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The importance of metabolomics in research into pathological processes leading to neurodegenerative diseases

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Abstract

Objective: The aim of this article is to review and analyse the current state of knowledge on the role of metabolomics in explaining the pathological processes underlying neurodegenerative diseases, in particular Alzheimer's, Parkinson's and Huntington's diseases. The analysis focuses on assessing the potential of this field in discovering early diagnostic biomarkers and identifying new therapeutic targets.
Materials and methods: A systematic review of the scientific literature was conducted using the PubMed, Scopus and Web of Science databases. The analysis included studies using mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy to profile metabolites in biological fluids (cerebrospinal fluid, plasma) and brain tissue from patients and preclinical models.
Results: Neurodegenerative diseases are characterised by common metabolic disorders, such as mitochondrial dysfunction, impaired energy metabolism and oxidative stress. Disease-

specific signatures have also been identified: xanthine metabolism disorders and impaired kynurenine pathway in Parkinson's disease, dysregulation of lipid (including ceramide and sphingolipid) and glucose metabolism in Alzheimer's disease, and early changes in the tryptophan/kynurenine pathway in Huntington's disease.
Conclusions: This work highlights the role of metabolic dysregulation as an early mechanism in the pathogenesis of Alzheimer's, Parkinson's, and Huntington's diseases. Metabolomics enables a systemic view of these disorders as disruptions of complex metabolic networks, providing a comprehensive picture of pathology rather than focusing on individual proteins. Its clinical potential includes the development of non-invasive biomarkers for early diagnosis and disease monitoring. Identification of key metabolic pathways, such as lipid and energy metabolism, also points to new therapeutic targets, forming the basis for precision medicine in neurodegenerative diseases.

Keywords: metabolomics, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Huntington's disease, metabolic biomarkers

1. Introduction

Neurodegenerative diseases (NDDs) are one of the greatest and ever-growing challenges to global public health. They are characterised by progressive loss of neurons in specific areas of the central nervous system, leading to irreversible motor, cognitive and behavioural disorders (Alzheimer's Association, 2023). These conditions, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), place a huge burden not only on patients and their families, but also on healthcare systems around the world (Bassett & Gazzaniga, 2011). Despite decades of intensive research, there is still a lack of therapies that can halt or reverse the neurodegenerative process, and the available treatments are mainly symptomatic, alleviating symptoms without addressing the cause of the disease (Alzheimer's Association, 2023).

One of the key problems in combating NDDs is the diagnostic dilemma. The disease is usually diagnosed at an advanced clinical stage, when significant and irreversible damage to nerve tissue has already occurred (Anderson, 2019). This long, latent preclinical period, lasting up to several years, represents a critical therapeutic window that remains unexploited d u e to the lack of appropriate diagnostic tools. There is therefore an urgent need to develop early, sensitive a n d specific biomarkers capable of detecting the pathology at its earliest, even asymptomatic, stages (Zacharias et al., 2022). Currently used methods, such as clinical assessment, costly neuroimaging techniques (e.g., PET) or invasive procedures (e.g., lumbar puncture to collect cerebrospinal fluid), have their limitations and are not suitable for large-scale screening (Vermunt et al., 2019). In response to these challenges, metabolomics – one of the youngest and most dynamically developing fields i n the "omics" sciences – is coming to the fore. It is defined as a comprehensive analysis of the metabolome, i.e. the complete set of small-molecule metabolites (usually with a molecular weight below 1.5 kDa) present in a biological system (Zampar et al., 2024). Metabolomics provides a direct "functional readout of the physiological state" of an organism, as metabolites are the end products of cellular processes (Ben-Shlomo et al., 2024). Changes i n their concentrations reflect the dynamic

interactions between genetic information (genome), its expression (transcriptome, proteome) and the influence of environmental factors such as diet or exposure to toxins (Ashton et al., 2021). This unique position makes metabolites extremely sensitive indicators of any disorders in cellular homeostasis, often appearing long before the clinical manifestation of disease (Brown et al., 2009).

