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REVIEW ARTICLE

Raman spectroscopy in the detection of trace elements and heavy metals associated with cognition and mood

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Abstract

Trace elements play essential roles in neural homeostasis by modulating energy metabolism, redox balance, neurotransmitter synthesis, and synaptic plasticity, processes directly related to cognition and mood. Elements such as zinc, iron, copper, selenium, iodine, and phosphorus act as enzymatic cofactors and regulators of neuronal excitability, while their imbalance has been associated with cognitive impairment, affective alterations, and increased vulnerability to neurodegenerative diseases. In contrast, heavy metals such as lead, mercury, cadmium, arsenic, aluminum, and bismuth are neurotoxic agents capable of triggering oxidative stress, neuroinflammation, mitochondrial dysfunction, and alterations in neurotransmission, thereby contributing to memory deficits, executive dysfunction, and symptoms of anxiety and depression. Given the need for methods capable of detecting early chemical alterations associated with metal dyshomeostasis, Raman spectroscopy has emerged as a promising analytical tool, as it enables the noninvasive identification of vibrational signatures related to biomolecules and metal–protein interactions in tissues and biofluids. In addition, surface-enhanced Raman spectroscopy (SERS) increases the sensitivity of the technique through metallic nanostructures, enabling detection at ultralow concentrations. The integration of Raman spectroscopy with machine learning methods has the potential to improve spectral pattern discrimination and to enable biomarkers capable of reflecting dysfunctional neurochemical states prior to clinical onset. Thus, Raman and SERS represent innovative approaches for investigating and monitoring the interface between metals, neurotoxicity, cognition, and mental health.

Keywords Trace elements · Heavy metals · Neurotoxicity · Cognitive function · Raman spectroscopy

Introduction

Trace elements play essential roles in neural homeostasis by modulating metabolic pathways, synaptic excitability, redox balance, neurotransmitter synthesis, and neuronal plasticity. Elements such as zinc (Zn), iron (Fe), copper (Cu), iodine (I), phosphorus (P), and selenium (Se) act as enzymatic cofactors, participate in oxidative phosphorylation, and modulate glutamatergic receptors, thereby influencing both cognitive function and affective and behavioral aspects [24, 39, 88, 94]. Zinc, which is highly concentrated in glutamatergic vesicles, regulates NMDA and AMPA receptors and is associated with learning, memory, and antidepressant mechanisms [25, 66, 75]. Fe and Cu are integral components of mitochondrial enzymes and oxidative systems, are essential for dopaminergic pathways and mood regulation, and their imbalance leads to oxidative stress, synaptic loss, and affective alterations [7, 8, 93].

Low concentrations of Zn and Se are correlated with major depression and anxiety, whereas elevated Cu levels may favor anxious states by modulating catecholaminergic enzymes involved in the synthesis of dopamine and norepinephrine [75]. Iron deficiency impairs frontostriatal dopaminergic pathways and is associated with apathy, fatigue, and progressive cognitive decline [6, 88]. Thus, both deficiency and excess of these elements may contribute to cognitive impairment and mood disorders.

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In addition to essential elements, heavy metals such as lead (Pb), mercury (Hg), cadmium (Cd), arsenic (As), aluminum (Al), and bismuth (Bi) can induce neurotoxicity through microglial inflammation, mitochondrial dysfunction, interactions with metallic centers of enzymes, and alterations in neurotransmission [36, 68, 80]. These metals have been associated with cognitive deficits, irritability, depression, aggressiveness, and an increased risk of neurodegeneration, including the accumulation of misfolded proteins and cortical damage [7, 9].

The need for methods capable of detecting these early chemical alterations has grown in parallel with the development of advanced analytical technologies. Raman spectroscopy enables noninvasive molecular characterization by identifying vibrational signatures of metal–protein bonds, redox states, and neuronal metabolites related to cognitive and affective dysfunction [14, 29, 34, 41]. Its variants, such as surface-enhanced Raman spectroscopy (SERS), increase sensitivity through the plasmonic resonance of metallic nanostructures, allowing detection of analytes at ultralow concentrations, including metallic microelements, blood biomarkers, and neurochemical compounds in biological fluids [27, 49, 64, 86].

