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Review

Integrative metabolomics science in Alzheimer's disease: Relevance and future perspectives

Simone Lista [a,*], Raúl González-Domínguez [b], Susana López-Ortiz [a], Álvaro González-Domínguez [b], Héctor Menéndez [a], Juan Martín-Hernández [a], Alejandro Lucia [c,d,e], Enzo Emanuele [f], Diego Centonze [g,h], Bruno P. Imbimbo [i], Viviana Triaca [j], Luana Lionetto [k,l], Maurizio Simmaco [k,l], Miroslava Cuperlovic-Culf [m,n], Jericha Mill [o], Lingjun Li [o,p], Mark Mapstone [q], Alejandro Santos-Lozano [a,c,1], Robert Nisticò [r,s,1]

[a] *i+HeALTH Strategic Research Group, Department of Health Sciences, Miguel de Cervantes European University (UEMC), Valladolid, Spain*
[b] *Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Hospital Universitario Puerta del Mar, Universidad de Cádiz, Cádiz, Spain*
[c] *Research Institute of the Hospital 12 de Octubre ('imas12'), Madrid, Spain*
[d] *Faculty of Sport Sciences, European University of Madrid, Villaviciosa de Odón, Madrid, Spain*
[e] *CIBER of Frailty and Healthy Ageing (CIBERFES), Madrid, Spain*
[f] *2E Science, Robbio, Pavia, Italy*
[g] *Department of Systems Medicine, Tor Vergata University, Rome, Italy*
[h] *Unit of Neurology, IRCCS Neuromed, Pozzilli, IS, Italy*
[i] *Department of Research and Development, Chiesi Farmaceutici, Parma, Italy*
[j] *Institute of Biochemistry and Cell Biology (IBBC), National Research Council (CNR), Rome, Italy*
[k] *Clinical Biochemistry, Mass Spectrometry Section, Sant'Andrea University Hospital, Rome, Italy*
[l] *Department of Neuroscience, Mental Health and Sensory Organs, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy*

Abbreviations: [18 F]-FDG-PET, [18 F]-fluorodeoxyglucose-positron emission tomography; 1 H NMR, 1 H-magnetic resonance spectroscopy; Aβ, amyloid-β; Aβ1–42, 42-amino acid-long amyloid-β peptide; ABCA1, ATP Binding Cassette Subfamily A Member 1; ABCA7, ATP Binding Cassette Subfamily A Member 7; AD, Alzheimer's disease; ADCS-ADL, AD Cooperative Study - Activities of Daily Living scale; ADMC, Alzheimer's Disease Metabolomics Consortium; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADP, adenosine diphosphate; AgeCoDe, German study on Aging, Cognition and Dementia; AGES-RS, Age, Gene/Environment Susceptibility-Reykjavik Study; AIBL, Australian Imaging, Biomarkers and Lifestyle flagship study of aging; aMCI, amnestic MCI; APCI, atmospheric pressure chemical ionization; APOE, apolipoprotein E; APOE ε4, ε4 allele of the APOE gene; APP, amyloid precursor protein; APPI, atmospheric pressure photoionization; ARIC, Atherosclerosis Risk in Communities; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; ATP, adenosine triphosphate; BAs, bile acids; BACE1, β-site APP cleaving enzyme 1; BBB, blood-brain barrier; BCAAs, branched-chain amino acids; BLSA, Baltimore Longitudinal Study of Aging; CE, capillary electrophoresis; CIL, chemical isotope labeling; CNS, central nervous system; CoA, coenzyme A; CPT1A, Carnitine Palmitoyltransferase 1 A; CSF, cerebrospinal fluid; Cyt c, cytochrome c; DAGs, diacylglycerols; DHA, docosahexaenoic acid; DIMS, direct infusion mass spectrometry; e-health, electronic health; ERF, Erasmus Rucphen Family Study; DTI, diffusion tensor imaging; ESI, electrospray ionization; FERMT2, fermitin family homolog-2; FIA, flow injection analysis; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; GC, gas chromatography; HC, healthy controls; GC-MS, gas chromatography coupled with mass spectrometry; GLUTs, glucose transporters; HILIC, hydrophilic-interaction liquid chromatography; HMDB, Human Metabolome Database; HO-1, Heme oxygenase-1; HPLC, high-performance liquid chromatography; HRMS, high-resolution mass spectrometry; IM-MS, ion mobility mass spectrometry; IMAS, Indiana Memory and Aging Study; LBD, Lewy bodies dementia; LC, liquid chromatography; LC-MS, liquid chromatography coupled with mass spectrometry; LTL, leukocyte telomere length; lysoPCs, lysophosphatidylcholines; lysoPEs, lysophosphatidylethanolamines; *m/z*, mass-to-charge ratio; MAP, Memory and Aging Project; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MRM, multiple reaction monitoring; MS, mass spectrometry; MS4A6A, membrane spanning 4-domains A6A; MS/MS, tandem mass spectrometry; MSI, mass spectrometry imaging; MUFAs, monounsaturated fatty acids; MWAS, metabolome-wide association study; NAD, nicotinamide adenine dinucleotide; NFTs, neurofibrillary tangles; NMR, nuclear magnetic resonance spectroscopy; p-tau, hyper-phosphorylated tau protein; PA, physical activity; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PET, positron emission tomography; PG, phosphatidylglycerol; PI, phosphatidylinositol; PKB, protein kinase B; PKC, protein kinases C; PKCaMII, Ca2 + /calmodulin-dependent protein kinase; PKD, protein kinases D; PRPP, phosphoribosyl diphosphate; PS, phosphatidylserine; PUFAs, polyunsaturated fatty acids; QOL-AD, Quality of Life in AD; QqQ, triple quadrupole mass analyzer; ROS, Religious Orders Study; ROSMAP, Religious Orders Study and Rush Memory and Aging Project; RPLC, reversed-phase liquid chromatography; RS, Rotterdam Study; S1P, sphingosine-1-phosphate; SCD, subjective cognitive decline; SFAs, saturated fatty acids; SID, stable isotope dilution; sMRI, structural magnetic resonance imaging; SMs, sphingomyelins; SOPs, standard operating procedures; t-tau, total tau protein; TAGs, triacylglycerols; TARCC, Texas Alzheimer's Disease Research Care Consortium; TCA, tricarboxylic acid cycle; TOF, time-of-flight; UPLC, ultra-performance liquid chromatography; WHAS II, Women's Health and Aging Study II; WHICAP, Washington Heights, Inwood Columbia Aging Project.

* Correspondence to: "i+HeALTH" Strategic Research Group, Department of Health Sciences, Miguel de Cervantes European University (UEMC), Padre Julio Chevalier, 2, 47012 Valladolid, Castilla y León, Spain.
E-mail address: slista@uemc.es (S. Lista).

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[m] Digital Technologies Research Center, National Research Council, Ottawa, Canada
[n] Department of Biochemistry, Microbiology, and Immunology, University of Ottawa, Ottawa, ON, Canada
[o] Department of Chemistry, University of Wisconsin-Madison, Madison, WI, USA
[p] School of Pharmacy, University of Wisconsin-Madison, Madison, WI, USA
[q] Department of Neurology, Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA
[r] School of Pharmacy, University of Rome "Tor Vergata", Rome, Italy
[s] Laboratory of Pharmacology of Synaptic Plasticity, EBRI Rita Levi-Montalcini Foundation, Rome, Italy

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ABSTRACT

Alzheimer's disease (AD) is determined by various pathophysiological mechanisms starting 10–25 years before the onset of clinical symptoms. As multiple functionally interconnected molecular/cellular pathways appear disrupted in AD, the exploitation of high-throughput unbiased omics sciences is critical to elucidating the precise pathogenesis of AD. Among different omics, metabolomics is a fast-growing discipline allowing for the simultaneous detection and quantification of hundreds/thousands of perturbed metabolites in tissues or biofluids, reproducing the fluctuations of multiple networks affected by a disease. Here, we seek to critically depict the main metabolomics methodologies with the aim of identifying new potential AD biomarkers and further elucidating AD pathophysiological mechanisms. From a systems biology perspective, as metabolic alterations can occur before the development of clinical signs, metabolomics – coupled with existing accessible biomarkers used for AD screening and diagnosis – can support early disease diagnosis and help develop individualized treatment plans. Presently, the majority of metabolomic analyses emphasized that lipid metabolism is the most consistently altered pathway in AD pathogenesis. The possibility that metabolomics may reveal crucial steps in AD pathogenesis is undermined by the difficulty in discriminating between the causal or epiphenomenal or compensatory nature of metabolic findings.

1. Introduction

In recent decades, scientists have undertaken extensive molecular characterization of the pathophysiological processes of Alzheimer's disease (AD), a complex and progressive neurodegenerative disease. Primary pathophysiological hallmarks of AD include the formation of extracellular amyloid β (Aβ) plaques (Guo et al., 2020), resulting from the aggregation of Aβ peptides that have been generated by the protease cleavage of the type I transmembrane amyloid precursor protein (APP) (Deyts et al., 2016); and the development of intraneuronal neurofibrillary tangles (NFTs) (Guo et al., 2020) resulting from the aggregation of tau proteins that are aberrantly hyperphosphorylated (p-tau) at multiple amino acid sites in several cortical brain regions (Neddens et al., 2018).

Aβ plaques initially develop in higher order neocortical regions and, subsequently, progress to the limbic system, subcortical nuclei, and arrive at primary sensorimotor cortex and the cerebellum at late stages of the disease (Thal et al., 2002). Tau pathology manifests as NFTs and neuropil threads and primarily accumulates in the entorhinal region, subsequently progressing to the limbic system and neocortical regions, as reflected by NFTs Braak stages (Braak et al., 2006). Notably, Aβ plaques deposition is assumed to precede and support the spreading of neocortical tau pathology, driving, in turn, neurodegeneration and cognitive deterioration (Jack and Holtzman, 2013). Several lines of evidence indicate the presence of Aβ deposition as prerequisite for the subsequent development of tau pathology in AD (Long and Holtzman, 2019).

Despite the general consensus that brain Aβ overaccumulation and p-tau formation are major suspects for driving AD pathogenesis, pharmacological treatments targeting Aβ deposition and p-tau have not been proven to be effective, therefore suggesting the existence of additional and alternative molecular players (Kent et al., 2020).

Notably, substantial evidence highlights that the complexity of AD is determined by an extensive list of pathophysiological mechanisms – beyond the acknowledged brain Aβ overaccumulation and tau pathology – that can present a minimum of 10–25 years prior to the appearance of the disease clinical signs (Jack et al., 2013). These can include, among others, synaptic dysfunction and loss (Camporesi et al., 2020; Colom-Cadena et al., 2020), immune response and inflammation (Kinney et al., 2018; Webers et al., 2020), lipid dyshomeostasis (Chew et al., 2020; Yin, 2023), altered energy metabolism and disturbed mitochondrial activity (Flannery and Trushina, 2019; Mi et al., 2021; Song et al., 2021; Wang et al., 2020), oxidative stress (Butterfield and Boyd-Kimball, 2018; Ionescu-Tucker and Cotman, 2021; Plascencia-Villa and Perry, 2021), dysfunctional glucose metabolism (Butterfield and Halliwell, 2019; Wang et al., 2022), Ca^{2+} dyshomeostasis (Cascella and Cecchi, 2021; Groblewska et al., 2015), dysregulation of cellular trafficking, involving autophagy and endo-lysosomal degradation pathways (Cao et al., 2019; Krance et al., 2022; Lai et al., 2021; Lee et al., 2022) and in the complement cascade pathway (Krance et al., 2021), vascular dysregulation (Iturria-Medina et al., 2016; Sweeney et al., 2019), impaired neurovascular coupling (Tarantini et al., 2017; Zhu et al., 2022), reactive astrogliosis (Garwood et al., 2017), and alterations in the status of some neurotransmitters, including acetylcholine, dopamine, gamma-aminobutyric acid (GABA), serotonin, histamine, and N-methyl-D-aspartate (Reddy, 2017).

1.1. Exploring the molecular complexity of Alzheimer's disease through metabolomics

Based on the extensive number of possible mechanisms contributing to or co-occurring with the primary proteopathy of AD, there have been many attempts to dissect its molecular heterogeneity. Recently, the study of > 1500 transcriptomes conducted along five brain regions in two AD cohorts, through an integrative network approach, robustly defined three major molecular clusters of AD referring to combinations of various dysregulated pathways, including predisposition to tau-mediated neurodegeneration, Aβ-pathway-driven neuroinflammation, synaptic signaling, immune activity, mitochondrial dysfunction, and demyelinating processes (Neff et al., 2021).

Because it appears that AD disrupts multiple functionally interconnected molecular/cellular pathways (Kodam et al., 2023), the exploratory systems biology framework, exploiting high-throughput omics sciences (Castrillo et al., 2018), is critical to better characterize the pathogenesis of AD at a network level. This will assist in the identification of biological markers (Aerqin et al., 2022; Hampel et al., 2021b) supporting the early diagnosis of the disease and the development of individualized therapeutic plans (Hampel et al., 2023).

[1] Both Authors equally contributed to this work.

Amid all currently recognized high-throughput omics sciences, metabolomics is a fast-growing discipline that simultaneously detects and quantifies hundreds of thousands of perturbed metabolites (small molecules within a mass range of 50 – 1500 Da) in tissues or biofluids, depicting the fluctuations of multiple networks affected by a certain disease (Huo et al., 2020). As of April 2023, the Human Metabolome Database (HMDB, available at https://hmdb.ca) contains over 220,000 metabolite entries, including both water-soluble and lipid-soluble metabolites. The measured metabolic compounds include both endogenous and exogenous molecules, with different chemico-physical properties and biological stabilities, that are substrates and products of chemical reactions occurring in biological systems (Liu and Locasale, 2017). As metabolites undergo a chemical transformation during metabolism, metabolite concentration/expression can provide essential readouts of the biological status of the system in question (Liu and Locasale, 2017). Differently from genes and proteins whose expression and activity are, respectively, under the control of epigenetic modulation and post-translational modifications, metabolites represent direct molecular signatures of biochemical activity; hence, they are highly suitable to be correlated with specific phenotypes (Patti et al., 2012) and provide a rich substrate for understanding disease pathophysiology.

Metabolomics primarily inspects polar (i.e., water-soluble) metabolites, including amino acids, carbohydrates, organic acids, and nucleotides (Liu and Xu, 2018), as well as lipids that, in general, are hydrophobic. Some lipids can be amphipathic, i.e., a portion of their structure is hydrophilic, while another larger portion is hydrophobic. Lipidomics, considered a complementary strategy of metabolomics, aims at identifying and quantifying the full complement of lipid classes and subclasses (Fahy et al., 2005; Kuo and Tseng, 2018).

1.2. Metabolomic analyses in various biological matrices: an overview

Notably, metabolomics-based approaches applied to clinical studies of AD and other neurodegenerative diseases can rely on different biological matrices, especially including brain tissues, cerebrospinal fluid (CSF), and blood (plasma/serum); this aspect stresses the potential clinical efficacy and usefulness of metabolomics (Wilkins and Trushina, 2018).

In general, metabolomic analyses performed on human tissues and biological fluids enable the detection of disease-associated metabolite dissimilarities between cognitively healthy individuals, mild cognitive impairment (MCI) individuals, and patients with AD, as predictors of AD advancement (Wilkins and Trushina, 2018). The use of diverse biological matrices and robust technological platforms makes the application of metabolomic investigation an important and rigorous tool for understanding AD pathophysiology.