The significance of metabolomics goes beyond that of just another diagnostic tool; it is a key link connecting genetic predisposition with environmental factors in shaping the final disease phenotype. Most cases of NDDs are sporadic rather than purely genetic, suggesting an important role for external factors in their aetiology. The metabolome is the platform where instructions encoded in genes integrate with signals from the environment to determine cell function (Ashton et al., 2021). Therefore, the analysis of metabolic changes is not only a search for disease markers, but also provides real-time insight into the pathophysiological process itself, revealing the dynamic interplay between nature and the environment. The motivation for this review is the need to synthesise the current state of knowledge on how metabolomics contributes to the understanding of the complex metabolic dysregulations underlying major neurodegenerative diseases. The aim of this work is to assess the potential of this field in discovering biomarkers and identifying new therapeutic targets by analysing both common and distinct metabolic signatures of these devastating diseases.

2. Materials and methods

This work is a systematic review. The literature search was conducted using three leading scientific databases: PubMed, Scopus and Web of Science. The analysis covered publications published between 1998 and 2024 to include both works defining the basics of metabolomics and the latest reports. The search strategy was designed to effectively combine two main research pillars: Metabolomics (using key phrases such as "metabolomics", "metabolome", "metabolic profiling") and Neurodegenerative Diseases (with particular emphasis on Alzheimer's, Parkinson's and Huntington's diseases). Both concepts were combined using the logical operator AND, and the search strings were adapted to the syntax of the searched database in each case.

Inclusion criteria included original articles (clinical and preclinical) and peer-reviewed reviews that focused on the analysis of pathophysiology, biomarkers, or therapeutic targets in AD, PD, or HD. A key technological requirement was the use of the main analytical platforms of metabolomics: mass spectrometry (MS) or nuclear magnetic resonance spectroscopy (NMR). Acceptable research matrices included samples from the central nervous system (PMR, brain tissue) and peripheral fluids. At the same time, exclusion criteria rejected publications on other neurodegenerative diseases, as well as studies from other omics fields that did not include a metabolomic component. The literature selection process was characterised by methodological rigour, which allowed for detailed verification of the eligibility of each study. As a result of this process, 44 publications were included in the final analysis, which constitute the fundamental substantive basis of the review. Due to the considerable methodological diversity of the studies (e.g., different MS platforms, sample types), a formal meta-analysis was not performed; instead, a narrative synthesis was used to summarise the key findings and identified metabolic pathways.

3. Fundamentals of Metabolomics

Metabolomics is a field of science that deals with the systematic study of unique "chemical fingerprints" left behind by specific cellular processes (Ben-Shlomo et al., 2024). Its subject is the metabolome – the complete set of small-molecule metabolites, such as amino acids, lipids, sugars, organic acids and nucleotides, present in a cell, tissue or organism (Zampar et al., 2024). Each type of cell and tissue has its own unique metabolic profile, which provides information about its specific functional state (Ben-Shlomo et al., 2024. Unlike genomics, which provides information about biological potential ("what can happen"), or proteomics, which describes the tools for action ("what is happening"), metabolomics provides snapshots of what has actually happened or is happening in a biological system at a given moment. Two main strategies are used in metabolomic studies. Targeted metabolomics focuses on the precise measurement and quantification of a predetermined, limited group of metabolites belonging to a specific biochemical pathway. It is characterised by high sensitivity and repeatability, making it an ideal tool for verifying specific research hypotheses. Non-targeted metabolomics, on the other hand, aims to provide the broadest possible, unbiased analysis of all detectable metabolites in a sample. It is an exploratory approach that does not require prior assumptions and is ideal for generating new hypotheses and discovering previously unknown disease biomarkers (Villain et al., 2025).