Thus, understanding how trace elements and heavy metals modulate cognition and mood, and how such alterations can be detected by Raman spectroscopy, offers a promising approach for monitoring disease progression and evaluating therapeutic responses in neurochemical disorders.

Principles of Raman spectroscopy and SERS

Raman spectroscopy is based on the inelastic scattering of light, known as the Raman effect, in which a small fraction of the incident photons interacts with the molecular vibrations of the sample, undergoing energy shifts that reflect the vibrational modes of chemical bonds. The resulting spectrum constitutes a molecular fingerprint capable of revealing the chemical composition, structure, and conformational state of biomolecules [14, 23, 34, 41, 43]. During the interaction between light and matter, most photons are elastically scattered, whereas a minimal fraction undergoes Raman scattering, giving rise to Stokes bands, when the incident photon loses energy, and anti-Stokes bands, when energy is gained. These bands are characteristic of each chemical bond and confer high molecular specificity to the technique, enabling discrimination among compounds with similar structures, such as amino acids, lipids, and nucleotides [40, 41].

The technique employs a monochromatic laser, typically in the visible or near-infrared range, and sensitive detectors such as charge-coupled devices (CCD) to capture the resulting spectrum. In biological samples, the use of 785 or 1064 nm lasers is preferred to reduce background fluorescence interference, one of the main challenges of the technique [14]. Raman spectroscopy stands out for being noninvasive, requiring minimal sample preparation, and allowing rapid and reproducible analyses, features that make it promising for biomedical and clinical applications [40].

Despite these advantages, the spontaneous Raman signal is intrinsically weak, which led to the development of SERS, a high-sensitivity variant that uses nanostructured metallic surfaces, typically composed of gold, silver, or copper. These surfaces promote strong amplification of the local electromagnetic field through the excitation of localized surface plasmons, a phenomenon known as plasmonic resonance [49, 64, 86]. When a molecule is adsorbed onto or located in close proximity to these metallic nanostructures, a marked enhancement of the local electric field occurs, which amplifies the Raman signal and dramatically increases detection sensitivity. This amplification enables the identification of analytes present at extremely low concentrations, reaching single-molecule detection levels, making the technique particularly useful for studying complex biological systems and biomarkers in biofluids [67].

The SERS enhancement mechanism results from the combination of two complementary phenomena: the electromagnetic effect and the chemical effect. The former arises from the excitation of localized surface plasmons in metallic nanoparticles, which increase the electric field near the molecule and amplify the intensity of the scattered signal. The latter involves charge transfer between the analyte and the metallic surface, modifying molecular polarizability and, consequently, enhancing Raman scattering [49], [46]. This synergy between electromagnetic and chemical effects confers unparalleled sensitivity to SERS, enabling the detection of biomolecules, metallic trace elements, and metabolites with high spectral resolution and without the need for chemical reagents or fluorescent labeling (Sharma et al. 2012; [27].

The combination of high sensitivity, molecular specificity, and noninvasive characteristics makes Raman spectroscopy and its variants among the most promising tools for biomedical applications, particularly for the study of subtle chemical alterations associated with metabolic and neurodegenerative processes [34, 43, 65].

Trace elements and their role in cognition and mood

Trace elements play a fundamental role in maintaining neural homeostasis by modulating biochemical processes involved in synaptic plasticity, neurotransmission, and energy metabolism. Elements such as Zn, Fe, Cu, I, Se, P act as cofactors for enzymatic reactions, participate in oxidative phosphorylation, and regulate neuronal excitability, directly

influencing cognitive function and emotional behavior [24, 39, 88, 94].

At the molecular level, these elements are involved in key neurobiological pathways. Zn modulates NMDA and AMPA receptors and is highly concentrated in glutamatergic synaptic vesicles, playing a central role in learning and memory processes [25, 66]. Fe and Cu are essential for mitochondrial function and neurotransmitter synthesis, particularly in dopaminergic pathways, and their imbalance is associated with oxidative stress, synaptic dysfunction, and affective alterations [6, 7, 8, 93]. Se contributes to antioxidant defense through selenoproteins and redox regulation, while I is critical for thyroid hormone synthesis and neurodevelopment [56, 94].