The biological matrix or tissue type for metabolomics analysis spans from individual cells to biofluids, to organ systems. Although CSF has the benefit of being continuous with the cerebral extracellular space, with a free flow of molecules between brain and CSF, CSF studies are affected by the invasive nature of the lumbar puncture, restricting its application in clinical practice to few specialized centers (Shaw et al., 2020). In contrast, blood collected by routine venipuncture procedures is very low in invasiveness and involves procedures most adults are familiar with. As a result, blood may be more appropriate for remote or repeated measurements from patients, both for clinical diagnosis or screening purposes as well as for recurrent sampling in clinical trials, thus making it more accessible in both low-resource and non-specialist sites (Alawode et al., 2021). Traditionally, several metabolites – including amino acids, fatty acids, cholesterol, glucose, creatinine, urea, uric acid, ammonia, bilirubin, bile acids, among the others – are already examined in blood samples delivered to clinical chemistry analysis services to provide biomarkers for individual health status (Yin et al., 2015). Because peripheral blood generally contains metabolites derived from all organ systems, blood can be useful as valid source for recurrent measurement of central nervous system (CNS)-derived metabolites. Since blood-brain barrier (BBB) disruption is associated with aging and cognitive impairment during AD progression, BBB shows increased permeability leading to intensified communication between brain and blood and exchange of metabolites between them (Baird et al., 2015). In addition, CSF is absorbed into the blood circulation each day and small-sized metabolites can be detected in blood following BBB weakening (Voyle et al., 2016).

Notably, blood-based metabolomic studies are showing encouraging results in characterizing metabolic molecular signatures of complex multi-factorial diseases, including cancer (Buentzel et al., 2021; Zhang et al., 2021), diabetes (Chevli et al., 2021; Zhou et al., 2021), and cardiovascular diseases (Chevli et al., 2021; Haase et al., 2021; Wolter et al., 2021). A similar outcome is potentially expected in the field of Neurology for various neurodegenerative diseases, including AD and its upstream pathomechanistic conditions (Castrillo and Oliver, 2016; Wilkins and Trushina, 2018).

Finally, the detection and measurement of metabolites in blood (and other biofluids) in clinical settings is gaining considerable attention following the development of innovative metabolomics platforms (Liu and Locasale, 2017; Reveglia et al., 2021).

In light of the relevance of biofluid-derived metabolomics to AD and the rapid advancement of metabolomic technology (González-Domínguez et al., 2021a; Hurtado et al., 2018; Reveglia et al., 2021; Sriwichaiin et al., 2021; Wang et al., 2021), in this review we seek to accomplish two main goals. First, we aim to provide a critical depiction of the most significant metabolomic investigations, especially those conducted in biofluids (such as blood [plasma/serum]), for the identification of candidate metabolomic biomarkers in AD. In addition, we will highlight future perspectives of metabolomics in the AD field to help understand the pathophysiological mechanisms underlying the phenotypes of the disease. Since the narrative inherent to the manuscript is based on the authors' knowledge and long-term experience in the field, no systematic literature search was performed.

2. Overview of metabolomics methodologies

2.1. State-of-the-art of analytical technologies used in metabolomics

Substantial efforts are currently focused on discovery and identification of human metabolites. Given the high complexity and heterogeneity of the human metabolome, several analytical platforms may now be used for the detection and quantification of the different categories of metabolites. Current state-of-the-art metabolomics studies rely on two principle analytical platforms applied for detection, quantification, and characterization of metabolites: (I) mass spectrometry (MS) and (II) nuclear magnetic resonance (NMR) spectroscopy. The extreme sensitivity and selectivity of MS platforms and the elevated reproducibility of NMR-based techniques designate both tools as superior over other analytical platforms (Wilkins and Trushina, 2018).

The benefits of NMR spectroscopy are the minimal procedures of sample preparation prior to analysis, the high reproducibility, the fact that it is a non-destructive analytical technique, allowing the examination of the nature and structure of organic analytes, the brief analytical run times and detection of metabolites diverging in terms of physicochemical features (Gonzalez-Riano et al., 2016), simple annotation of discriminant signals, hence generating reduced times (few minutes) needed for the high-throughput examination of samples. Also, NMR spectroscopy can be executed for in vivo studies (Emwas et al., 2013). In contrast, NMR spectroscopy is limited by its moderately low sensitivity versus that shown by MS platforms (Kohler et al., 2016) and the low spectral resolution.

On the other hand, MS facilitates the study of various categories of metabolites at physiological levels and their subsequent accurate identification via fragmentation techniques. Additionally, the availability of different procedures of sample introduction and sources of ionization considerably enlarges the analytical coverage offered by MS

methodologies and stresses their versatility (Theodoridis et al., 2011). As a result, MS integrates the major strategies for the metabolomic characterization of complex systems and, since it provides a remarkable combination of sensitivity and selectivity, it represents a consistent platform for a wide range of metabolomics research (Emwas, 2015; González-Domínguez et al., 2018a). In addition, compared with NMR spectroscopy, MS has the advantage of providing the examination of secondary metabolites, showing detection levels ranging from picomole (10^{-12} M) to femtomole (10^{-15} M). Furthermore, as the various MS technologies show a wide array of available operational principles (for instance, different ionization procedures), the amount of potentially measurable metabolites is amplified. However, MS has a lower degree of reproducibility than NMR spectroscopy since MS is a destructive technique and requires rigorous sample preparation to circumvent potential matrix effects (Emwas, 2015; González-Domínguez et al., 2018a; Wilkins and Trushina, 2018).

Another shortcoming of NMR spectroscopy is its elevated cost in terms of purchasing and maintenance (Kohler et al., 2016; Trushina and Mielke, 2014), the large spaces needed for NMR platform, and the need for highly experienced operators. Therefore, MS instruments are more frequently distributed in clinical centers and hospitals versus NMR spectroscopy (Emwas, 2015). Most recent AD metabolomic biomarker studies have relied on MS as the analytical tool, versus NMR spectroscopy, mainly owing to its superior sensibility, larger range of measurable metabolites, and high-throughput (Emwas et al., 2013).

Table 1 reports the key features (as well as benefits and limitations) of MS and NMR spectroscopy as analytical platforms commonly used in the field of metabolomics (Emwas, 2015; Liu and Locasale, 2017; Wilkins and Trushina, 2018).

2.2. Complementary mass spectrometry-based platforms

MS is an analytical platform quantifying the molecular masses of the analytes and their fragments to establish their identity. Briefly, a mass spectrometer consists of three components: an ion source, a mass analyzer, and a detector. The ion source is a device creating atomic and molecular ions; an extraction system ionizes the sample; the ions are then targeted through the mass analyzer and into the detector. The mass analyzer includes electric and magnetic fields exerting forces on the charged particles. The mass differences of the ion fragments flying into the analyzer enable their separation according to their mass-to-charge ratio (m/z). Then, the streams of sorted ions travel to the detector that allows for calculating the relative abundance of each ion type. Because MS platforms have the desirable qualities of high sensitivity and high-resolution, it is widely applied to support a large coverage of the metabolome and the detection of unknown analytes. Therefore, MS allows profiling metabolites in mixed specimens (i.e., biological samples). Unfortunately, no MS-based method is able to entirely cover all classes of metabolites, therefore different MS approaches need to be applied to attain an all-inclusive metabolic profiling (Emwas, 2015; Gonzalez-Riano et al., 2016). Sometimes, two or more mass analyzers can be coupled together to have tandem MS (MS/MS) to increase the ability in analyzing samples and to definitively identify interesting metabolites by comparing to known metabolite standards (Haag, 2016).

Accordingly, the implementation of analytical multi-platforms based on the combination of complementary techniques is nowadays the most common strategy to deal with the high physicochemical complexity of the human metabolome (González-Domínguez et al., 2018a; González-Domínguez et al., 2017a).

At present, there are two commonly used MS-based systems: multiple reaction monitoring (MRM) and high-resolution MS (HRMS). MRM mode is widely used for targeted analyses and, frequently, performed on a triple quadrupole (QqQ) mass analyzer to achieve inherent reproducibility as well as unparalleled sensitivity and selectivity to accurately discriminate molecules (Vidova and Spacil, 2017). The first quadrupole filters ions (parent ion) with an established molecular weight; the second quadrupole fragments the selected precursor ion; and the third quadrupole selects its distinctive fragments, resulting in a tandem MS process. Consequently, prior to data acquisition, the parent and fragment ions need to be defined, and the adjusted energy for the fragmentation of each metabolite is required (Liu and Locasale, 2017). HRMS depends on the elevated mass resolution of the mass analyzer. A typical instrument here applied for mass analysis is the Orbitrap™, characterized by elevated mass resolution and extremely high mass accuracy (Hu et al., 2005). Another common instrument is the time-of-flight (TOF), registering the time needed by ions to fly across an electric field (Zhu et al., 2013). HRMS is highly appropriate in untargeted analyses. Indeed, complex mixtures can normally include hundreds of metabolites showing very slight differences in terms of mass; thus, a resolution of 0.1 mDa, at a minimum, is essential to help separate all the created ions (Marshall and Hendrickson, 2008).

From an operational standpoint, the biological sample, consisting of a complex mixture of metabolites, needs to be injected into the mass spectrometer either directly or following a separation method developed

Table 1
Advantages and limitations of MS and NMR spectroscopy as analytical platforms for metabolomics research.

Feature	Mass spectrometry	NMR spectroscopy
Sample preparation	Relatively demanding; it needs different columns and optimization of chromatographic and ionization conditions Metabolite extraction is required GC-MS requires volatile samples, often derivatization LC-MS can form adducts	Minimal preparation needed It can be directly applied to biofluids and intact tissues Sample recovery is possible
Sample measurement	It requires the combination of multiple techniques for a comprehensive analysis of the metabolome It usually needs different chromatography techniques for different classes of metabolites	It detects all metabolites in a single measurement within detectable range Spectral analysis is demanding All metabolites that have NMR concentration level can be detected in one measurement
Sample recovery	Destructive technique but it needs a small amount of sample	Non-destructive; sample can be recovered and stored for a long time; several analyses can be carried out on the same sample
Sensitivity	High: detection levels ranging from picomolar (10^{-12} M) to femtomolar (10^{-15} M) It detects most organic molecules and some inorganic molecules Broad metabolite coverage	Low; however, it can be improved with higher field strength, cryo- and micro-probes, and dynamic nuclear polarization Low detection range (micromolar, 10^{-6} M) It requires compounds to have protons It detects most organic molecules Less metabolite coverage
Selectivity	It can be used for both selective and nonselective (targeted and untargeted) analyses	In general, it is used for non-selective analysis
Reproducibility	Moderate since MS is a destructive technique	Very high
Analysis	Targeted analysis (superior for targeted analysis) Untargeted analysis	Untargeted analysis
Platform costs	Moderate	High
In vivo studies	No	Yes (used for ^{1}H magnetic resonance spectroscopy)

Abbreviations: AD, Alzheimer's disease; GC-MS, gas chromatography-mass spectrometry; LC-MS liquid chromatography-mass spectrometry; MS, mass spectrometry; NMR, nuclear magnetic resonance spectroscopy.

by gas chromatography (GC) or liquid chromatography (LC). Direct infusion MS (DIMS) is the simplest instrumental configuration, based on direct infusion of arranged specimens in the MS with no need for chromatographic separations (Anand et al., 2017; González-Domínguez et al., 2017b, 2014b). The absence of a time-consuming separation step enables reducing total analysis times, simplifying the analytical process (e.g., avoiding common chromatography-related troubles such as column clogging, retention time drifts), and increasing metabolome coverage. Accordingly, DIMS has been proposed as a "first pass" screening tool, facilitating a considerable coverage of metabolites and high-throughput investigations (Abdelnur et al., 2014; Biasioli et al., 2011), with great applicability in AD research (González-Domínguez et al., 2018b). As an alternative, GC coupled with MS (GC-MS) is a tool delivering elevated sensitivity and good resolution for low-molecular-weight metabolites, namely organic acids, amino acids, amines, carbohydrates, fatty acids, and some lipids (González-Domínguez et al., 2018a). However, GC-MS has several restrictions, including a relatively complicated sample preparation requiring a derivatization of non-volatile analytes, a high degree of variability, and the loss of thermolabile analytes (since not all metabolic compounds can be volatilized or made sufficiently thermally stable) (Gonzalez-Riano et al., 2016; Kohler et al., 2016). Thus, this platform alone cannot generate a comprehensive depiction of the AD metabolome. With complementary analytical performance, LC coupled with MS (LC-MS) permits the direct analysis of metabolites displaying evident physicochemical diversity, through the use of complementary retention mechanisms (e.g., reversed-phase liquid chromatography [RPLC]; hydrophilic-interaction liquid chromatography [HILIC]), ion exchange chromatography (IEC), and ionization techniques (e.g., electrospray ionization [ESI]; atmospheric pressure chemical ionization [APCI]; atmospheric pressure photoionization [APPI]) – with high-throughput, selectivity, and sensitivity (González-Domínguez et al., 2018a; Kuehnbaum and Britz-McKibbin, 2013; Reveglia et al., 2021). Specifically, RPLC is recommended for separating non- to mid-polar compounds, e.g., lipids, aromatic amino acids, and their microbiota products, and helps explore the non-polar and semi-polar fraction of the human metabolome. HILIC is advocated for polar molecules as it separates metabolites according to their hydrophilicity, with hydrophobic compounds being eluted faster and hydrophilic polar molecules being well-retained (Harrieder et al., 2022; Zeng et al., 2017). Hydrophilic metabolites encompass numerous categories of analytes, including several amino acids and derivatives, biogenic amines, carbohydrates, and organic acids, all of which participate in various essential metabolic pathways, including energy-related metabolism (glycolysis, tricarboxylic cycle), the urea cycle, and one-carbon metabolism, among others (González-Domínguez et al., 2021a). IEC is recommended for the analysis of ionic solutes, such as inorganic anions and cations. Hence, RPLC and HILIC are complementary methods and are frequently used orthogonally to comprehensively explore the AD metabolome in untargeted analyses (González-Domínguez et al., 2021a; Harrieder et al., 2022; Mill and Li, 2022). LC is frequently defined as high-performance LC (HPLC, also known as high-pressure LC) or ultra-performance LC (UPLC, also known as ultra-pressure LC). While HPLC operates at lower pressures (psi <6000), UPLC works at higher pressures (15,000 psi), therefore increasing analyte resolution and sensitivity as well as shortening run times. In addition to chromatography, MS can be combined with capillary electrophoresis (CE), leading to effective separation of polar and weakly/strongly ionic metabolites, with reduced specimen volumes. Nevertheless, CE-MS is rarely applied in metabolomics experiments because of its modest reproducibility and instrumental limitations (Kohler et al., 2016; Kohler and Giera, 2017).