The implementation of these strategies is based on advanced analytical platforms, two of which play a key role. Nuclear magnetic resonance (NMR) spectroscopy is a highly repeatable, non-destructive technique (the sample can be reused) and allows for absolute quantification of metabolites, often without the need for internal standards. Its main limitation, however, is its lower sensitivity and resolution compared to the second technique (Graham et al., 2018). Mass spectrometry (MS), most often coupled with chromatographic techniques (gas chromatography, GC-MS, or liquid chromatography, LC-MS), offers exceptionally high sensitivity, allowing the detection of trace amounts of metabolites in complex biological matrices. Its disadvantages are the destructive nature of the analysis and lower repeatability of results. Both techniques are complementary, and a growing trend in research is the integration of data from both platforms (so-called data fusion), which allows for a more complete picture of the metabolome (Jack et al., 2018).

4. Common Pathological Mechanisms in Neurodegenerative Diseases

Despite differences in clinical presentation and the types of neurons they attack, neurodegenerative diseases share a number of common pathological mechanisms at the molecular level, forming a complex network of processes leading to nerve cell death.

The central element in the pathogenesis of NDDs is proteinopathy, i.e. the process of abnormal folding, aggregation and accumulation of proteins (Alzheimer's Association, 2023). In Alzheimer's disease, the extracellular deposition of beta-amyloid (Aβ) peptide in the form of senile plaques and the intracellular accumulation of hyperphosphorylated tau protein, forming neurofibrillary tangles, play a key role (Bertram et al., 2010). In Parkinson's disease, the pathological sign is the aggregation of α-synuclein in Lewy bodies in dopaminergic neurons (Lawson, 2019). In Huntington's disease, on the other hand, the cause is a mutation in

the huntingtin gene, leading to the formation of a protein with an elongated polyglutamine tract (mHTT), which tends to form toxic aggregates (Anderson, 2019).
Another key mechanism is mitochondrial dysfunction and the resulting bioenergetic collapse. As the energy centres of the cell, mitochondria are essential for the survival of neurons, which have an exceptionally high energy demand.
In NDDs, mitochondrial damage occurs, leading to ATP production deficits, calcium homeostasis disturbances, and membrane potential destabilisation (Alzheimer's Association, 2023). Importantly, a decline in brain metabolism is one o f the earliest detectable signs o f Alzheimer's disease, preceding the onset of clinical symptoms (Livingston et al., 2020). Mitochondrial dysfunction is inextricably linked t o the third key mechanism – oxidative stress a n d neuroinflammation. Damaged mitochondria become a major source of reactive oxygen species (ROS), which in excess lead to oxidative stress, damaging lipids, proteins and DNA. Oxidative stress, together with the presence of protein aggregates, activates glial cells – microglia and astrocytes. Chronic activation of these cells leads to a state of chronic neuroinflammation, i n which pro-inflammatory cytokines a n d chemokines are released, further exacerbating neuronal damage and death (Alzheimer's Association, 2023).
The three mechanisms mentioned above – proteinopathy, mitochondrial dysfunction and oxidative stress – are not isolated phenomena, but form a vicious circle, a self-perpetuating loop in which metabolism plays a key role. Protein aggregates, such as Aβ oligomers or α-synuclein, can directly damage mitochondria, disrupting their structure and function (Dong et al., 2024). Damaged mitochondria produce less ATP and more ROS (Lichtman, Pfister, & Shavit, 2014). The cellular systems responsible for removing misfolded proteins, such as the ubiquitin-proteasome system and autophagy, are highly energy-dependent and require a constant supply of ATP (Alzheimer's Association, 2023). Thus, the energy deficit caused by mitochondrial damage impairs the cell's ability to remove the very protein aggregates that caused the damage in the first place. At the same time, increased oxidative stress can cause oxidative damage to proteins, leading to their misfolding and aggregation, which further fuels the cycle ((Long & Holtzman, 2019). This creates a vicious circle of increasing cell damage. Metabolomics, by measuring the functional consequences of this cycle – such as changes in the concentrations of citric acid cycle intermediates, lipid peroxidation products or antioxidant levels – provides a dynamic picture of disease activity.