Disruptions in trace element homeostasis are strongly associated with cognitive impairment and mood disorders. Deficiencies in Zi and Se have been linked to depression and anxiety, while excess copper may exacerbate oxidative stress and dysregulate catecholaminergic pathways [75]. Iron deficiency impairs frontostriatal dopaminergic signaling, contributing to attentional deficits, fatigue, and cognitive decline [6, 88]. Importantly, metal dyshomeostasis is not an isolated phenomenon but interacts with broader neurobiological mechanisms, including mitochondrial dysfunction, oxidative stress, and neuroinflammation, which are central to the pathophysiology of neuropsychiatric and neurodegenerative disorders [36, 68].

Evidence from experimental and clinical studies suggests that alterations in trace element levels may precede the onset of clinical symptoms, indicating their potential role as early biomarkers of cognitive and affective dysfunction [13]. These early biochemical changes are particularly relevant in the context of neurodegenerative diseases, where disruptions in metal homeostasis contribute to protein aggregation, synaptic loss, and progressive neuronal damage.

Given their central role in brain function, trace elements represent important targets for analytical approaches aimed at detecting early neurochemical alterations. In this context, Raman spectroscopy has emerged as a promising tool for identifying molecular signatures associated with metal dyshomeostasis. Studies have demonstrated that Raman-based techniques, especially when combined with machine learning algorithms, can discriminate biochemical patterns associated with neurodegenerative conditions and cognitive impairment in biological samples, supporting their potential as noninvasive biomarker strategies [29, 60, 65, 86] (Table 1).

Table 1 Trace elements: physiological roles, dysregulation mechanisms, neurological effects, and detection approaches

Element (Symbel)	Physiological role (essentiality)	Sources of exposure	Dysregulation mechanisms (deficiency or excess)	Neurological and behavioral effects
Iron (Fe)	Oxygen transport, mitochondrial function, neurotransmitter synthesis.	Red meat, leafy vegetables, fortified	Deficiency: impaired myelination, reduced dopamine. Excess: oxidative stress, ferroptosis.	Cognitive impairment, attention deficits, neurodegenetion.
Zinc (Zn)	Enzymatic cofactor, synaptic plasticity, neurotransmission.	Shellfish, meat, nuts, legumes	Deficiency: impaired synaptic function, reduced neurogenesis. Excess: oxidative stress, Cu dyshomeostasis.	• Learning deficits, depression, anxiety. • Learning deficits, depression.
Copper (Cu)	Redox reactions, neurotransmitter synthesis, iron metabolism.	Liver, shellfish, seeds, nuts	Deficiency: impaired myelination. Excess: ROS production.	• Cognitive decline, neurodegeneration. • Excess: thyroid dysfunction.
Selenium (Se)	Antioxidant defense, (selenoproteins), redox balance, thyoid function.	Fish, Brazil nuts, cereals, eggs	Deficiency: reduced antoxidant capacity. Excess: pro-oxidant effects.	• Mood disorders, cognitive decline, neuropathy. • Excess: thyroid dyfsfunction.
Iodine (I)	Thyroid hormone synthesis, neuro-development.	Iodized salt, seafood, dairy	Deficiency: hypotryhroidism. Excess: thyroid dysfunction.	• Cognitive impairment, developmental delay.
Phosphorus (P)	Energy metabolism (ATP), membrane structure, signaling.	Meat, dairy, grains,	Deficiency: impaired Excess: metabolic imbalance.	• Neuromuscular dysfunction, cognitive changes.