Over the last years, significant improvements have been made in MS instrumentation, which have further increased the applicability and versatility of MS-based approaches in metabolomics research. On the one hand, the development of mass spectrometry imaging (MSI) techniques has enabled the spatial localization of metabolites within tissues and cells without labeling (Ma et al., 2023). In this regard, significant advances have also been made in MS-based single-cell metabolite analysis, of great utility to study cell-to-cell variability and thus provide a more accurate reflection of the cellular phenotype (Wang et al., 2023a). The use of ion mobility mass spectrometry (IM-MS) demonstrated great advantages compared to conventional MS systems, including improved confidence in identifications thanks to the measurement of cross-section values, increased peak capacity and signal-to-noise, and the capacity of being coupled with various fragmentation modes to facilitate structural characterization and molecular annotation (Paglia et al., 2022). Finally, the combination of MS with chemical isotope labeling (CIL) has been described for improving sensitivity, selectivity, accuracy, coverage, and analytical throughput (Gao et al., 2023). To complement these technical developments, significant efforts have also been made in the field of computational metabolomics, thereby facilitating the processing, annotation, modeling, and interpretation of MS data (Ebbels et al., 2023).

2.3. Targeted versus untargeted metabolomics

Typically, two different strategies can be applied in MS-based metabolomics, namely (I) untargeted (i.e. global) and (II) targeted analyses.

Untargeted metabolomics does not require a priori knowledge of the metabolome and its primary objective is to detect, in an unbiased way, and semiquantify (in terms of relative percentage) the largest range of metabolites within the sample under investigation. Briefly, untargeted MS allows for the comprehensive and systematic exploration of metabolites derived from the organisms, thus offering a robust hypothesis-generating approach to identify and validate candidate metabolomic biomarkers. However, separation/extraction/analytical procedures used can affect the classes of metabolites obtained (Johnson et al., 2016). A large volume (on the order of gigabytes) of complex, multi-faceted data set is generated that necessitates advanced statistical/bioinformatics tools, online platforms/softwares, and free databases/libraries to generate biological information needed to properly identify metabolites, study their correlation among samples, and explore their interconnectivity in metabolic pathways concerning the phenotype or the aberrant process (Johnson et al., 2016; Reveglia et al., 2021). This unbiased approach was considered to be most appropriate in AD as a way to boost the knowledge of pathophysiological mechanisms arising in the diseased brain (Reveglia et al., 2021).

On the other hand, targeted metabolomics aims at examining metabolites according to a priori knowledge of the metabolome and is typically driven by a specific biochemical hypothesis (hypotheses-driven approach) that encourages the inspection of a particular physiological and/or pathophysiological pathway. Here, different methodologies are applied to scrutinize well-defined metabolites or clusters of metabolites and, consequently, specifically related metabolic pathways of interest. Usually, this approach provides a greater sensitivity and selectivity than untargeted metabolomics. However, such a strategy is not useful for the discovery of novel molecules involved in the studied process or diseases (Johnson et al., 2016; Reveglia et al., 2021). Please, see Fig. 1 for a schematic representation of the untargeted and targeted workflows, as highlighted by Patti et al. (2012).

Notably, in the interface of the two above-mentioned analytical strategies, the use of large-scale targeted metabolomics emerged, in recent years, to bring together the advantages of both approaches, thereby enabling comprehensive and quantitative fingerprinting analysis (González-Domínguez et al., 2020; K. Li et al., 2017; Yan and Yan, 2015). Before selecting the appropriate metabolomic approach, it is crucial to address the scientific question and establish an effective experimental design. Since metabolomic experiments produce a significant volume of composite data from each type of biological specimen, efficient and precise bioinformatic/computational tools, such as the softwares MATLAB® and R (Li, 2020), as well as online platforms, such

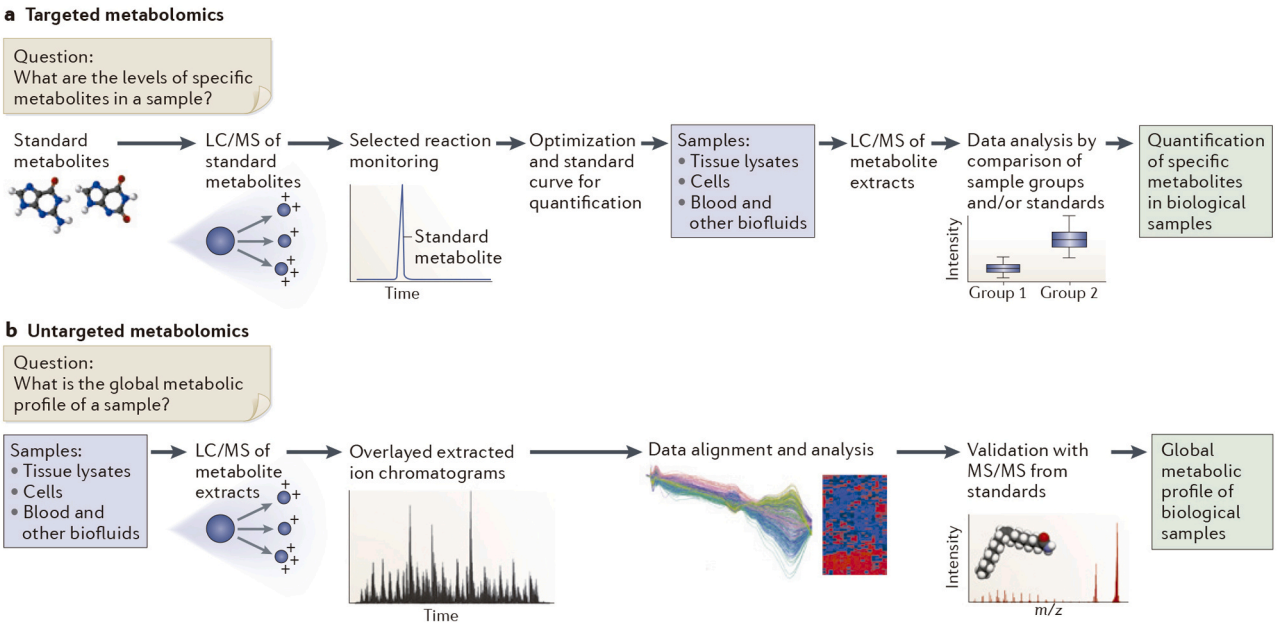

Fig. 1. The targeted and untargeted workflow for LC/MS-based metabolomics. Panel a. In the triple quadrupole (QqQ)-based targeted metabolomic workflow, standard compounds for the metabolites of interest are first used to set up selected reaction monitoring methods. Here, optimal instrument voltages are determined and response curves are generated for absolute quantification. After the targeted methods have been established on the basis of standard metabolites, metabolites are extracted from tissues, biofluids or cell cultures and analysed. The data output provides quantification only of those metabolites for which standard methods have been built. Panel b. In the untargeted metabolomic workflow, metabolites are first isolated from biological samples and subsequently analysed by liquid chromatography followed by mass spectrometry (LC/MS). After data acquisition, the results are processed by using bioinformatic software such as XCMS to perform nonlinear retention time alignment and identify peaks that are changing between the groups of samples measured. The *m/z* values for the peaks of interest are searched in metabolite databases to obtain putative identifications. Putative identifications are then confirmed by comparing tandem mass spectrometry (MS/MS) data and retention time data to that of standard compounds. The untargeted workflow is global in scope and outputs data related to comprehensive cellular metabolism. Note: ***from Patti, G.J., Yanes, O., Siuzdak, G., 2012. Innovation: Metabolomics: the apogee of the omics trilogy. Nat Rev Mol Cell Biol 13, 263–269. https://doi.org/10.1038/nrm3314 Copyright © 2012, Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. Reproduced with permission from Springer Nature Customer Service Center GmbH.*** *Abbreviations*: LC-MS, liquid chromatography coupled with mass spectrometry; MS/MS, tandem mass spectrometry; *m/z*, mass-to-charge ratio; QqQ, triple quadrupole mass analyzer.

as XCMS Online (Forsberg et al., 2018; Huan et al., 2018) and MetaboAnalyst (Howell and Yaros, 2023; Pang et al., 2021), are employed to deal with the complexity of the produced data in order to obtain relevant biological information (Reveglia et al., 2021). In general, efforts are underway to optimize the metabolomics analysis workflow to deliver valuable insights for researchers that can establish a preferable pipeline of metabolomics investigation and multi-omics integration analysis (Chen et al., 2022). Please, see Fig. 2 for a schematic overview of metabolomic data analysis.

3. Relevance of metabolomics in Alzheimer's disease research and biomarker discovery

3.1. Primary metabolites scrutinized

In general, alterations in circulating metabolites have been assumed to be related to impairments in cognition and dementia. Hence, improving the knowledge and comprehension of this link is expected to facilitate the elucidation of dementia pathogenesis, for AD and other forms of this disease. Metabolites, including amino acids, carbohydrates, lipids, bile acids, and fatty acids, show many potential roles in AD development and progression. Several investigations, some of which are discussed below, aim to detect and quantify AD-relevant metabolites in AD patients, MCI individuals, and cognitively normal individuals (Cuperlovic-Culf and Badhwar, 2020), in different tissues, including blood (plasma/serum), CSF or brain, therefore leading to an improved understanding of metabolic processes involved in AD pathogenesis and progression.

3.2. Amino acids and related metabolic compounds

The key function of amino acids as neurotransmitters, neuromodulators, or modulators of metabolism within the CNS is globally acknowledged. Numerous blood metabolomic examinations have reported altered concentrations of specific amino acids in AD patients. For instance, an LC-MS/MS platform disclosed a significant decrease of plasma tryptophan concentrations in AD versus older healthy controls (HC) (Li et al., 2010). Interestingly, tryptophan and its related metabolites can inhibit enzymes involved in Aβ biosynthesis. In particular, one metabolite, 3-hydroxyanthranilate, can directly impede $A\beta_{1-42}$ oligomerization. While some tryptophan-derived metabolites exert a neuroprotective role, other metabolites, including quinolinic acid, induce neurotoxicity and promote AD progression. Furthermore, some tryptophan metabolites regulate the neuroinflammatory and neuroimmune factors eliciting pro-inflammatory cytotoxicity in AD. Tryptophan metabolites have also the ability to affect microglia and associated cytokines in order to modulate the neuroinflammatory and neuroimmune factors triggering pro-inflammatory cytotoxicity in AD (Savonije and Weaver, 2023). The gut microbiota can also metabolize tryptophan to produce a myriad of indole derivatives with potential neuroactivity. For instance, patients with AD showed increased plasma concentrations of 3-indoleacetic acid, a metabolite found to be strongly correlated with various neurocognitive scores (Lin et al., 2023). Similarly, another study evidenced that 3-indolepyruvic acid, together with other microbiota-derived metabolites (short chain fatty acids, lithocholic acid), can serve as biomarkers for discrimination and prediction of AD (Wu et al., 2021).

In another study, a gradual reduction in serum values of aspartate,

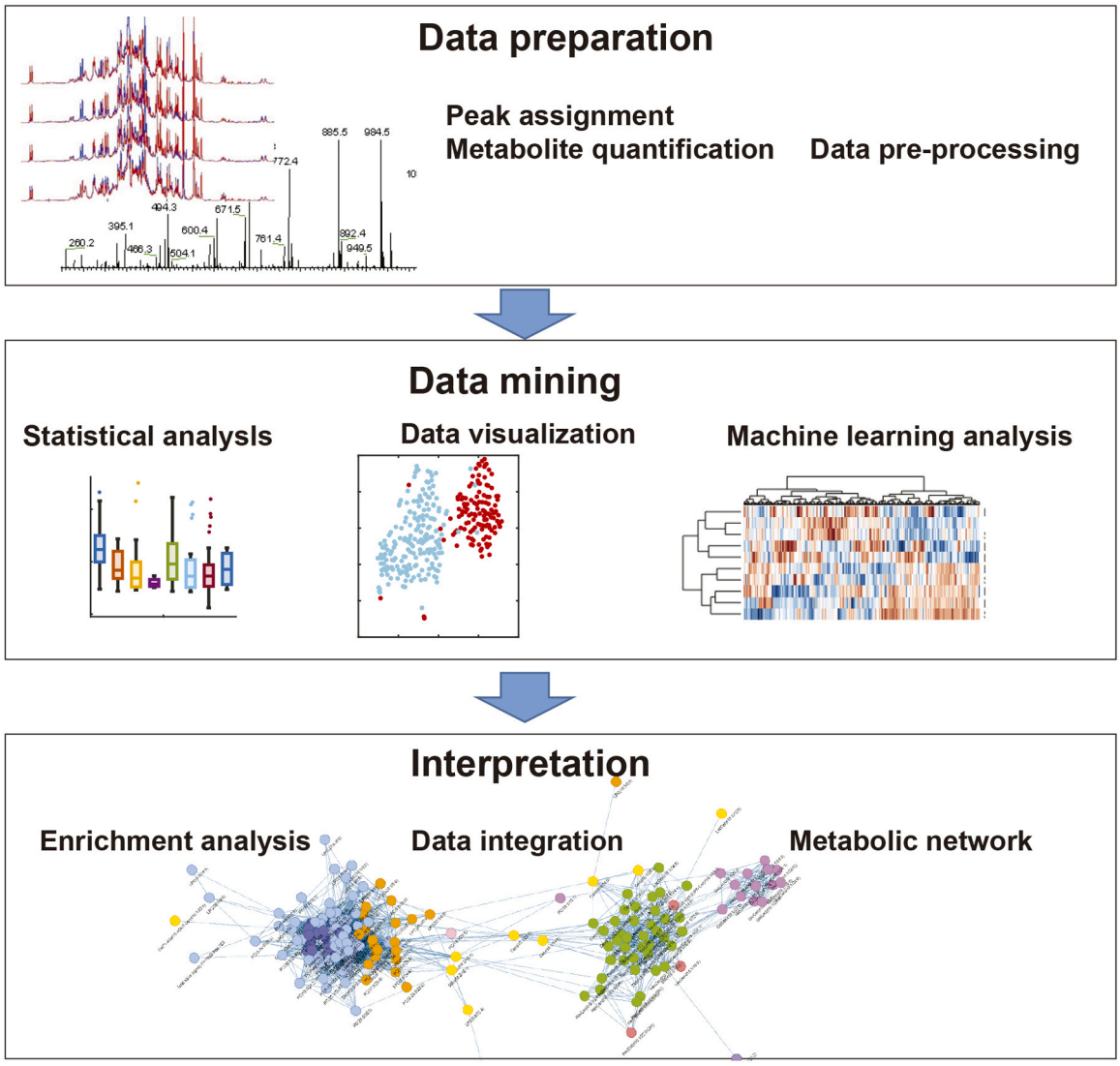

Fig. 2. Schematic overview of metabolomic data analysis. Metabolomics data analysis, regardless of the experimental platform, can be divided into data preparation, data mining and result interpretation. Data preparation includes metabolite assignment and quantification as well as data pre-processing (e.g., normalization). Data mining step should generally include both statistical and machine learning analysis followed by result interpretation through enrichment or network analysis. Metabolomics data can be integrated with other types of omics or clinical data for further interpretation.