5. Metabolomic Signatures in Alzheimer's Disease

Alzheimer's disease, the most common cause of dementia, is defined by the presence of extracellular amyloid plaques (composed of the Aβ peptide) and intracellular neurofibrillary tangles (composed of tau protein) (Zheng & Wang, 2025). Metabolomic studies strongly suggest that metabolic abnormalities are one of the earliest features of AD pathology, often preceding the clinical manifestation of the disease by many years (Livingston et al., 2020). One of the best-documented phenomena is glucose hypometabolism in the brain. Using neuroimaging techniques such as FDG-PET, it has been shown that impaired glucose utilisation in specific regions of the brain (temporoparietal cortex) is a constant feature of AD, already present at the stage of mild cognitive impairment (MCI). This energy collapse forces neurons to seek alternative energy sources, such as ketone bodies and fatty acids, which is reflected in the metabolic profile (Livingston et al., 2020). At the same time, extensive

dysregulation of lipid metabolism is observed. Lipids, as key components of cell membranes and signalling molecules, play a fundamental role in neuronal function. In AD, there are disturbances in the metabolism of phospholipids, sphingolipids and cholesterol, which can lead to membrane destabilisation, impaired intracellular signalling and synaptogenesis (Geschwind & Konopka, 2009). These changes are closely related to the metabolism of amyloid precursor protein (APP) and the generation of toxic Aβ peptide.

An equally important new direction of research is the gut-brain axis. A growing body of evidence indicates that gut microbiota dysbiosis in AD leads to changes in the production of bacterial metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, and trimethylamine N-oxide (TMAO). These compounds can modulate the integrity of the blood-brain barrier and exacerbate neuroinflammatory processes, which directly contributes to disease progression (Zou et al., 2024).

Metabolomic studies have identified a number of potential biomarkers in biological fluids. Cerebrospinal fluid (CSF), which is in direct contact with the extracellular space of the brain, is considered the best source of information on pathological processes in the CNS (Morgan & Orrell, 2016). CSF analyses of AD patients showed elevated concentrations of glyceryl and N-acetylneuraminic acid and reduced levels of serine and 2-hydroxybutyrate compared to patients with other conditions (Nichols & Vos, 2022). In contrast, plasma, which is much more readily available, has been found to have elevated levels of glutamine, which may be associated with glutamatergic excitotoxicity, and decreased levels of piperine, a dietary alkaloid with neuroprotective properties (Geschwind & Konopka, 2009). Advanced machine learning techniques are also becoming increasingly important, allowing the creation of diagnostic panels based on dozens or hundreds of blood metabolites, achieving efficacy comparable to recognised PMR biomarkers (Corder et al., 1993).

6. Metabolic Changes in Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disorder, whose pathological features include selective loss of dopaminergic neurons in the substantia nigra and the presence of intra-neuronal protein aggregates, Lewy bodies, composed mainly of α-synuclein (Lawson, 2019). As in AD, metabolic dysfunction is central to the pathogenesis of PD.

Particularly strong evidence points to the role of mitochondrial dysfunction and oxidative stress. Dopaminergic neurons are particularly sensitive to oxidative stress due to dopamine metabolism, which itself generates reactive oxygen species. In PD, there is an impairment of respiratory chain complex I function, leading to an energy crisis and further exacerbation of ROS production (Flores-Torres et al., 2025). Metabolomic studies confirm these observations, showing disturbances in pathways related to βoxidation of fatty acids and energy metabolism (Oliver et al., 1998).

More recent analyses have revealed significant changes in the concentrations of medium- and long-chain acylcarnitines in the plasma of PD patients, indicating systemic impairment of mitochondrial β-oxidation as a key component of the disease (Saiki et al., 2017). Furthermore, there is growing interest in the kynurenine pathway, which is associated with neuroinflammation. It has been found that in PD patients, there is a shift in tryptophan metabolism towards the production of neurotoxic metabolites, such as quinolinic acid, at the

expense of neuroprotective metabolites. This process is associated not only with motor progression, but also with cognitive impairment in the course of the disease (Chen & Geng, 2023).