Overview of trace elements, including their physiological roles, dysregulation mechanisms, neurological effects, and detection approaches. Alterations in metal homeostasis are associated with oxidative stress, mitochondrial dysfunction, and neurobehavioral changes. Conventional and Raman-based detection methods are also summarized. Arrows and symbols indicate the balance between deficiency and excess states and their associated biological consequences

Heavy metals, neurotoxicity, cognition, and mood

Heavy metals are nonessential elements that can accumulate in the central nervous system, interfering with critical biochemical pathways, including redox homeostasis, synaptic signaling, and energy metabolism. Among the main metals associated with neurotoxicity are lead (Pb), mercury (Hg), cadmium (Cd), arsenic (As), aluminum (Al), and bismuth (Bi). Although they exhibit distinct mechanisms, these elements share common characteristics: high affinity for protein sulfhydryl groups, competition with essential metals, induction of oxidative stress, and mitochondrial dysfunction [36, 68, 80]. From a translational perspective, several of the metals discussed are relevant due to their documented exposure in human populations and their association with neurological disorders, including cognitive impairment, neurodevelopmental alterations, and neurodegenerative processes [21, 73, 79]. In addition, studies have shown that even low-level exposure to Pb, Hg, As, and Cd is associated with cognitive decline, impaired executive function, and increased risk of neurodevelopmental and neurodegenerative conditions [21, 73, 79]. These findings support the clinical relevance of the selected metals and justify their inclusion in the present review.

Pb is one of the most extensively studied heavy metals in the context of cognition, particularly during development, when it disrupts glutamatergic pathways, modulates NMDA receptors, and compromises synaptic plasticity. Chronic Pb exposure increases the expression of the NR2A subunit of the NMDA receptor in the hippocampus, affecting excitatory signaling and memory processes [51]. Structural synaptic alterations have also been described, including reduced density and complexity of dendritic spines in hippocampal neurons, which are associated with impairments in learning and memory [89]. From a biochemical standpoint, Pb induces oxidative stress and mitochondrial dysfunction in hippocampal neurons, contributing to neurodegeneration and cognitive decline [5]. Behavioral evidence confirms deficits in memory, attention, and executive function following prolonged Pb exposure, as well as emotional alterations linked to dopaminergic and hippocampal circuits [15, 83].

Hg, particularly in organic forms such as methylmercury (MeHg), affects dopaminergic and serotonergic systems in different brain regions, altering the profiles of dopamine, norepinephrine, serotonin, and their metabolites [21, 78], [87]. In addition, MeHg exposure is associated with cognitive deficits, motor alterations, and behavioral symptoms, including irritability, fatigue, and executive-like impairment in humans and animal models [22, 30, 50]. These effects largely result from mitochondrial damage, oxidative stress, and alterations in calcium handling in neurons, as well as synaptic dysfunction (including impaired vesicular glutamate uptake) and microglial activation with a persistent neuroinflammatory response [17, 18, 45, 76, 84].

Cd, although less studied in humans in the behavioral context, induces neuronal apoptosis, blood–brain barrier dysfunction, and inflammatory responses in the central nervous system. In rats, chronic Cd administration leads to hypotrophy and apoptosis of hippocampal neurons, associated with impaired recognition memory [58]. In human cerebral microvascular endothelial cells, Cd reduces cell viability and compromises functions related to blood–brain barrier integrity [37, 74], and in murine models, exposure promotes neuroinflammation with increased proinflammatory cytokines and glial activation [53, 54]. In animal models, Cd exposure is associated with memory deficits, depression-like behavior, and reduced hippocampal neurogenesis [44, 46, 85, 86, 92]. Mechanistically, Cd induces oxidative stress with alterations in antioxidant enzymes and mitochondrial damage in hippocampal tissue [47, 77] and interacts with Zn and Fe homeostasis, as supplementation with these metals attenuates Cd-induced oxidative stress and enzymatic alterations [33].

These metals interfere with the synthesis of dopamine, norepinephrine, and acetylcholine, in addition to impairing neurogenesis and synaptic plasticity. Their effects predominantly affect the hippocampus and striatum, contributing to memory deficits, emotional alterations, and an increased risk of late-onset neurodegeneration [55, 73, 79]. In dopaminergic systems, As reduces the expression of transporters and enzymes related to biosynthesis, affecting motivation, mood, and executive function [52, 81].