glutamine, and phenylalanine in parallel to a rise in argininosuccinic acid, citrulline, and homocitrulline values was observed along the clinical continuum of AD – i.e., from the healthy status across subjective memory complaint and MCI to probable AD – with MS/MS (Corso et al., 2017). Similarly, the application of GC-MS analysis to serum samples from AD patients revealed decreased contents of aromatic amino acids (i.e. phenylalanine, tyrosine, and tryptophan) and branch chain (e.g. valine), and other amino acids (e.g. aspartate, glutamine, asparagine, histidine) (González-Domínguez et al., 2015a). Supporting these data, a recent multi-omics study based on the integration of MS-based metabolomics and proteomics evidenced profound perturbations in the metabolism of arginine, alanine, aspartate, glutamate, and pyruvate (François et al., 2022). Two recent analyses disclosed a correlation between greater dementia risk and higher plasma values of both glutamic acid and glutamine (Chouraki et al., 2017; Lee et al., 2018). An untargeted high-resolution metabolomics analysis, carried out in two independent cohorts, revealed increased plasma concentrations of glutamine and an unknown halogenated compound (m/z 246.9550) and decreased values of piperine (a dietary alkaloid with anti-oxidant and anti-inflammatory activities) in AD dementia. High concentrations of both glutamine and the halogen-containing molecule were also observed in CSF, highlighting the specificity of this finding to the CNS and their possible synthesis and/or access into the CNS (Niedzwiecki et al., 2020). Higher plasma concentrations of the sulfur-containing amino acid taurine and hypoxanthine (a purine derivative precursor of uric acid) (Chouraki et al., 2017) as well as the amino acid derivative creatinine in serum (Tynkkynen et al., 2018) were associated with reduced dementia risk. In contrast, greater plasma values of the aromatic amino acid anthranilic acid, an intermediate metabolite of the kynurenine pathway, were related to a more elevated risk of incident dementia (Chouraki et al., 2017). Moreover, diminished plasma concentrations of phenylalanine were observed in both amnestic MCI and mild AD (Mapstone et al., 2014). An investigation using HRMS followed by pathway enrichment analysis – conducted on stable MCI individuals, MCI converting to AD dementia patients, and age-matched HC – stressed that polyamine and L-arginine metabolisms were the only two metabolic pathways affected across all group comparisons. Particularly, the polyamine metabolism was more considerably affected than that of L-arginine. In addition, the two metabolic pathways were interconnected by sharing common metabolite intermediates. Both stable MCI and MCI

converters exhibited a significant rise in plasma L-arginine values together with a reduction in L-ornithine. Notably, stable MCI participants presented a substantial reduction of GABA; however, GABA was not subject to further decrease in MCI converters, thus highlighting a potential function of GABA decline as an early contributor to cognitive impairment (Graham et al., 2015). Metabolomic investigations showed that the known essential proteinogenic branched-chain amino acids (BCAAs) – leucine, isoleucine, and valine, consisting of an aliphatic side chain connected by a branch – were associated with AD dementia. A large longitudinal study conducted in eight prospective cohorts, overall including 22,623 participants and 995 incident dementia cases, used both NMR and MS-based (LC-MS/MS) platforms to analyze blood fraction and reported the association of increased serum concentrations of the three BCAAs with diminished AD dementia risk (Tynkkynen et al., 2018). A comparable outcome had been previously observed by Toledo et al. (2017) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, where lower plasma valine concentrations correlated with the rate of cognitive decay (Toledo et al., 2017). Another investigation reported that AD patients recruited in the Texas Alzheimer's Disease Research Care Consortium (TARCC) had elevated serum BCAAs concentrations versus HC, and that a metabolite of isoleucine (called sotolone) was inversely correlated with Mini-Mental State Examination (MMSE) scores. Thus, circulating BCAAs and/or their metabolic compounds were positively related to AD advancement (Siddik et al., 2022). Nevertheless, data linking BCAAs and AD are subject to discrepancies; for instance, a targeted LC-MS/MS analysis reported upregulated serum BCAAs in AD versus age-matched HC (H. Li et al., 2018).

Interestingly, more elevated baseline serum concentrations of asparagine were associated with a more rapid decay in global cognition follow-up. Asparagine is a non-essential amino acid critical for the development and metabolic control of the brain (Ruzzo et al., 2013). In this regard, previous analyses conducted in mouse models found that the activation of the asparagine endopeptidase enzyme during aging promoted tau aggregation and caused neurodegeneration (Zhang et al., 2014). Moreover, inhibition of this enzyme might induce therapeutic effects for the treatment of neurodegenerative diseases (Zhang et al., 2016).

A targeted quantitative metabolomics approach exploiting CE-MS was conducted on brain samples in regions both susceptible and resistant to AD pathology; these brain samples were collected from AD patients, asymptomatic AD individuals, and HC, all enrolled in the Baltimore Longitudinal Study of Aging (BLSA). Major variations in terms of metabolite expression were observed in AD versus HC, as well as associations of metabolites with disease severity, primarily in the inferior temporal gyrus. The concerned metabolic compounds participated in biochemical reactions belonging to the methionine cycle, transsulfuration and glutathione synthesis, polyamine synthesis/catabolism, the urea cycle, glutamate-aspartate metabolism, and neurotransmitter metabolism, especially of gamma-aminobutyric acid. The integration of these results with transcriptomic studies, performed in the entorhinal cortex and hippocampus, led to the observation of a substantial AD-associated dysregulation of transmethylation and polyamine synthesis/catabolism, including anomalies in neurotransmitter signaling, the urea cycle, aspartate-glutamate metabolism, and glutathione synthesis (Mahajan et al., 2020).

In examining the distinct metabolic variations in different brain regions associated with AD and the application of spatial metabolomics, a study conducted in 2016 employed GC-MS to analyze seven specific brain areas. These regions included the hippocampus, entorhinal cortex, and middle-temporal gyrus, known to be severely impacted by AD, as well as the sensory cortex, motor cortex, and cingulate gyrus, which are moderately affected, and the cerebellum, which remains unaffected. This extensive metabolomic investigation revealed disruptions in critical biological pathways, including glucose metabolism and amino acid metabolism, particularly in the severely affected regions and the cingulate gyrus. However, the regional information obtained through MS remains limited (Xu et al., 2016). MSI is a promising spatial technique with the potential to offer further insights into regional changes associated with AD. A limited number of MSI-based studies have been conducted, primarily utilizing AD mouse models due to their smaller brain size. These investigations identified dysregulation in several pathways, such as purine metabolism (Esteve et al., 2017) and glutamine-glutamate metabolism (Wang et al., 2023b). Human samples are less frequently used, as the entire human brain cannot be analyzed on a single slide, unlike mouse brain. However, a recent comprehensive review explored the numerous applications of MSI on human brains in AD and other related disorders (Ajith et al., 2021). One notable study examined sulfatide species and discovered differences in sulfatide hydroxylation between grey matter and white matter. Interestingly, no differences were observed in sulfatide expression between AD patients and HC (Yuki et al., 2011). Incorporating sophisticated methods like GC-MS and MSI collectively holds the promise of elevating our comprehension of regional variations in brain metabolism and molecular pathways associated with AD in the future.

The metabolism of homocysteine, a non-proteinogenic α-amino acid biosynthesized from methionine, was found to be involved in several age-related diseases, including AD (Morris, 2003; Smith et al., 2018). Raised blood concentration of homocysteine (hyperhomocysteinemia), which is a well-known cardiovascular risk factor, has been reported to be closely associated with the development of AD (Seshadri et al., 2002; Smith et al., 2018) and represents a potential biomarker of disease progression (Farina et al., 2017). In this respect, it was shown that AD and MCI were characterized by vascular-related metabolic alterations, as reflected in elevated serum concentrations of homocysteine-cysteine disulfide (one of the most abundant oxidized forms of homocysteine), asymmetric dimethyl-arginine (endogenous inhibitor of nitric oxide synthase), and phenylalanyl-phenylalanine (a peptide derived from a vasoactive oligopeptide cleaved by the angiotensin converting enzyme) (González-Domínguez et al., 2014a). Furthermore, an association between increased homocysteine values and memory impairment exists even in a healthy population, determined through a longitudinal untargeted metabolomics analysis carried out on plasma samples of dementia-free middle-aged adults using UPLC-HRMS; the results of this study corroborate the important role of homocysteine in cognitive aging and disorders (Hajjar et al., 2020). Notably, results of metabolomic analyses of serum homocysteine indicated that it can downregulate metabolic compounds involved in lipid and fatty acid metabolism pathways such as glycerolipids, glycerophospholipids, and polyunsaturated fatty acids (PUFAs) (Kumar et al., 2021; B. Li et al., 2018). A multi-dimensional study, exploring the link between leukocyte telomere length (LTL, measured by quantitative PCR) and serum metabolite concentrations (determined by a targeted metabolomics platform using ESI-MS/MS), reported positive or negative associations of LTL with some compounds implicated in homocysteine metabolism, inflammation, and oxidative stress (van der Spek et al., 2019).

Since the hippocampus, one of the most relevant brain regions involved in learning and memory, is widely recognized as the most vulnerable region in AD pathology, a study used untargeted NMR spectroscopy to identify the hippocampal metabolic profiles specifically altered in an animal model of AD-like cerebral amyloidosis (McGill-R-Thy1-APP transgenic rat). Overall, 26 metabolites were identified, including amino acids, carboxylic acids, and nucleotides. In particular, a panel of nine metabolites – nicotinamide adenine dinucleotide (NAD), nicotinamide (an amide of nicotinic acid), taurine, valine, tyrosine, N-acetylaspartate, glutamate, glutathione, and creatine – were significantly altered in transgenic rats versus controls, with two notable signals essentially attributed to NAD and nicotinamide. Subsequent analyses revealed that NAD expression levels were significantly lower in the hippocampus of AD-like transgenic rats compared with control animals. The translational value of these findings was confirmed by a significant reduction in plasma nicotinamide concentrations (measured by targeted GC-MS) in patients with AD included in the German study on Aging,

Cognition and Dementia (AgeCoDe) longitudinal cohort. Conversely, individuals within the highest tertile of plasma nicotinamide concentrations had a 27% risk reduction of progressing to AD over a 2.5-year follow-up. Hence, a reduction of plasma nicotinamide concentrations was reported a couple of years prior to conversion to AD, thus suggesting its potential usefulness as biomarker for AD progression (Dalmasso et al., 2023). In this regard, other studies also reported profound hippocampal metabolic perturbations in the APP/PS1 transgenic mouse model, encompassing abnormal homeostasis of amino acids, acyl-carnitines, nucleotides, and various lipid classes (González-Domínguez et al., 2015g). Although these disturbances were mostly expressed in the hippocampus and cortex, the areas that are primarily affected in AD, the authors found similar changes in other brain regions (e.g. cerebellum) and the peripheral system (e.g. blood, liver, kidneys) (González-Domínguez et al., 2015c, 2015d, 2015e).

3.3. Carbohydrates

The human brain, which relies almost completely on glucose as a substrate for energy production, accounts for approximately 25% of whole-body glucose utilization. One of the key metabolic features of AD pathology is brain glucose hypometabolism. Growing evidence indicates that a disruption in glucose utilization occurs very early in the clinical trajectory of the disease, being evident even in preclinical stages (Calsolaro and Edison, 2016).

In addition, dysglycemia, including both chronic hyperglycemia and repeated hypoglycemia, has been consistently identified as a risk factor for the development of AD (Hsieh et al., 2019). Given the key role played by an altered glucose metabolism in the etiology and progression of AD (Mullins et al., 2018), some authors conceptualized AD as a novel "diabetes type 3" (González et al., 2022). This possibility was originally prompted by the observation that an impaired glucose metabolism due to reduced glycolytic flux may be intrinsic to AD pathogenesis, beginning several years before the onset of clinical symptoms (An et al., 2018). Several potential mechanisms have been proposed to explain the well-known link between diabetes and AD. First, chronic hyperglycemia may lead to the accumulation of neurotoxic advanced glycation end products. Second, reduction of insulin signaling in the brain can induce the formation of cerebral amyloid deposits and promote tau hyperphosphorylation. Third, diabetic micro- and macro-angiopathy may act as a contributing factor to blood-brain barrier (BBB) dysfunction, which is central to the onset and progression of neurodegeneration. Fourth, hyperglycemia may promote recruitment and activation of microglia, thereby resulting in neuroinflammation and neuronal damage (Hsieh et al., 2019). Finally, both vascular and non-vascular brain glucose transporters (GLUTs), including GLUT1 and GLUT3, are dysfunctional and/or poorly expressed in AD brains, a process which could starve the brain of glucose and accelerate cognitive decline (Chornenkyy et al., 2019).

By taking advantage of ^{1}H-nuclear magnetic resonance spectroscopy (^{1}H NMR), a recent metabolomic analysis was conducted on serum samples collected from 32 individuals categorized as "subjective cognitive decline (SCD) plus" – a more severe form of SCD that is likely to be an expression of preclinical AD (Jessen et al., 2014). Perturbations of glucose and BCAA metabolism were identified as the most prominent features of "SCD plus" individuals (Yang et al., 2022). Importantly, the occurrence of glucose metabolic dysfunction has been identified in patients with SCD in two independent studies (Dong et al., 2021; Liu et al., 2020). In this regard, Hajjar et al. (2020), by using an untargeted metabolomics approach based on high-resolution LC-MS, found that perturbed regulation of sugar metabolism, characterized by altered CSF concentrations of N-glycan, sialic acid, amino sugars, and galactose, correlated with AD-related phenotypes (Hajjar et al., 2020).

In a study analyzing a total of 122 CSF metabolites with LC-MS, five of them – phosphoenolpyruvate, 2-phosphoglycerate, 3-phosphoglycerate, pyruvate, and dihydroxyacetone phosphate – were found to be significantly lower in AD patients compared with HC (Bergau et al., 2019). These metabolic alterations in the CSF are reflective of central glucose hypometabolism and are in accordance with the results reported in [^{18}F]-fluorodeoxyglucose (FDG)-positron emission tomography ([^{18}F]-FDG-PET) imaging studies (Verclytte et al., 2016). Another shotgun MS study found that, in patients with AD, glyceraldehyde-3-phosphate dehydrogenase – a classical glycolytic enzyme that also displays a number of non-glycolytic functions – is hyperexpressed in the proteome of the temporal neocortex (Musunuri et al., 2014). Currently, glycolytic dysfunction is widely regarded as a prominent metabolic anomaly in the very early development of AD (Mamelak, 2012). In turn, glycolytic robustness, mediated at least in part by hexokinase upregulation, can be a contributing factor to resilience against AD.

3.4. Lipids and fatty acids – Lipidomics

Lipids have key functions in the CNS and periphery since they preserve cell membrane architecture and arrangement (directly affecting the fluidity and solubility of the membrane itself) and critically participate in several signaling pathways (Trushina and Mielke, 2014; Wilkins and Trushina, 2018). Notably, the significant cerebral atrophy that characterizes AD implies the depletion of structural lipids. It is well-known that changes in brain lipid levels due to their diminished synthesis or altered metabolism may lead to homeostatic dysregulation and, ultimately, neurodegeneration (Mielke and Lyketsos, 2006). Such a dyshomeostasis of lipid metabolism leads to cerebral aberrant activities characterizing the progression of AD pathophysiology, as depicted by Chew and colleagues (2020) (Chew et al., 2020) (Fig. 3).