A particularly characteristic metabolic feature of PD is xanthine metabolism disorders. Many independent studies have shown reduced plasma uric acid levels in PD patients, even many years before diagnosis (Forsyth, 2018). Uric acid is a powerful antioxidant, and low levels may increase the susceptibility of neurons to oxidative damage. At the same time, elevated concentrations of uric acid precursors, such as hypoxanthine and xanthine, are observed, indicating complex dysregulation of the entire purine pathway (Oliver et al., 1998). Other studies, involving large cohorts of patients in the prodromal and clinical phases, have identified changes in amino acid, acylcarnitine and lipid concentrations that correlate with disease progression (Forsyth, 2018). Plasma metabolomic analysis has proven to be a promising tool not only for diagnosis but also for monitoring PD progression. A panel of 15 plasma metabolites, including xanthine and fatty acid compounds, has been shown to strongly correlate with the severity of motor symptoms over a two-year follow-up period (Sadigh-Eteghad, Talebi, & Farhoudi, 2012). In addition, plasma metabolic profiling may help differentiate PD from atypical parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Elevated concentrations of formate and succinate have been found to be common markers for these conditions, indicating a common pathway of mitochondrial dysfunction (Przedborski, Vila, & Jackson-Lewis, 2003).

7. Metabolomic Profiling in Huntington's Disease

Huntington's disease is a rare, autosomal dominant inherited disorder caused by a mutation in a single gene – the expansion of CAG trinucleotide repeats in the gene encoding the huntingtin protein (HTT)(Chen et al., 2020). Despite its clear genetic cause, its pathogenesis is complex, and metabolic disorders play an important role in it.

Post-mortem studies of brain tissue from HD patients have revealed significant changes in energy and phospholipid metabolism. Reduced concentrations of acylcarnitines, which are essential for the transport of fatty acids to the mitochondria for β-oxidation, and creatine, which is an energy reservoir in the form of phosphocreatine, were found in the striatum and frontal cortex. Extensive changes i n the phospholipid profile were also observed, indicating disturbances in cell membrane integrity (Purves et al., 2008).

As in Parkinson's disease, there is growing evidence that disturbances in tryptophan metabolism play an important role in Huntington's disease. Plasma metabolomic analyses have shown that significant changes in this pathway occur even in the pre-symptomatic phase, in carriers of the HTT gene mutation without clinical symptoms of the disease. There is a decrease in serotonin concentration with a simultaneous increase in the level of its precursor, N-acetylserotonin, as well as changes in the metabolites of the kynurenine pathway and tryptophan derivatives produced by the gut microbiota, such as indole-3- propionic acid, which has strong antioxidant properties (Tullo et al., 2024). These early and progressive changes indicate that dysregulation of tryptophan metabolism is a fundamental element in the pathogenesis of Huntington's disease.

Activation of the kynurenine pathway leads to increased synthesis of neurotoxic metabolites such as 3- hydroxykinurenine (3-HK) and quinolinic acid (QUIN), while reducing levels of

neuroprotective kynurenine (KYNA). The results of metabolomic studies conducted in plasma, cerebrospinal fluid and preclinical HD models confirm that these disorders appear already in the preclinical stage and correlate with the severity of neuronal degeneration (Veres et al., 2015) (Chen & Geng, 2023). The kynurenine pathway is therefore a promising therapeutic target and a potential source of prognostic and diagnostic biomarkers in Huntington's disease.
Another important, though less studied, aspect is cholesterol dyshomeostasis in the brain. The mutant huntingtin protein (mHTT) disrupts cholesterol synthesis in neurons and astrocytes and its transport via apolipoprotein E (ApoE). This leads to cholesterol deficiencies in neurons, impaired synaptic function and cell membrane integrity, which may exacerbate neurodegeneration. In the context of metabolomics, these changes reflect abnormalities in sterol and oxysterol metabolites, which may be potential biomarkers of disease progression and therapeutic targets (González-Guevara et al., 2020).
Studies in animal models further confirm these observations and point to the role of oxidative stress as another pathogenic factor (Ramautar et al., 2011).
Techniques such as magnetic resonance spectroscopy (MRS) enable non-invasive, longitudinal monitoring of metabolites in the brain. MRS studies have shown that in the putamen (a brain structure particularly affected in HD), patients with HD have lower concentrations of N-acetylaspartate (NAA), a marker of neuronal integrity, and higher concentrations of myo-inositol, a marker of glial activation, compared to healthy individuals. Although these concentrations remained stable over a 24-month period, their baseline values strongly differentiated the groups, making them valuable biomarkers of disease status (Villoslada et al., 2009).