Al and Bi exhibit low elimination efficiency and can accumulate in nervous tissue. Al is associated with protein aggregation, altered membrane fluidity, and cholinergic dysfunction, contributing to progressive cognitive decline [20, 36]. Its presence in cortical and hippocampal regions is also related to microglial activation and increased reactive oxygen species, mechanisms described in etiological hypotheses of Alzheimer's disease [10, 82]. Bi can interfere with mitochondrial pathways and oxidative balance, contributing to neurofunctional impairment, as suggested by studies demonstrating Bi accumulation in cortical, cerebellar, and hippocampal neurons in cases of intoxication, with selective degeneration of CA1 neurons in organotypic rat hippocampal cultures and clinical signs of encephalopathy in humans [11, 48, 63, 70].

In addition, Bismuth oxide (Bi_2O_3) nanoparticles have been associated with the generation of reactive oxygen species, loss of cell viability, and activation of apoptotic pathways in different human cellular models, indicating a strong

potential to disrupt redox metabolism and mitochondrial integrity [3, 31]. In antitumor nanotechnology, Bi_2O_3 has also been reported to induce oxidative stress and inflammation in SH-SY5Y neuronal cell lines, further reinforcing its neurotoxic potential under experimental conditions [1].

Taken together, heavy metals disrupt neural networks involved in learning, memory, and emotional processing. The convergence of mechanisms such as oxidative stress, bioenergetic dysfunction, neuroinflammation, and neurotransmitter imbalance supports a biochemical interface between metal toxicity and cognitive and affective symptoms. This relationship underscores the need for analytical methods capable of identifying, monitoring, and correlating early chemical alterations with neuropsychological dysfunction, particularly at subclinical stages (Fig. 1).

Raman spectroscopy applied to cerebral bioelements and neurotoxic metals

Raman spectroscopy has become established as a powerful tool for the in situ and in vitro analysis of chemical signatures in brain tissue, enabling the detection of structural, molecular, and elemental variations induced by essential trace elements and heavy metals [26, 29, 35, 59, 71]. Conventional techniques for metal detection, such as atomic absorption spectroscopy (AAS), inductively coupled plasma mass spectrometry (ICP-MS), and X-ray fluorescence (XRF), provide high sensitivity and accurate quantification, however, they are generally limited by their destructive nature, extensive sample preparation, and lack of molecular and spatial information. In contrast, Raman-based approaches enable non-destructive, label-free analysis and provide insights into biochemical alterations associated with metal dyshomeostasis, rather than solely measuring elemental concentrations. These characteristics support the use of Raman spectroscopy as a complementary tool in neurobiological research [14, 40, 43]. As a vibrational technique based on the inelastic scattering of light, the method provides a highly sensitive molecular "fingerprint" capable of revealing subtle alterations in proteins, lipids, nucleic acids, and metallic components, central elements in the pathophysiology of neurotoxicity and in bioelement homeostasis [28, 29]. It is important to emphasize that Raman spectroscopy does not directly quantify most metal ions in biological systems, but rather captures indirect biochemical