Moreover, genomic studies repeatedly demonstrate that the *ε4* allele of apolipoprotein E gene (*APOE ε4*) is the crucial susceptibility factor for sporadic, late-onset AD (Yamazaki et al., 2019). Since the brain is the most lipid-rich organ in the human body and lipid molecules play a major role in inflammation and signaling, the development and application of lipidomics – the omic analysis consisting of large-scale studies of all classes of lipid molecular species and networks in biological systems (Schmelzer et al., 2007) – to AD pathophysiology is becoming rapidly relevant. In addition to "lipidology", the pure examination of lipids, lipidomics incorporates the examination of lipid-metabolizing enzymes and transporter proteins, as well as their genes and activity regulation (Reinisch and Prinz, 2021; Ware et al., 2019); the spatio-temporal quantitative analysis of lipids; and the investigation of their function (Hu and Zhang, 2018). As a result, lipidomics requires the use of appropriate technologies to measure the location, expression/-concentration, and regulation of lipids, enzymes, transporters, and genes in time, including integrative high-throughput applications (van Meer et al., 2007). Because of their predominant hydrophobic nature, lipids need to be treated and analyzed separately (e.g., requiring different solvent systems) from other small-molecule metabolites (Huynh et al., 2017).

Lipidomic technologies progressed to enable both global (i.e., non-targeted) lipid investigations and targeted analyses (i.e., studies of definite classes of lipids) (Trushina and Mielke, 2014; Wilkins and Trushina, 2018). The examination of the structure and function of various lipid species – usually classified into eight main categories, namely fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, polyketides, prenols, and sterols (Fahy et al., 2005; Kuo and Tseng, 2018) – is expected to explain the mechanisms underlying cellular lipid homeostasis, clarify the roles of lipids in several human diseases, and help discover potential diagnostic and prognostic biomarkers of AD.

Various lipid compounds associated with AD pathophysiology have been increasingly identified by lipidomic research, strengthened by rapid progress in analytical chemistry that allows for reproducible and high-throughput assessment of numerous lipid classes (Quehenberger et al., 2010). Given the considerable commonalities in metabolic

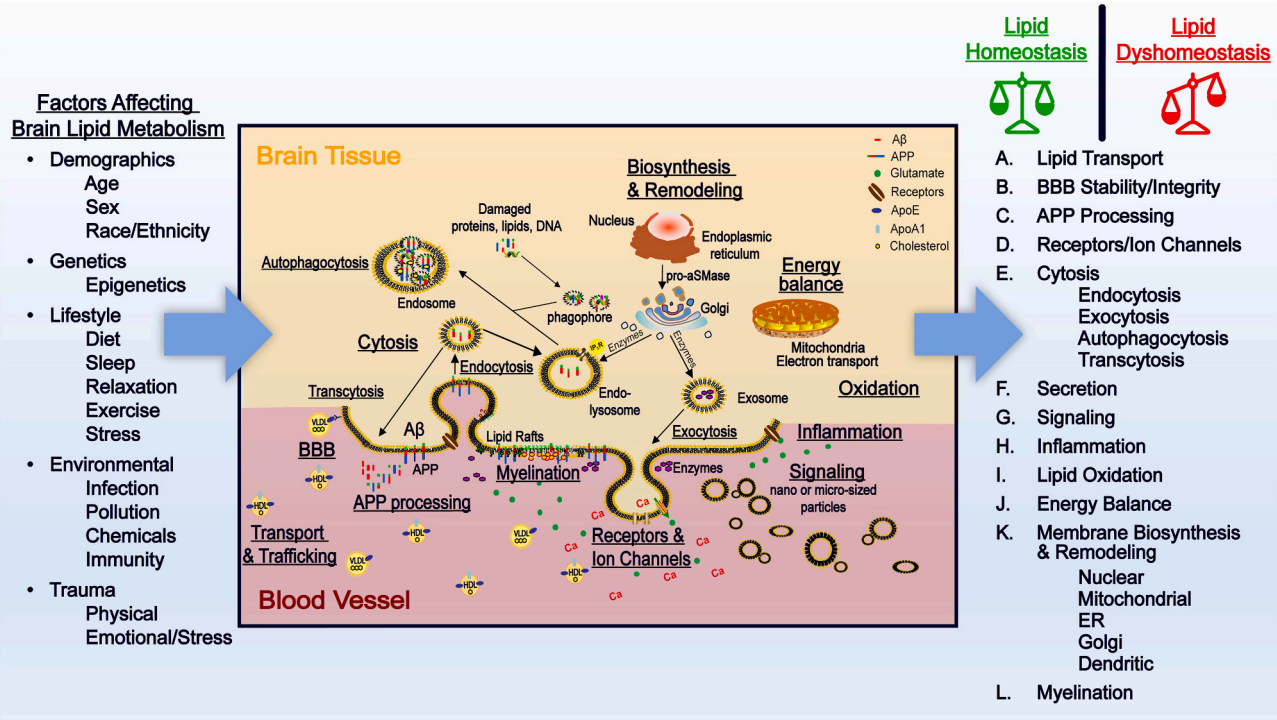

Fig. 3. Factors that affect brain lipid metabolism and the importance of lipids in healthy aging and AD. Factors that affect brain lipid metabolism. Demographic factors, genetics, lifestyle, the environment, and trauma can influence lipid metabolism in the brain. Interestingly, these factors that influence lipid metabolism are also recognized risk factors of AD. Abnormalities in lipid metabolism can contribute to dysfunctional brain networks that associate with AD pathology. Importance of lipid metabolism in brain function and AD pathology. In healthy aging, normal transport of lipids through apolipoproteins contribute to the function of the brain. Homeostatic control of the brain lipid environment is responsible for sustaining a normal BBB, providing the right environment for normal APP processing, the right composition for ion channels and receptors, cytosis, vesicle formation, and secretion, signaling, inflammation, oxidation, energy balance, and membrane biosynthesis and remodeling. Dyshomeostasis in lipid delivery into the brain and its metabolism attributes to disturbed BBB, abnormal APP processing, disturbance in cytosis, signaling, energy balance, and enhanced/sustained inflammation and oxidation. Over time, these processes lead to neuronal death that is the hallmark of AD pathology. *Note*: ***from Chew, H., Solomon, V.A., Fonteh, A.N., 2020. Involvement of Lipids in Alzheimer's Disease Pathology and Potential Therapies. Front Physiol 11. https://doi.org/10.3389/fphys.2020.00598 Copyright © 2020 Chew, Solomon and Fonteh. Reproduced under the terms of the Creative Commons Attribution License (CC BY)*** (https://creativecommons.org/licenses/by/4.0/). *Abbreviations*: Aβ, amyloid-β; AD, Alzheimer's disease; APOE ε4, ε4 allele of the APOE gene; APP, amyloid precursor protein; BBB, blood-brain barrier.

fluctuations between CSF and blood (Trushina et al., 2013), brain-related variations in lipid molecular profiles are anticipated to be useful blood biomarkers (Wong et al., 2017a, 2017b). Indeed, lipidomics is increasingly gaining relevance in the discovery of biomarkers for AD, with analyses exploring quantitative lipid profiles being performed in blood samples via lipidomics-based strategies, exploring different lipid classes mediators and categories.

3.4.1. *Sphingolipids*

Among the numerous compounds associated with AD detected by lipidomic research, sphingolipids are often in the spotlight. Sphingolipids are a group of phospholipids that include a sphingosine backbone; they are constituents of the phospholipid bilayer in the plasma membranes of eukaryotic cells and participate in the regulation of cell growth, death, senescence, adhesion, migration, inflammation, angiogenesis, and intracellular trafficking (Hannun and Obeid, 2008; Kraft, 2017).

Sphingomyelins (SMs) are the simplest and the most common sphingolipids (each one containing a fatty acid, a phosphoric acid, sphingosine, and choline); they largely reside in two locations within the brain: lipid rafts, found in neurons, astrocytes, and microglia where they are involved in several aspects of signal transduction and homeostasis of the brain, and the membranous myelin sheath that insulates many nerve cell axons. As part of lipid rafts, SMs are involved in signal transduction and the regulation of inflammatory processes as well as response to oxidative stress (Kao et al., 2020; Schneider et al., 2019). Lipidomic assays in AD brains found significant associations between severity of AD pathology at autopsy and increased serum concentrations of SMs, namely those with acyl residue sums C16:0, C18:1, and C16:1, and hydroxysphingomyelin with acyl residue sum C14:1 (SM (OH) C14:1). This association was conserved throughout preclinical and prodromal stages of AD as well (Varma et al., 2018). In contrast, a more recent targeted metabolomic approach carried out in a cohort of normal controls, pre-conversion individuals, and MCI/AD patients, via an ESI-LC-MS/MS system, reported no major difference in the concentrations of SMs (fourteen distinct SM species were quantified) between these groups. Remarkably, the amounts of only one molecule, SM (OH) C14:1, were decreased in the pre-conversion and MCI sets versus normal controls (Fote et al., 2021). In another study including histopathologically-confirmed AD patients and control cases, erythrocytes, analyzed by UPLC-MS/MS, were investigated as a metabolically active and accessible source for discovering AD candidate biomarkers, being observed a consistent decrease in the content of some sphingolipids and sphingolipid-related species (Mill et al., 2022). Plasma SMs concentrations have been frequently observed to be either increased or decreased (D. Li et al., 2019; Lin et al., 2017; Tajima et al., 2013). Such contradictions emerged from the literature are thought to be caused by several issues, including which patient samples or animal models are investigated, which tissue is studied, demographics of the study participants, or even exact timing of sample collection (Hammad et al., 2010).

Ceramides are a subcategory of bioactive lipids belonging to the sphingolipid family (Chaurasia and Summers, 2015). They are secondary messengers synthesized de novo in the endoplasmic reticulum, starting with the conjugation of the amino acid serine with palmitate.

Besides the generation by *de novo* synthesis, cells can produce ceramide by SM hydrolysis through the activation of sphingomyelinases (Garcia-Ruiz et al., 2015). These molecules assist in several cellular activities, such as controlling proliferation, senescence, and cell death; indeed, as a result of toxic stimuli, cells can activate sphingomyelinases inducing a rapid and transient release of ceramide in definite sites involved in specific signaling pathways (Garcia-Ruiz et al., 2015). They can initiate a cascade of biochemical alterations, ultimately resulting in neuronal death by different mechanisms, primarily along the pathways linked protein kinase B (PKB, also known as Akt) and mitogen-activated protein kinases (Jazvinšćak Jembrek et al., 2015). The sphingomyelinase-ceramide pathway has been directly linked to Aβ peptide-induced apoptosis; results from a 2004 study suggest that Aβ induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide cascade (Lee et al., 2004). Interestingly, ceramides have also been linked to insulin resistance and atherosclerosis in AD (Ichi et al., 2006; Summers, 2010). Lipidomic analyses based on ESI-MS/MS reported increased ceramide expression in AD brains, mainly ceramides C16:0, C18:0, C20:0, and C24:0 (Filippov et al., 2012). Notably, LC-ESI-MS analysis of AD brains disclosed that laser micro-dissected senile plaques were enriched in saturated ceramides Cer (d18:1/18:0) and Cer(d18:1/20:0) (Panchal et al., 2014). In addition, CSF concentrations of ceramides were increased in AD patients versus age-matched amyotrophic lateral sclerosis patients and other neurological controls (Satoi et al., 2005). Higher baseline serum ceramide concentrations were related to a greater risk of all-cause dementia and AD; such associations were more evident in AD than in all-cause dementia in older women from the Women's Health and Aging Study II (WHAS II) (Mielke et al., 2012). In another investigation, plasma ceramide C22:0 and C24:0 concentrations, cross-sectionally measured by HPLC-ESI-MS/MS, were significantly perturbed in amnestic MCI versus both HC and AD; longitudinally, increased plasma ceramide C22:0 and C24:0 concentrations predicted cognitive impairment and hippocampal volume loss among amnestic MCI individuals, thus indicating a predictive value of peripheral ceramides (Mielke et al., 2010). Recently, a metabolome-wide association study (MWAS), executed via UPLC-MS, demonstrated an association between abnormal homeostasis of ceramides and AD-related single-nucleotide polymorphisms in the *ABCA7* (ATP binding cassette subfamily A member 7) gene. In particular, it was proposed that the activation of microglia might trigger the expression of the sphingosine kinase enzyme and, thus, increased intracellular concentrations of hexosylceramides (Dehghan et al., 2022). A longitudinal analysis of probable AD patients, quantifying sphingolipids via ESI-MS/MS, reported that a greater plasma SM/ceramide ratio predicted slower disease progression among AD patients, thus representing a potential blood-based biomarker for clinical AD advancement (Mielke et al., 2011). A multi-dimensional MS-based shotgun lipidomics analysis, conducted on AD patients and cognitively HC to measure plasma concentrations of over 800 molecular species of lipids, revealed substantially reduced values of some SM species (especially those containing long aliphatic chains) and increased values of several ceramide species in AD compared to HC. Furthermore, the ceramide/SM ratio (species containing identical fatty acyl chains) differed between AD patients and HC (Han et al., 2011).

In analyzing the molecular underpinnings of SM and ceramide disruption in AD, multi-omics analyses (i.e., post-mortem brain transcriptomics/plasma lipidomics/metabolic flux examination) supported by multimodal neuroimaging inspection have been carried out to characterize the central and peripheral metabolic changes affecting this pathway. In particular, by means of plasma metabolomic and lipidomic analysis, the SM(d43:1)/SM(d34:1) ratio was identified as a key intermediate trait for sphingolipid dysregulation in patients with AD. In addition, metabolite genome-wide association studies revealed that the sphingosine-1-phosphate (S1P) metabolite may serve as a potential drug target in AD. Finally, they found that prolonged exposure to fingolimod – a S1P receptor modulator that has previously gained regulatory approval for the treatment of multiple sclerosis (Vasiliou, 2010) – was able to alleviate AD-associated deficits in amyloidogenic APP/PS1 mice. Collectively, these data support the usefulness of multi-omics analyses to comprehensively capture the specific molecular perturbations affecting pathways known to be altered in AD. This knowledge has significant implications for treatment and holds promise to expand the current therapeutic armamentarium (Baloni et al., 2022).

A study conducted by Barupal and colleagues (2018) using UPLC-MS on a large, published AD lipidomics data set within ADNI Phase 1 cohort ($N > 800$) (Barupal et al., 2018) made it possible to explore 349 serum lipids and to test the association of sets of co-regulated lipids with disease diagnosis, CSF core neurochemical markers ($A\beta_{1–42}$ and t-tau) and imaging markers (brain atrophy) of AD, and cognitive function. AD diagnosis was related to 7 out of 28 lipid sets, four of which showed remarkable association with cognitive impairment, including monounsaturated fatty acids (MUFAs) and PUFAs, such as omega-3 and omega-6 fatty acids. A positive link was observed between MUFA-containing complex lipids and brain atrophy and t-tau accumulation; a negative link was reported between PUFA-containing complex lipids and AD diagnosis and cognitive deterioration. Interestingly, CSF $A\beta_{1–42}$ concentrations were associated with glucosylceramides, lysophosphatidylcholines (lysoPCs), and unsaturated triacylglycerols; both CSF t-tau and brain atrophy were associated with monounsaturated SMs and ceramides, as well as eicosapentaenoic acid-containing lipids (Barupal et al., 2019). Similarly, in another analysis scrutinizing 60 participants from an Icelandic memory clinic via untargeted CSF lipidomic analysis with UPLC-MS, it was observed that ceramide C18 was a discriminating feature between the CSF profile of AD patients and that of non-AD individuals (Teitsdottir et al., 2021). Another correlative analysis investigating the clinical and pathological phenotypes of AD and Lewy bodies dementia (LBD) disclosed that plasma ceramides C16:0, C18:1, C20:0, and C24:1, as well as monohexosylceramides C18:1 and C24:1 (measured by ESI-MS/MS) were up-regulated in patients with autopsy-confirmed AD pathology versus cognitively normal individuals. However, these lipids could not help distinguishing between autopsy-confirmed AD and LBD pathologies (Savica et al., 2016).