8. Common and Differentiating Metabolic Pathways in NDDs

Synthesis of the presented data allows for the identification of both convergent and unique metabolic signatures for the analysed neurodegenerative diseases. Undoubtedly, the common denominator is profound dysregulation of central metabolic pathways. Mitochondrial dysfunction, impaired energy metabolism (both glucose and fatty acids) and increased oxidative stress are universal pathological themes present in all three diseases (Alzheimer's Association, 2023). This demonstrates the fundamental role of energy homeostasis in maintaining neuronal health and suggests that therapies aimed at supporting mitochondrial function may have broad applications in neuroprotection.
At the same time, each disease has its own specific metabolic signature that may reflect unique aspects of its pathogenesis. Distinct and consistently repeated in studies appears to be characteristic of Parkinson's disease (Oliver et al., 1998). In Alzheimer's disease, extensive changes in lipid metabolism, closely related to Aβ pathology, and early glucose hypometabolism come to the fore (Matthews et al., 2018). In contrast, Huntington's disease appears to be characterised by early and profound disturbances in the tryptophan pathway, already visible in the pre-symptomatic stage (Tullo et al., 2024). These differences pave the way for the development of specific biomarker panels that could not only detect the presence of neurodegeneration, but also differentiate between individual disease entities.
It is also crucial to note that metabolic changes detected in peripheral biological fluids, such as plasma, often reflect pathological processes occurring in the central nervous system. However, caution is required when interpreting these results. Some metabolites freely cross

the blood-brain barrier, providing direct insight into brain metabolism. Others may reflect systemic metabolic disorders (e.g., insulin resistance) (Ramautar et al., 2011), which are themselves risk factors for NDDs, or originate from other sources, such as the gut microbiota (Tullo et al., 2024). This means that a plasma biomarker may not be a direct readout of a specific neural process, but rather an indicator of a systemic metabolic state that promotes or contributes to neurodegeneration. This perspective shifts the focus from looking exclusively at "what is happening in the brain" to understanding the complex dialogue between the brain and the rest of the body, suggesting that effective therapeutic strategies may require interventions targeting systemic metabolism rather than just the CNS.
The table below summarises key metabolomic findings for the diseases discussed.

Table 1: Key metabolic changes and potential biomarkers in selected neurodegenerative diseases.

Disease	Sample Type	Main Altered Pathways Metabolic	Potential Biomarkers (direction of change ↑↓)
Alzheimer's Disease	PMR, Plasma	Glucose metabolism, Lipid metabolism (phospholipids, sphingolipids), Oxidative stress, Amino acid metabolism, Metabolites of the gut microbiota	PMR: ↑Glycerate, ↑Nacetylneuraminic acid, ↓Serine; Plasma: ↑Glutamine, ↓Piperine, , ↓Serine; Plasma: ↑Glutamine, ↓Piperine, ↑Ceramides, ↑TMAO
Parkinson's disease	Plasma, PMR	Xanthine metabolism, β-oxidation of fatty acids , Mitochondrial dysfunction, Amino acid metabolism, Kynurenine pathway (neuroinflammation)	Plasma: ↓Uric acid, ↑Glutathione, ↑Xanthine metabolites, ↑Formate, ↑Succinate, ↑Quinolinic acid (QUIN), ↓Kynurenic acid (KYNA), Altered acylcarnitine concentrations
Huntington's disease	Brain tissue, Plasma, PMR	Energy metabolism (acylcarnitines), Phospholipid metabolism, Tryptophan/kynurenine pathway Cholesterol metabolism, Oxidative stress	Brain/Plasma/PMR: 3-hydroxykynurenine (3-HK) ↑, quinolinic acid (QUIN) ↑, kynurenic acid (KYNA) ↓ Brain: ↓Creatine, ↓Phospholipids; Plasma: ↓Serotonin, ↑N-acetylserotonin, ↓Indole-3-propionic acid indole-3-propionic acid