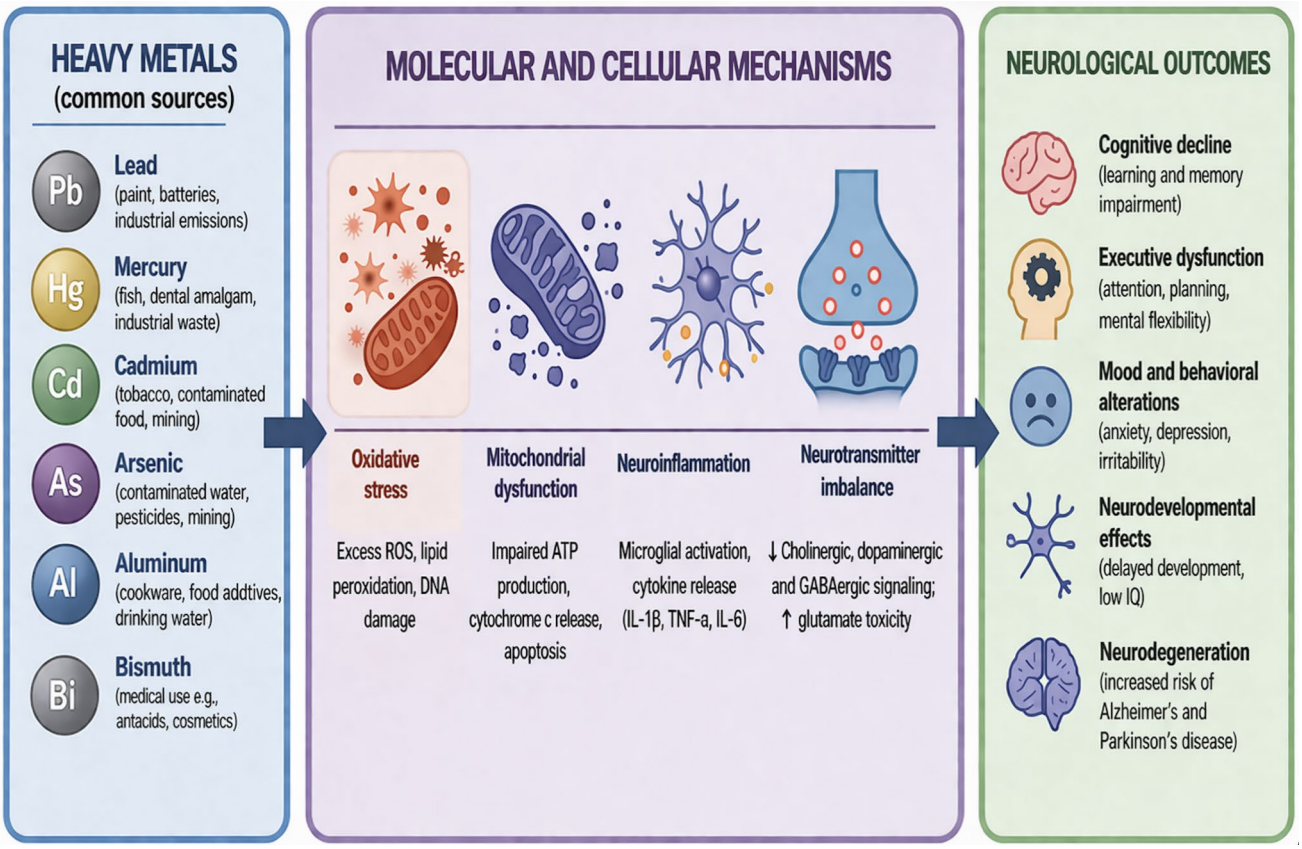

Fig. 1 Schematic overview of heavy metals, their neurotoxic mechanisms, and associated neurological outcomes. Metal exposure induces oxidative stress, mitochondrial dysfunction, neuroinflammation, and neurotransmitter imbalance, leading to cognitive and behavioral alterations

signatures reflecting metal–ligand interactions and downstream molecular alterations. Consequently, its interpretation in the context of metal dyshomeostasis relies on inferential analysis and often requires validation through complementary techniques such as mass spectrometry or atomic absorption spectroscopy [40, 41, 43, 61].

The use of Raman spectroscopy is particularly relevant in the study of cerebral bioelements because both trace elements and heavy metals modulate chemical structures that are detectable by Raman vibrations, such as phosphate groups, lipid chains, and protein motifs, which can be differentiated in normal and tumoral brain tissue [2, 38, 61]. SERS studies further demonstrate that metal ions such as Pb, Hg, Cd, As, and Zn can be detected with high sensitivity, reinforcing the potential of the technique for monitoring toxic metals and metallic microelements in biological samples [72, 90].

In parallel, studies on metal dyshomeostasis in neurodegenerative diseases show that Fe, Cu, Zn, and Al participate in pathways of oxidative stress, protein aggregation, and neuronal structural damage, processes that are reflected in changes in chemical signatures that can be explored by vibrational methods such as Raman spectroscopy [16, 19]. In addition, advances such as SERS have enabled the amplification of metallic microelement signals, making it possible to detect minute quantities of metals and their effects on the biomolecular organization of proteins and lipids in brain tissue [60]. The use of metallic nanoparticles as signal-enhancing substrates dramatically increases the sensitivity of Raman spectroscopy, generating enhancement factors on the order of 10^6 due to electromagnetic field effects in plasmonic "hot spots" [32, 57, 64]. These highly amplifying substrates allow early detection of chemical and structural perturbations in biomolecules, even before cellular damage becomes morphologically detectable [32, 64].