3.4.2. *Glycerophospholipids*

Besides sphingolipids, altered concentrations of glycerophospholipids (also referred to as phospholipids) in AD have been deeply explored. Glycerophospholipids are ubiquitous in nature and are crucial components of the cell phospholipid bilayer, constituting around 80% of total membrane lipids, as well as being implicated in the metabolism of cell signaling. They are amphiphilic molecules, characterized by acyl chains and glycerol (as the hydrophobic moiety) and by a phosphate group and polar head (as the hydrophilic part). Various subcategories of glycerophospholipids with diverse polar heads, including phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI), and phosphatidylserine (PS), can be generated (Hachem and Nacir, 2022; Kao et al., 2020). An analysis using UPLC-TOF-MS found reduced serum concentrations of PCs (incorporating choline as a headgroup), as well as SMs and sterols, in AD patients versus MCI and HC (Orešič et al., 2011). Lower plasma values of three PCs – PC 16:0/20:5, PC 16:0/22:6, and PC 18:0/22:6 – were observed in AD patients and MCI individuals versus age-matched HC, through a multiplatform screen consisting of LC-MS and NMR spectroscopy (Whiley et al., 2014). The reduction of the same PCs was also associated with poor memory performance in healthy older individuals, stressing that phospholipid dyshomeostasis is a common factor in AD and age-related memory impairment (Simpson et al., 2016). A milestone targeted quantitative metabolomic/lipidomic analysis conducted by Mapstone and colleagues (2014), using stable isotope dilution (SID)-MRM MS (SID-MRM-MS) to definitely detect and quantify lipids, amino acids, and biogenic amines in plasma, disclosed and validated a 10-phospholipid biomarker signature. Decreased concentrations of this metabolite panel – consisting of various PCs (PC diacyl (aa)

C36:6, PC aa C38:0, PC aa C38:6, PC aa C40:1, PC aa C40:2, PC aa C40:6, and PC acyl-alkyl (ae) C40:6), a lysophosphatidylcholine (lysoPC a C18:2), and acylcarnitines (propionyl acylcarnitine (C3) and C16:1-OH) – was able to predict conversion from HC to amnestic MCI (aMCI) or AD, within 2–3 years, with elevated (>90%) accuracy (Mapstone et al., 2014). PCs and acylcarnitines are phospholipid classes showing crucial activity in the integrity and functionality of cell membranes (Jones et al., 2010; van Meer and de Kroon, 2011). Thus, it was speculated that this plasma 10-phospholipid biomarker signature might characterize the disruption of neural cell membranes in participants progressing to aMCI or AD and may designate the conversion from preclinical states, where synapse dysfunction/loss and early neurodegeneration start inducing subtle cognitive alterations (Mapstone et al., 2014). Then, this molecular profile was expanded to a 24-metabolite panel, with increased sensitivity and specificity, including 22 perturbed lipids, comprising several PCs (Fiandaca et al., 2015).

A targeted UPLC-MS/MS-based metabolomic approach by Huo and colleagues (2020) was applied to ante-mortem peripheral blood (serum) and post-mortem brain samples from two large community-based longitudinal cohort studies of risk factors for cognitive decline and incident AD dementia, namely the Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP), together referred to as ROSMAP (Bennett et al., 2018). This study disclosed that increased serum concentrations of three acylcarnitines (tetradecadienylcarnitine (C14:2), decanoylcarnitine (C10), and pimelylcarnitine (C7-DC), significantly predicted a decreased risk of incident AD following a 4.5-year follow-up, independent of age, sex, and education. When combined altogether, the effect of C14:2, C10, and C7-DC was associated with over 60% decrease in risk for incident AD. Furthermore, higher concentrations of C14:2, C10, and C7-DC were related to a slower cognitive impairment over time (Huo et al., 2020). Octadecadienylcarnitine (C18:2) and hexanoylcarnitine [C6 (C4:1-DC)] showed higher concentrations in blood than in CSF in patients not experiencing post-operative delirium, an indicator of AD risk while the opposite is true in delirium prone group (Cuperlovic-Culf et al., 2021). Acylcarnitines are esters arising from the conjugation of carnitine (3-hydroxy-4-N-trimethylammoniobutanoate, a quaternary ammonium compound biosynthesized from the essential amino acids lysine and methionine in the liver and kidneys (STEIBER, 2004) with fatty acids (i.e., acyl groups) (S. Li et al., 2019). Acylcarnitines are a large class of metabolites that are members of the non-proteinogenic amino acid family (S. Li et al., 2019). They are involved in long-chain fatty acid metabolism by acting as carriers of long-chain fatty acids into mitochondria for β-oxidation, thereby generating energy to support cellular activities (Jones et al., 2010). In addition, acylcarnitines participate in BCAA metabolism (Mihalik et al., 2010), insulin resistance (Schooneman et al., 2013), cellular stress responses (McCoin et al., 2015), and cholinergic neurotransmission (Jones et al., 2010). Earlier investigations reported lower serum concentrations of several acylcarnitines in AD patients versus cognitively HC, in line with the above-described analysis (Ciavardelli et al., 2016; Cristofano et al., 2016).

Using an integrative systems biology framework to systematically interrogate genetic, transcriptomic, proteomic, and clinical data from the ADNI cohort participants and metabolomics data available from the Alzheimer's Disease Metabolomics Consortium (ADMC), Horgusluoglu et al. (2022) sought to identify specific blood metabolites highly associated with AD pathology, as well as key biological processes underlying their modifications. The results revealed an altered balance between essential amino acids/BCAAs and a disturbed short-chain acylcarnitine homeostasis, with medium/long-chain acylcarnitine serum concentrations being significantly different (in the opposite direction) in AD patients versus HC. Notably, two genes – ATP Binding Cassette Subfamily A Member 1 (ABCA1) and Carnitine Palmitoyltransferase 1 A (CPT1A) – and two proteins (adiponectin and neutrophil gelatinase-associated lipocalin) were identified as key regulators of acylcarnitines and amines. Increased expression levels of both the *ABCA1* gene and the adiponectin protein were primary drivers for the decrease in short-chain acylcarnitines and amines observed in AD. These results highlight the usefulness of large-scale multi-omics efforts to identify the most relevant metabolic disturbances in AD and their underlying biological regulators (Horgusluoglu et al., 2022).

Notably, various attempts were carried out to replicate the original 10-phospholipid signature (Mapstone et al., 2014). An Austrian multi-cohort study using UPLC-QTrap-MS found that three lipid metabolites in plasma, PC aa C34:4, PC aa C38:3, and PC aa C40:5, could significantly discriminate HC from MCI and AD. Moreover, the ratio between PC aa C34:4 and lysoPC a C18:2 could distinguish HC from MCI and AD with further higher significance, thus highlighting the relevance of PCs in AD pathophysiology (Klavins et al., 2015). Another investigation in a subset of participants recruited from the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (ARIC-NCS) reported that only PC aa C40:2 and PC aa C36:6 were related to the prevalence of MCI and dementia, respectively (Li et al., 2016). More recently, analyses conducted in two distinct large independent cohorts – the BLSA and the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS) – were not successful in replicating the previous findings (Casanova et al., 2016), therefore underscoring the essential need for a consensus on harmonized methods and platforms across laboratories (Gross et al., 2018). In another analysis, increased plasma concentrations of some PCs (PC aa C32:1, PC aa C34:1, PC aa C42:1, PC ae C34:1, and PC ae C36:1) and lysoPCs were observed in HC that converted to AD within a 7-to-9-year follow-up period. Such a long phase enabled the assessment of plasma lipid variation in very early stages within the AD clinical continuum. Moreover, four PCs were increased at the MCI stage: PC aa C34:1, PC aa C40:6, PC ae C34:1, and PC ae C40:3 (Blasko et al., 2021). The aforementioned targeted metabolomic-driven ROSMAP study – using flow injection analysis (FIA) with tandem MS (FIA-MS/MS) in both ante-mortem blood and post-mortem brain samples – detected baseline serum concentrations of ten glycerophospholipids that were predictive of longitudinal alterations in cognitive functions. In particular, three glycerophospholipids (PC aa C30:0, PC ae C34:0, and PC ae C36:1) were associated with both AD neuropathology and cognitive alterations (Huo et al., 2020).

Despite an inability to exactly replicate definite panels of metabolites, there is a growing consensus that lipid dyshomeostasis may be a crucial feature of early AD pathophysiology. A landmark multi-cohort (ADNI-1, Indiana Memory and Aging Study [IMAS], Rotterdam Study [RS], and Erasmus Rucphen Family Study [ERF]) investigation, conducted by Toledo et al. (2017), used metabolomics and network approaches to detect the alterations of serum lipid concentrations (as measured by targeted UPLC-MS/MS) associated with the different AD stages and correlate them to CSF AD biomarkers tracking Aβ and tau pathologies, neuroimaging markers (brain volume changes), and cognitive performance measurements. Some lipid categories, specifically SMs and PCs with ether bonds, were subject to changes related to early stages of AD (Toledo et al., 2017). Lipid alterations are assumed to mirror membrane structure/function modifications early in the disease evolution; moreover, modification in lipid rafts can induce alterations in Aβ processing (Rushworth and Hooper, 2011). Furthermore, modifications associated with mitochondrial energetics and energy utilization were reported. These might be due to alterations of mitochondrial lipid membranes leading to elevated lipid oxidation, loss of membrane potential, and variations in membrane transport (Jha et al., 2017).

González-Domínguez and colleagues (2014) performed the first deep comprehensive examination of serum phospholipids profiling modifications in AD patients via shotgun metabolomics on UPLC-QTOF-MS platform. Substantial alterations in lipid concentrations were reported, including changes in PCs, PEs, plasmenylcholines, plasmenylethanolamines, and lysophospholipids. A multifactorial cause for all these modifications, involving overactivation of phospholipases, more elevated anabolism of lysophospholipids, peroxisomal dysfunction, and dissimilarities in the levels of fatty acids saturated/unsaturated ratio,

was assumed (González-Domínguez et al., 2014b, 2014c). In particular, the most relevant perturbations were associated with a reduction in the levels of circulating phospholipids containing PUFAs, which was accompanied by a parallel increase of lipid species composed of saturated fatty acids (SFAs), which could provoke membrane destabilization processes (González-Domínguez et al., 2014b, 2014c). Next, the same authors investigated serum samples from a cohort of AD, MCI, and HC participants, using UPLC-QTOF-MS, and observed compromised metabolism of phospholipids and sphingolipids, resulting in membrane disruption, where the biology of the fatty acids integrated in the lipids structure as acyl chain length and extent of unsaturation seems to be critical (González-Domínguez et al., 2016). An untargeted plasma lipidomic analysis, using UPLC-MS, revealed a signature of 10 metabolites distinguishing AD patients from HC with high accuracy. Six metabolites were long chain cholesteryl esters and were reduced in AD (Proitsi et al., 2015). A larger untargeted plasma lipidomic analysis conducted with the same platform allowed the detection of a lipid panel including cholesteryl esters/triglycerides and PCs (in particular PC 40:4), associated with disease progression and brain atrophy (Proitsi et al., 2017). Interestingly, these AD-related alterations in glycerolipids and fatty acid metabolic pathways could also be detected in urine, a non-invasively and simply collectable biofluid with elevated potential usefulness in clinical practice (Watanabe et al., 2021).

As part of the ADNI study, Sakr and colleagues (2022) examined the association between different lipid classes characterized by lipidomics and traditional AD biomarkers (CSF p-tau/$Ab_{1–42}$ ratio) in cases with preclinical and prodromal AD. They also assessed the prognostic significance of lipidomic signatures with respect to the clinical trajectories of cognitive decline. After adjusting for *APOE ε4* status, they found that ether-glycerophospholipids, lyso-glycerophospholipids, free-fatty acids, cholesterol esters, and complex sphingolipids were significantly associated with the CSF p-tau/$Ab_{1–42}$ ratio. They also identified five specific lipidomic endophenotypes as being related to the clinical course of the disease in prodromal cases, as reflected by clinical dementia rating score conversion. Pending independent validation, these findings highlight the potential usefulness of lipidomics for both prognostication and implementation of enrichment strategies in clinical trials (Sakr et al., 2022).

3.4.3. Diacylglycerols

Diacylglycerols (DAGs), esters generated from two fatty acids chains and a glycerol molecule, play several major biological roles. First, they act as mediators of diverse signal transduction pathways by activating various protein kinases involved in synaptic transmission – for instance, the protein kinases C (PKC) and D (PKD) as well as the Ca^{2+}/calmodulin-dependent protein kinase (PKCaMII). They also have structural roles – for instance, they act as precursors for glycerophospholipids, triacylglycerols (TAGs), and monoacylglycerols (MAGs) – as well as acting as key lipids in the nuclear envelope and endoplasmic reticulum (Wood et al., 2018). In general, DAG expression and concentrations are accurately modulated to preserve their activity, especially in some major metabolic pathways, namely conversion to glycerophospholipids, hydrolysis catalyzed by some lipases to produce MAGs, acylation by DAG acyltransferase to synthesize TAGs (Wood et al., 2015b).

A quantitative lipidomic profiling method comparing the biochemical profiles of brain tissues from mild and severe AD patients with age-matched, cognitively HC allowed the detection of increased DAG (14:0/14:0), TAG (58:10/FA20:5), and TAG (48:4/FA18:3) expressions when comparing AD with HC (Akyol et al., 2021). Non-targeted lipidomic analyses found augmented values of DAGs in both frontal cortex (Chan et al., 2012; Wood et al., 2015a) and serum (González-Domínguez et al., 2015b; Wood et al., 2014) of AD patients, suggesting that modifications of DAGs content are common in AD. Moreover, increased DAGs expressions and concentrations in frontal cortex (Wood et al., 2015a) and plasma (Wood et al., 2014), respectively, were reported in MCI individuals. Thus, brain DAGs and circulating DAGs may start increasing early during the AD clinical continuum. These findings were corroborated by a targeted lipidomic examination of DAGs (and MAGs) in the frontal cortex and plasma of MCI individuals, using HRMS/MS, thus suggesting the involvement of circulating DAGs in the MCI-to-overt-dementia conversion (Wood et al., 2015b).

A study focusing on lipidomics explored whether a battery of plasma lipids could distinguish between patients with AD and cognitively HC. In this work, authors also assessed whether an association exists between plasma lipid profiles and the genetic risk for AD. After examining lipid species at the group level, DAGs were the only group found to be significantly increased in AD. At the species level, cholesterol esters, TAGs, and SMs showed good discrimination ability (area under curve >80%) for identifying patients with AD. Individual lipids that were significantly different between AD and HC were further explored in relation to both AD-associated genes and polygenic risk scores. The results revealed that the fermitin family homolog-2 (*FERMT2*) gene – encoding for a member of the fermitin family of proteins involved in cell-matrix adhesion complexes – and the membrane spanning 4-domains A6A (*MS4A6A*) gene – previously associated with cortical and hippocampal atrophy – showed significantly differential association with all lipid classes across disease groups. Taken together, the authors documented specific lipid changes associated with AD, which can not only inform disease pathophysiology but may also have the potential to be transformed into a clinically applicable testing procedure (Liu et al., 2021).

