clearly significant overall treatment effect has been demonstrated ¹⁴¹
Chloride-homeostasis restoration	NKCC1 inhibition to reduce intracellular Cl ⁻ accumulation	Bumetanide (NKCC1 cotransporter inhibitor)	Adjunctive treatment of neonatal seizures	Preclinical evidence only ¹⁴²⁻¹⁴³⁻¹⁴¹

tant limitations.¹³⁸

The third-tier targets metal dyshomeostasis. Iron chelation has attracted particular attention because labile iron can promote Fenton chemistry, lipid peroxidation and ferroptosis. In randomized trials in early PD and AD, deferiprone reduced MRI-detectable brain iron but did not improve clinical outcomes; instead, motor disability worsened in PD and cognitive decline accelerated in AD.¹³⁹⁻¹⁴⁰ In the i-DEF trial, deferoxamine was acceptably safe after intracerebral hemorrhage but did not achieve the prespecified threshold for a clinically meaningful improvement in favorable 90-day functional outcome.¹⁴¹ Several explanations have been proposed. First, disease-associated iron elevation may include physiologically essential or adaptively sequestered iron. Its removal may therefore induce functional iron deficiency and disrupt iron-dependent processes, including iron-dependent tyrosine hydroxylase activity and dopamine synthesis. Second, the regional heterogeneity of brain iron deposition limits the effectiveness of non-targeted chelation, and a reduction in MRI-detectable iron may not reflect the removal of pathogenic iron in damaging pools. Third, systemic chelation may deplete peripheral iron stores and is associated with hematological toxicity, particularly neutropenia and agranulocytosis. These negative findings highlight the substantial challenges in translating metal-chelation therapies into clinical practice.

The fourth tier remains mostly preclinical or early translational, including strategy focused on ferroptosis and lipid-peroxidation pathways chloride homeostasis. Preclinical stroke studies suggest that ferroptosis inhibitors such as ferrostatin-1 or liproxstatin-1 analogues can reduce ischemic injury, BBB disruption or rtPA-associated hemorrhagic transformation.¹⁴²⁻¹⁴³ Related approaches include activation of GPX4, preservation of system Xc⁻ function, Nrf2 pathway activation and suppression of endothelial ferroptosis. NKCC1 inhibition and KCC2 enhancement aim to restore hyperpolarizing GABAergic inhibition by correcting intracellular Cl⁻ accumulation. Bumetanide has been

tested as an adjunctive therapy for neonatal seizures, and broader KCC2/NKCC1 targeting is being explored in epilepsy and neurodevelopmental disorders.¹⁴⁴⁻¹⁴⁵ However, limited brain penetration, systemic diuretic effects and cell-type specific roles of chloride transporters remain major obstacles.

OUTLOOK AND PERSPECTIVES

Ion homeostasis is increasingly recognized as an important factor in maintaining brain function. In neurological diseases, disruption of this ionic network can transform physiological signaling into pathological cascades that ultimately lead to brain dysfunction. The next phase of the field will depend on whether these cascades can be measured as networks rather than as isolated abnormalities.

One important direction is the construction of dynamic ionic atlases of the brain. Current maps remain incomplete at the level of cell type, organelle, microenvironment and disease stage. Spatial ionomics, molecular imaging, single-cell and spatial omics, and live ion sensing should be combined to define how Ca²⁺, Fe^{2+/3+}, Cu²⁺, Zn²⁺, Na⁺, K⁺, Cl⁻ and Mg²⁺ are organized under physiological and pathological conditions. Such atlases would clarify why specific brain regions or cell populations are vulnerable and when intervention is still reversible.

Another key challenge is the precise and dynamic monitoring of ionic networks in the brain. Many high-sensitivity platforms are endpoint assays, whereas ionic pathology is often transient and state-dependent. Future probes, optical sensors, electrochemical microsensors, implantable or wearable devices, and microfluidic platforms should aim to capture ionic fluctuations in defined circuits, vascular niches or organelles.^{129,146} The goal is not only higher resolution, but the ability to distinguish adaptation from injury. In acute neurological settings, such as stroke, epilepsy and perioperative brain monitoring, real-time ionic sensing may have significant clinical value by

supporting point-of-care risk assessment and time-sensitive therapeutic decision-making.

Equally important is the translational interpretation of ionic-network dysregulation in neurological diseases. Ionic therapies will be most successful when matched to patient subgroup, disease stage, anatomical compartment and measurable target engagement. AI-assisted multimodal models may help identify these therapeutic windows by linking ion signatures to pathology, prognosis and treatment response. However, shared standards for sample handling, imaging calibration, data reporting, external validation and model interpretability will be required before ionic signatures can become reliable clinical biomarkers.

In conclusion, ionic-network dysregulation provides a unifying but clinically actionable framework for neurological diseases. It connects membrane excitability, synaptic signaling, mitochondrial metabolism, metal homeostasis, ferroptosis, neuroinflammation and neurovascular integrity across spatial and temporal scales. By integrating spatial ionomics, dynamic sensing, AI-assisted decoding and mechanism-guided therapy, the field can move from descriptive imbalance towards earlier diagnosis, better risk stratification and precision intervention.

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S.H. searched the literatures and wrote the first draft. E.F. made the figures and revised the manuscript. L.X. proposed the concept of the review and revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not Applicable

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.