9. Limitations and Future Directions

Despite its enormous potential, the field of metabolomics in NDD research faces significant limitations that must be overcome in order to fully exploit its capabilities. One of the biggest challenges is the lack of standardisation and low reproducibility of results. Differences in

study design, sample collection and storage methods, analytical platforms used, and approaches to data analysis lead to high heterogeneity of results, making them difficult to compare and replicate. Many published studies are based on small groups of patients, and their findings are often not validated in larger, independent and, most importantly, longitudinal cohorts. Furthermore, a key issue remains whether the observed metabolic changes are the cause of the disease, its consequence, or a compensatory mechanism (Palmqvist et al., 2021). The metabolome is also extremely sensitive to confounding factors such as diet, medication, lifestyle, and gut microbiota composition, requiring rigorous study design to isolate disease-specific signals (Fiehn, 2002).

There is a critical gap between the discovery of potential biomarkers and their clinical implementation, which can be called the "validation valley of death". Non-targeted techniques generate long lists of biomarker candidates (Villain et al., 2025), but each must undergo a rigorous, costly, and time-consuming validation process in large, well-characterised patient cohorts that are often unavailable (Brown et al., 2009). A statistically significant difference in metabolite levels does not automatically make it a clinically useful biomarker; it must demonstrate high sensitivity, specificity and robustness in diverse populations. The future of research lies not only in discovering new markers, but in creating a global, collaborative infrastructure for standardised validation, similar to that which has been created for Aβ and tau biomarkers in PMR in Alzheimer's disease (Tang-Wai et al., 2004). In light of these limitations, future research directions should focus on several key areas. It is essential to conduct large, multicentre, longitudinal studies that follow patients from the preclinical phase to advanced stages of the disease. This will allow for the validation of biomarkers and understanding of dynamic metabolic changes over time (Tarawneh & Holtzman, 2012). Multi-omic integration, combining data from metabolomics with genomics, proteomics and transcriptomics, will be crucial for building comprehensive, multi-level models of the disease. This approach will allow genetic risk factors to be linked to their functional consequences at the metabolic level (Brown et al., 2009). Advanced analytical methods, including artificial intelligence and machine learning, which are capable of analysing complex multi-omic datasets to identify robust biomarker panels and predict disease trajectories, will play an indispensable role (Corder et al., 1993). Finally, to move from static "snapshot" measurements to dynamic assessment of metabolic flows, wider use of isotope tracing techniques will be necessary, as they provide deeper insight into cellular mechanisms (Ashton et al., 2021).

10. Conclusions

The presented literature review provides compelling evidence that metabolic dysregulation is a strong, early and ubiquitous feature of the pathogenesis of Alzheimer's, Parkinson's and Huntington's diseases. Metabolomics, as a field of science, allows for in-depth investigation of these changes, shifting the research paradigm of NDDs from a focus on the pathology of individual proteins towards a more holistic, systemic view of disease as a breakdown of complex metabolic networks. The identified "pathological triad," comprising the mutually reinforcing processes of proteinopathy, mitochondrial dysfunction, and oxidative stress, with metabolism at its centre, provides a useful model for understanding the complexity of these disorders.

The clinical potential of metabolomics is enormous. It offers a real prospect for the development of noninvasive or minimally invasive diagnostic tests that will enable the detection of disease at the preclinical stage, opening a critical window for neuroprotective interventions. Furthermore, metabolic signatures can be used to stratify patients in clinical trials, allowing for more precise testing of new drugs, as well as to objectively monitor disease progression and response to treatment. The identification of key disrupted metabolic pathways also points to new potential therapeutic targets.
In summary, although metabolomics still faces many challenges, it represents a promising new frontier in the fight against neurodegenerative diseases. It offers unprecedented hope for a future in which early diagnosis, effective treatment and perhaps even prevention of these diseases will be possible, based on the principles of precision and personalised medicine.

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