3.4.4. Sterols

Sterols are essential signaling molecules involved in metabolism, development, and homeostasis. Cholesterol, the dominant sterol in animal cells, is not only a structural component of cell membranes but also serves as the building block for the biosynthesis of steroid hormones, vitamin D, and bile acids (BAs) (Babu et al., 2022).

The potential role of sex steroid metabolites in the pathogenesis of dementia has been reported by Bressler and colleagues (2017) in middle-aged community-dwelling African American individuals enrolled in the Atherosclerosis Risk in Communities (ARIC) study. After a median follow-up of 17.1 years, the authors identified one metabolite (4-androstene-3beta, 17 beta-diol disulfate 1) as being significantly associated with the risk of incident dementia, a finding consistently replicated in European Americans (Bressler et al., 2017). Given that 4-androstene-3beta, 17 beta-diol disulfate 1 is an intermediate in the synthesis of testosterone from dehydroepiandrosterone (Kihel, 2012), that study lent further support to the idea that aging-related sex steroid depletion is associated with cognitive decline.

Dysregulation of cholesterol catabolism, through its conversion to primary BAs, was also recently associated with the pathogenesis of dementia both in animal models and clinical studies. The presence of BAs and their receptors in the brain suggests these molecules play a direct role in the regulation of cerebral functions. Notably, an altered brain and serum BA profile has been reported in the AppNL-G-F mouse model of AD. The multi-compartmental characterization of APP/PS1 transgenic mice evidenced reduced contents of various BAs in serum (González-Domínguez et al., 2015f), brain (González-Domínguez et al., 2015g), and liver (González-Domínguez et al., 2015h). Moreover, abnormal BA levels have been described in biological samples collected from patients with AD (Cuperlovic-Culf and Badhwar, 2020).

In a study by Marksteiner and colleagues (2018), concentrations of 20 BAs were measured by LC-MS in plasma samples obtained from 30 cognitively HC, 20 MCI participants, and 30 AD patients. The authors found increased levels of lithocholic acid in AD patients compared with HC; additionally, concentrations of glycochenodeoxycholic acid, glycodeoxycholic acid, and glycolithocholic acid were significantly higher in AD than MCI. Interestingly, increased plasma lithocholic acid levels predicted conversion to AD in initially healthy individuals followed for 8–9 years (Marksteiner et al., 2018).

More recently, the reciprocal associations between serum levels of

BAs, quantified using LC-MS, and traditional imaging and CSF biomarkers of AD were examined in the ADNI cohort. An abnormal BA profile was found to be associated with both structural (brain atrophy) and metabolic (glucose hypometabolism) imaging markers of AD. Additionally, three BA ratios (glycodeoxycholic acid/cholic acid, taurodeoxycholic acid/cholic acid, and glycolithocholic acid/chenodeoxycholic acid) were associated with both imaging and CSF biomarkers (lower $A\beta_{1-42}$ concentrations) of AD. The authors concluded that BAs might be pathogenetically involved in AD through the Aβ cascade (Nho et al., 2019). Similarly, following the LC-MS measure of the abundance of plasma circulating factors, especially lipid molecules, in normal cognition, MCI, and dementia due to probable AD participants, glycocholic acid was found to act as a potential mediator of mitochondrial bioenergetics in AD (Amick et al., 2022).

Given that the BA pool is manipulated by the gut microbiota, metabolomics analyses were carried out in the ADNI cohort with the goal of assessing whether gastrointestinal microbiota-related alterations of BA metabolism occur in AD, resulting in a higher proportion of secondary BAs. Compared with age-matched cognitively HC, patients with AD were characterized by significantly lower serum levels of cholic acid, a primary BA, and increased concentrations of deoxycholic acid, a (bacterially produced) secondary BA. An increased ratio of deoxycholic acid/cholic acid, which reflects 7α-dehydroxylation of cholic acid by gut bacteria, showed a strong association with cognitive decline. Collectively, these results support a direct link between intestinal metabolism, liver homeostasis, and neurodegeneration/cognition (MahmoudianDehkordi et al., 2019).

These results were confirmed by a recent analysis exploring changes in cholesterol and BA metabolism in AD. In particular, targeted metabolomic quantification of primary and secondary BAs in post-mortem brain samples from the dorsolateral prefrontal cortex of AD patients, MCI individuals, and cognitively HC individuals of the ROSMAP study showed that deoxycholic acid, lithocholic acid, glycochenodeoxycholate, chenodeoxycholic acid, taurodeoxycholic acid, glycodeoxycholic acid, ursodeoxycholic acid, allolithocholate, and taurocholic acid were increased in AD versus HC, thus proposing a potential association of such BAs with cognitive impairment in AD. Furthermore, increased serum concentrations of taurine, needed for the conjugation of primary and secondary BAs, were observed in AD versus HC (Baloni et al., 2020).

3.4.5. *Fatty acids*

Fatty acids are directly implicated in the structure of most nervous system lipids, being responsible for their biological and chemical features. They are related to neurogenesis, neuronal inflammation, and neurotransmitter production, processes that are crucial for the physiological development of the brain (Youdim et al., 2000). Moreover, fatty acids (as well as their metabolic products) can affect MCI individuals and AD patients through their activities in brain structure and function, neurotransmission, cell membrane structure organization, inflammation, and oxidative stress (Calder, 2006; McNamara et al., 2010).

Quantitative targeted GC-MS-based analysis of fatty acid methyl esters was carried out to screen all measurable fatty acid species in post-mortem neocortical tissue (Brodmann 7 region) in late-stage AD patients and age-matched HC. A 24-fatty acid signature was revealed; specifically, the expression of nine fatty acids was increased in AD brains, with cis-13,16-docosenoic acid being the most elevated. Docosahexaenoic acid (DHA) expression was significantly increased. Interestingly, sex might affect brain fatty acid expression in AD, since seven fatty acid species were found to be more elevated in males than females (Nasaruddin et al., 2016).

A recent meta-analysis reported a 27.2% decrease of plasma/serum total fatty acid concentrations in AD compared with controls; in particular, DHA was significantly lower in both MCI and AD, thus indicating a potential role for this metabolic compound as driver of AD pathology (Hosseini et al., 2020).

In general, PUFAs (fatty acids that contain more than one double bond in their backbone), especially DHA, linoleic acid, and eicosapentaenoic acids, are thought to have a considerable role in AD pathophysiology. Indeed, DHA, an omega-3 fatty acid, represents the primary PUFA structural constituent of brain lipids and is necessary for regular brain development, growth of synapses, and maintenance of membrane fluidity. A large-scale cross-sectional investigation found a significant correlation between blood DHA concentrations and increased cognitive ability (Lee et al., 2018). The effects of high supplementation of DHA on cognitive benefit and AD prevention were examined, since eating fatty fish leads to increased DHA plasma concentrations. In particular, high-dose intake of DHA in *APOE ε4* carriers prior to onset of AD dementia might reduce the risk for or delay the onset of AD symptoms, thus representing an effective approach to lower the incidence of AD (Yassine et al., 2017). Following a blood-based analysis integrating spectroscopy methods with an HPLC-HRMS-based metabolomic platform, plasma concentrations of arachidonic acid, an omega-6 fatty acid, were found to be reduced in AD; in contrast, its precursor, linoleic acid, was increased, suggesting disruption of fatty acid metabolism (Habartová et al., 2019). A targeted metabolomic study using GC-MS revealed significant increases in the expression of cis-13,16-docosenoic acid and DHA in post-mortem brains of late-stage AD patients versus age-matched controls, while other fatty acids were found to be unaltered or decreased (Nasaruddin et al., 2016). Metabolomic profiling performed on post-mortem brains of participants recruited from the BLSA study – AD patients, “asymptomatic Alzheimer’s disease” individuals (ASYMAD, individuals with significant AD neuropathology at death but without evidence for cognitive impairment during life), and HC – discovered dysregulated expressions of six UFAs: linoleic acid, linolenic acid, DHA, eicosapentaenoic acid, oleic acid, and arachidonic acid. These UFAs were significantly associated with AD (Snowden et al., 2017). However, there is no general agreement on whether they are increased or decreased in AD pathology.

A multi-omic (transcriptomic/metabolomic/lipidomic) study was conducted in plasma samples from a cohort of cognitively normal individuals facing subjective memory complaint, dichotomized in Aβ-positron emission tomography (PET) positive versus Aβ-PET negative (i.e., with and without brain Aβ overaccumulation on Aβ-PET imaging, respectively). This study allowed the detection of three medium chain fatty acids – undecanoic, octanoic, and hydroxy-nonanoic acids (together with a panel of 64 transcripts and 4-nitrophenol) – associated with inflammatory pathways and fatty acid metabolism, discriminating the two groups. This finding indicated a potential metabolic signature for Aβ burden, established in peripheral blood (Xicota et al., 2019).

In one of the most comprehensive investigations ever undertaken of the human lipidome in AD, Huynh et al. (2020) examined 569 lipid species across 32 different lipid classes and subclasses using plasma samples from the Australian Imaging, Biomarkers and Lifestyle flagship study of aging (AIBL) and serum from the ADNI studies. In cross-sectional analyses, positive associations of PE, DAG, and TAG with AD were observed; conversely, alkyl and alkenyl ether lipids were negatively associated with the disease. A number of n-acylated ceramides were associated with AD. On the one hand, the authors found positive associations with species containing 18:0, 20:0, and 24:1 fatty acids. On the other hand, negative or neutral associations were identified for species containing 22:0, 24:0, and 26:0 fatty acids, regardless of the sphingoid base. The minute class-wide and species-specific changes in the lipidome of subjects included in the AIBL and ADNI cohorts highlight the potential pathogenetic role of lipid dysregulation in AD and call for further confirmation in population-based studies (Huynh et al., 2020).

The complementary application of GC- and LC-MS platforms allowed the measurement of over 2000 metabolites in 48 post-mortem tissue samples collected from the superior frontal gyrus of male and female participants divided in normal HC, cognitively normal individuals designated as high pathology controls, individuals with non-specific

MCI, and AD patients. A nine-metabolite signature including one monounsaturated fatty acid (palmitoleic acid), four saturated fatty acids (lauric acid, stearic acid, myristic acid, and palmitic acid), and four unidentified mass spectral features was detected. This metabolite panel exhibited high predictive accuracy to differentiate the four groups. Pathway analysis disclosed significant disruptions in fatty acid metabolism, as well as lysine and BCAAs degradation (Jasbi et al., 2021). In a recent study, higher serum concentrations of propionic acid were associated with increased odds of cognitive decline and significantly correlated with blood glucose (Neuffer et al., 2022).

3.5. Other metabolites

After conducting extensive research on various metabolites associated with AD pathophysiology, it has been determined that organic acids, nucleosides, and alkaloids may be linked to different stages of AD, particularly as a result of high-throughput metabolomics analyses. Utilizing an untargeted LC-MS approach on whole blood samples from dementia patients and healthy older individuals, researchers identified and quantified 33 metabolites as potential biomarkers for AD diagnosis. These metabolites were categorized based on their possible functions. A subset of compounds, exhibiting increased concentrations in AD patients, were suggested to be potential neurotoxins. This group included indoxyl-sulfate, quinolinic acid, adenosine, dimethyl-guanosine, N6-acetyl-lysine, pseudouridine, and kynurenine (Teruya et al., 2021). Kynurenine and quinolinic acid have previously been proposed as candidate biomarkers for AD (Gulaj et al., 2010). The remaining 26 compounds displayed lower concentrations in AD patients and were believed to possess neuroprotective properties. These compounds encompassed antioxidants such as ergothioneine, a natural amino acid and thiol antioxidant obtained from the diet, as well as oxidoreductants like NADP+, glutathione, adenosine triphosphate, pantothenate, S-adenosyl-methionine, and gluconate. Additionally, the whole blood concentrations of neuroprotective compounds, including glycerophosphocholine, dodecanoyl-carnitine, and 2-hydroxybutyrate, were found to be reduced in AD patients. While this investigation revealed promising leads for further research, it is important to note that some of the observed alterations could be attributed to changes in diet and behavior among AD patients (Teruya et al., 2021).

The potential involvement of nucleotides in neurodegenerative processes has been the subject of recent review (Sebastián-Serrano et al., 2019). Within the CNS, nucleotides function as neurotransmitters, activating specific receptors, such as the P2 purinergic receptors. It was proposed that nucleotides may modulate the molecular mechanisms underlying neurodegeneration. In particular, a significant increase in extracellular nucleotides triggers the activation of purinergic receptors, thereby initiating purinergic signaling pathways that play a critical role in oxidative stress, neuroinflammation, and synaptic alterations (e.g., reduced axonal growth). These pathways may also contribute to the production of protein aggregates, such as Aβ peptides, which are implicated in the onset and progression of AD and other ND. Further research is necessary to comprehensively elucidate the role of nucleotides in these processes, potentially revealing valuable therapeutic opportunities to prevent or slow the progression of ND (Sebastián-Serrano et al., 2019).

In the realm of therapeutic natural products, numerous studies investigated the potential of natural alkaloids as multi-targeted agents in AD treatment. Following the approval of the *Amaryllidaceae* alkaloid galanthamine as an anti-dementia drug, a comprehensive collection of selected naturally occurring plant and marine alkaloids has been suggested as promising multi-target candidates for developing new anti-AD medications. These alkaloids showed significant inhibitory effects on key enzymes associated with AD pathophysiology. Notably, the β-carboline alkaloid harmine is a natural monoamine oxidase-A inhibitor and appears to be the most promising candidate due to its broad range of anti-AD activities. The isoquinoline alkaloid berberine inhibits Aβ production by blocking the expression of the β-site APP cleaving enzyme 1 (BACE1). Additionally, the benzophenathridine alkaloids avicine and nitidine exhibit dual cholinesterase inhibitory activity, with a stronger effect on acetylcholinesterase compared to butyrylcholinesterase (Vrabec et al., 2023). A recent study examined the abilities of three nicotinic alkaloids – nicotine, cotinine, and anatabine – to modulate nicotinic acetylcholine receptor activity and suppress scopolamine-induced spatial memory deficits in rodents. Interestingly, cotinine and anatabine primarily affected short-term spatial memory, while nicotine demonstrated a broader role in memory regulation. Consequently, nicotinic acetylcholine receptor-activating alkaloids may possess varying procognitive properties depending on the memory type (Callahan et al., 2021).

3.6. Redox proteomics

Heme oxygenase-1 (HO-1) is an inducible enzyme that catalyzes the conversion of heme into biliverdin, free ferrous iron, and carbon monoxide (Hettiarachchi et al., 2014). This enzyme plays a significant role in the pathogenesis of AD. Accordingly, it has been observed that HO-1 is overexpressed in astrocytes and neurons in the hippocampus and cerebral cortex, co-localizing with neurofibrillary tangles, senile plaques, and corpora amylacea (Schipper, 2011). It was reported that microglial HO-1 expression increases with aging and is particularly pronounced during AD progression, suggesting that HO-1 could serve as a potential biomarker or therapeutic target for AD (Fernández-Mendívil et al., 2020). In another study, MS was employed to identify the heme degradation pathway as a promising serum biomarker for early detection of AD (Mueller et al., 2010). Intriguingly, a brain proteomic study found that heme-binding protein 1, which has a functional association with HO-1, is elevated in the brains of both 3 ×Tg-AD mice and patients affected by rapidly progressing forms of AD (Yagensky et al., 2019). Moving forward, redox proteomics approaches will prove invaluable in investigating the specificity of oxidative stress-related biomarkers, including HO-1, in relation to AD pathophysiology (Cioffi et al., 2021).