In the context of essential trace elements, studies demonstrate that Raman spectroscopy can identify vibrational patterns associated with the redox states of Fe and Cu, as well as reflect changes in Zn coordination in synaptic proteins and the presence of Se in antioxidant selenoproteins [12, 59, 61]. Alterations in these vibrational profiles have been correlated with impairments in memory, learning, and emotional regulation, suggesting that Raman spectroscopy may function as a tool for functional biomarker development [29, 69]. With regard to heavy metals, the technique is even more promising. Compounds of Pb, Hg, and Cd generate specific signatures associated with lipid peroxidation, oxidative protein damage, and nucleic acid modification, effects directly linked to cognitive decline, executive dysfunction, and mood disorders described in experimental models. Studies using brain tissue and biofluids show that Raman spectroscopy detects these toxic patterns with high sensitivity, indicating its utility in the noninvasive assessment of metal intoxication and in the identification of subclinical stages of neurotoxicity [29, 60].

The integration of Raman spectroscopy with machine learning approaches has significantly expanded its analytical and translational potential. Advanced algorithms, including support vector machines, random forests, and deep learning models, have been applied to Raman spectral data to improve pattern recognition and classification of complex biological signatures. These approaches enable the identification of subtle biochemical variations associated with metal dyshomeostasis, neurodegeneration, and cognitive impairment that may not be detectable through conventional spectral analysis alone [29, 42, 60, 65, 91]. Importantly, machine learning techniques facilitate the development of Raman-based digital biomarkers by integrating multidimensional spectral features into predictive models capable of distinguishing between physiological and pathological states. In neurobiological contexts, these models have demonstrated high accuracy in differentiating healthy and diseased tissues, as well as detecting biochemical alterations associated with toxic exposures and metabolic dysfunction [4, 29, 62].

Despite its growing potential, the clinical translation of Raman spectroscopy for the detection of metal-related neurotoxicity remains limited. Most current evidence is derived from experimental or small-scale studies, with a lack of robust validation in large and diverse human populations. Furthermore, the absence of standardized protocols for spectral acquisition, preprocessing, and analysis, combined with inter-study variability, poses a significant barrier to its integration into routine clinical practice. Consequently, large-scale, multicenter, and longitudinal studies are required to determine its diagnostic performance, reproducibility, and real-world applicability [14, 40, 43, 61].

Limitations and challenges of Raman-based metal detection

Despite its potential, Raman spectroscopy presents important limitations in the context of metal detection in neurobiological systems. First, the technique does not directly quantify most metal ions, but rather detects indirect biochemical signatures such as metal–ligand interactions and redox-related molecular changes, requiring validation with complementary analytical methods [14, 41, 43, 61]. Second, reproducibility remains a challenge, particularly in SERS-based approaches, due to variability in nanoparticle properties and experimental conditions [43, 49, 57, 64]. Third, the complexity of biological samples may lead to overlapping spectral features and reduced specificity, in addition to fluorescence interference that can compromise signal detection [14, 40, 41]. Furthermore, Raman spectroscopy is predominantly qualitative or semi-quantitative, limiting its

applicability for precise measurement of metal concentrations [43, 57, 61]. Finally, most current evidence remains preclinical, with a lack of standardized protocols and large-scale validation studies, which restricts its immediate clinical translation [14, 40, 43, 61]. Therefore, Raman spectroscopy should be considered a complementary tool within a multimodal analytical framework rather than a standalone method.

Conclusion

Taken together, Raman spectroscopy should not be viewed merely as a tool for chemical detection, but rather as a functional platform capable of capturing early biochemical signatures associated with alterations in metal homeostasis and neurobiological dysfunction. When integrated with advanced analytical approaches such as machine learning, this technique holds promise for the development of noninvasive, mechanism-based biomarkers for the early detection and monitoring of cognitive and affective disorders.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest. All authors read and approved the final manuscript.

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