4. Discussion

Given that metabolites, such as amino acids, carbohydrates, and lipids, reflect the ultimate effect of gene- and protein-based pathophysiological mechanisms, metabolomic science is expected to play an essential role in biomarker discovery and drug development. Specifically, metabolomics can offer several unique benefits, such as (I) providing information on disease molecular mechanisms via examination of the dynamic alterations within biological systems; (II) detecting and discovering of novel candidate molecular biomarkers and their associated pathways; and (III) predisposed to more effective clinical applications (Hurtado et al., 2018), and (IV) possible selection of biomarker panels of molecules reducing confounding effects. In general, given that numerous metabolites linked to AD pathophysiology are interconnected through complex metabolic pathways/networks and share several intermediate compounds, changes occurring in an individual metabolic compound can elicit modifications in other related metabolites and impact other co-regulated pathways (Toledo et al., 2017).

4.1. The landscape of altered metabolic pathways in Alzheimer's disease

Metabolomic and lipidomic profiling of different matrices – biofluids (blood [plasma/serum]/CSF) and brain tissues – enabled the detection of considerable changes in the concentration/expression of several metabolic compounds and, therefore, the examination of relevant metabolic pathways modified in AD. These pathways are mainly involved in fatty acid biosynthesis and lipid metabolism, amino acid metabolism, and mitochondrial bioenergetics (Wilkins and Trushina, 2018) (Fig. 4). The studies presented in this review suggest a strong role

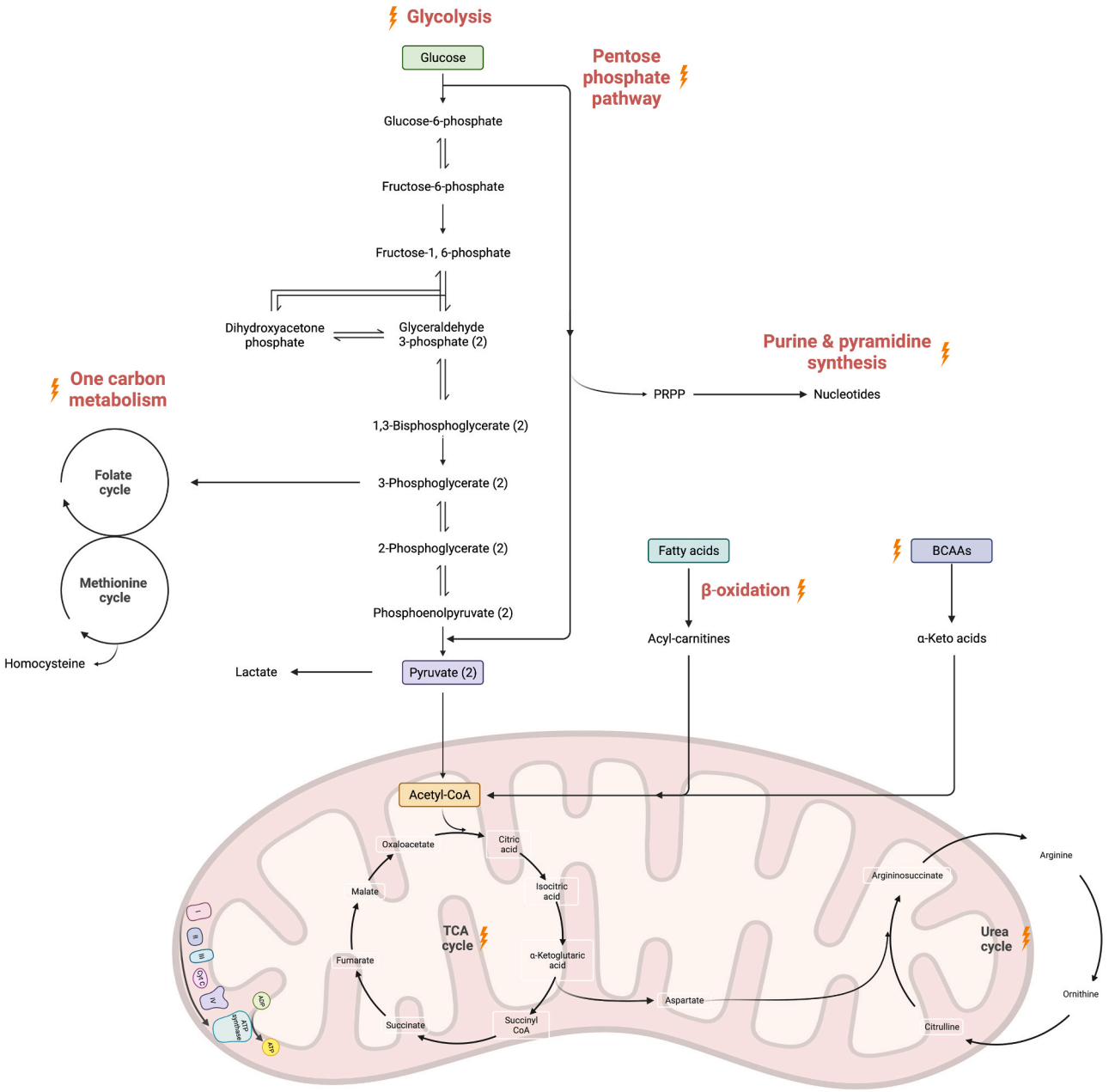

Fig. 4. Schematic representation of relevant metabolic pathways altered in AD. Metabolomic/lipidomic studies allow exploring significant alterations of numerous metabolites and, consequently, scrutinizing relevant metabolic pathways altered in AD, primarily those related to fatty acid biosynthesis and lipid metabolism, amino acid metabolism, and mitochondrial bioenergetics. *Abbreviations*: AD, Alzheimer's disease; ADP, adenosine diphosphate; ATP, adenosine triphosphate; BCAAs, branched-chain amino acids; CoA, coenzyme A; Cyt c, cytochrome c; PRPP, phosphoribosyl diphosphate; TCA, tricarboxylic acid cycle.

of lipid dyshomeostasis either alone or in combination with other metabolic pathways in AD (see Yin et al., 2023 for additional coverage). Lipid dysmetabolism may be a primary contributor to the pathophysiology of AD or, alternately, may reflect the convergence of multiple pathways. Lipids are essential for physiological function, encompassing membrane architecture, β-oxidation, cell signaling, and biosynthesis of BAs. Furthermore, the discovery of the *APOE ε4* allele as a central genetic risk factor for sporadic AD emphasized the contribution of lipid dyshomeostasis in AD pathogenesis (Yamazaki et al., 2019). Apolipoprotein E is acknowledged for its main role in lipid uptake and transport in cells; moreover, the association between the *ε4* allelic variant and raised expressions of toxic brain Aβ oligomers is well established (Huang et al., 2017). Besides apolipoprotein E, other lipids also participate in the modulation of membrane-bound proteins linked to AD, such as the APP, the BACE1 enzyme, and the presenilins (Eckert and Müller, 2009; Grimm et al., 2017; Hattori et al., 2006). Additionally, lipid vesicles are highly effective in inducing the phosphorylation and aggregation of tau proteins (Elbaum-Garfinkle et al., 2010).

Numerous amino acid metabolic pathways are dysregulated in AD, such as arginine, aromatic amino acids, BCAAs, methionine, and cysteine metabolisms (Cuperlovic-Culf and Badhwar, 2020; González-Domínguez et al., 2021a; Mill and Li, 2022; Wilkins and Trushina, 2018). Remarkably, the disruption of energy-related metabolism is a central finding emerging along metabolomics analyses. Modified glucose values are consistently found in both the CNS and the peripheral system in AD, thereby indicating an anomalous metabolic rate of carbohydrates, the primary brain energy source. This perturbation is complemented by disturbances in other metabolic compounds

involved in glycolysis, the pentose phosphate pathway, gluconeogenesis, the tricarboxylic cycle, and beta-oxidation of fatty acids, hence showing intense disruptions of the whole energy metabolic system (Cuperlovic-Culf and Badhwar, 2020; González-Domínguez et al., 2021a; Mill and Li, 2022; Wilkins and Trushina, 2018), as well as major alterations in fructose metabolism with an increased role of fructose in energy generation (Johnson et al., 2023).

Ultimately, efforts have been made to develop comprehensive maps of metabolic brain alterations associated with AD. A large, untargeted metabolomic analysis of 500 dorsolateral prefrontal cortex samples from the ROSMAP study revealed widespread metabolic dysregulation associated with AD, covering 298 metabolites from several AD-relevant pathways. These encompassed (I) bioenergetics (including glycolysis, BCAA metabolism, and mitochondrial β-oxidation), (II) cholesterol metabolism and sterol pathway (with degradation products of cholesterol correlating with AD-related traits), (III) neuroinflammation and oxidative stress (with correlations of metabolites in the glutathione pathway with AD), (IV) osmoregulation (impacting aspects of AD pathology, including protein folding, neural excitation, and autophagy), and (V) metabolic consequences due to the neurotransmitter glutamate/GABA ratio imbalances (Batra et al., 2022). A multi-dimensional study interrogating metabolic signatures in AD brains (post-mortem parietal cortical tissue samples) was carried out to characterize three genetically defined AD subgroups, namely sporadic AD, autosomal dominant AD, and carriers of the triggering receptor on myeloid cells 2 (*TREM2*) gene risk variants. A 16-metabolite profile was significantly altered across the three groups and associated with AD duration. Notably, the pathways related to the 16-metabolite signature were associated with amino acid metabolism (glutamate, β-citrylglutamate, N-acetylglutamate, aspartate, 3-hydroxy-2-ethylpropionate). Moreover, CDP-ethanolamine, CDP-choline, and glycerophosphoinositol were linked to phospholipid metabolism, while α-tocopherol (vitamin E), retinol (vitamin A), and nicotinamide (vitamin B3) were constituents of the vitamin metabolism. Since AD genetic variants present distinctive metabolic perturbations, exploring such metabolites may help critically elucidate the AD etiology (Novotny et al., 2022). Finally, a lipidomic approach applied using untargeted and targeted analyses in plasma samples allowed to disclose differential lipid profiles between patients at the early stages of AD and HC. Therefore, the plasma lipid profile could be useful in the early and minimally invasive detection of AD. Among lipid families, relevant results were obtained from DAGs, lysophosphatidylethanolamines (lysoPEs), lysoPCs, MAGs, and SMs. In particular, MAGs showed a potential diagnostic usefulness in AD detection, DAGs were associated with the MCI stage, while lysoPEs, lysoPCs, and SMs were more specifically associated with AD preclinical stage. The targeted analysis enabled to determine reduced plasma concentrations of some lipid species thought to be beneficial as potential biomarkers for AD diagnosis (18:1 lysoPE, 18:0 lysoPC, 16:1 SM (d18:1/16:1), and 16:0 SM (d18:1/16:0). Although the accuracy was satisfactory for all these molecules, only 18:1 lysoPE was characterized by significantly raised concentrations in preclinical AD and MCI converting to AD dementia patients versus HC. In addition, other lipid families, including phosphatidylglycerol, phosphocholine, glycerophosphocholine, glycerophosphoserine, glycosphingolipids, terpenes, steroids, flavonoids, glycosyl diacylglycerols, glucosylceramides, and fucopentaoses, were found to be modified in early AD stages, thus giving a clear idea about the extensiveness of this map of lipidomic blood alterations (Peña-Bautista et al., 2022).

Follow-up examinations are required to complete our understanding of the specific dysregulated metabolisms and pathological pathways characterizing the AD brain. Collectively, there is growing general evidence that progressive perturbations of key metabolic processes responsible for adequate brain energy supply are anatomically and functionally associated with AD. While a number of metabolic changes have been linked to AD-type symptoms, the central role of energy metabolism in sustaining neuronal function is emphasized by the wide spectrum of neurological manifestations associated with metabolic diseases in humans. Unfortunately, the intrinsic cellular heterogeneity of brain tissue currently limits the granular investigation of metabolic alterations taking place in specific neuronal subsets. Interestingly, there is pilot evidence that neurons can accommodate a significant amount of metabolic plasticity. This might open a therapeutic window during which key hallmarks of metabolic stress can be fully reversed, ultimately preventing neuronal degeneration. In this scenario, novel therapeutic approaches to sustain neuronal viability during early metabolic stress are eagerly awaited (Cuperlovic-Culf and Badhwar, 2020).

4.2. Clinical implication of metabolomic analyses in Alzheimer's disease

Upcoming comprehensive biomarker investigations in the area of AD, especially using blood samples, should aim at examining the longitudinal variation of metabolite concentrations in HC and in individuals later progressing to MCI or AD, in order to disclose candidate biomarkers that help: (I) predict the progress of the disease and (II) recognize individuals at risk of AD for selection in clinical trials (Wong et al., 2017a, 2017b).

Notably, the growing understanding of the pathophysiological mechanisms responsible for AD shows that, besides Aβ and tau pathologies and neurodegenerative processes, the AD brain can be subject to several other cellular and molecular alterations (Hampel et al., 2021a; Tarawneh, 2020). At present, the common agreement would be to propose an integrated strategy where blood-based candidate metabolomic biomarkers should be combined with all other biofluid indicators of AD pathophysiology and with neuroimaging markers. The latter would be brain atrophy measurements, namely hippocampal/entorhinal cortex/basal forebrain volume reduction as well as cortical thickness decrease, obtained using structural magnetic resonance imaging (MRI) techniques; alterations of brain white matter microstructures, detected via diffusion tensor imaging methods; and modifications of the functional integrity of brain networks, using functional MRI (fMRI) tools. In addition, the integration and implementation of genomic profiling tests might be crucial to better refine this approach. The incorporation of suitable cost-effective and time-efficient evaluations of cognitive, neurological, and psychiatric symptoms would be also necessary.

Developing such a large integrated action plan, where consistent methods are carried out across biofluids (blood / CSF) and brain tissues, will be critical to attain information about whether central and peripheral alterations occur in parallel, or independently of each other (Wong et al., 2017a, 2017b). This composite approach is expected to generate distinct multi-dimensional biomarker profiles according to different contexts-of-use, namely: (I) diagnosing AD dementia, (II) monitoring the spatio-temporal evolution of the disease over time, and (III) predicting the conversion from preclinical AD to MCI to overt AD dementia stages (Hampel et al., 2018; Lovestone, 2014). In summary, the potential diagnostic usefulness of blood-based candidate metabolomic biomarkers can be improved through the specific information provided by Aβ and tau (the established core biomarkers for AD diagnosis), other promising candidate fluid biomarkers, as well as neuroimaging markers (Wong et al., 2017a, 2017b).

Notably, one of the key advancements in applying metabolomics to AD is expected to be the identification of predictive biomarkers, informing the response of the individual patient to the therapy, based on the patient's metabolome (Wong et al., 2017a, 2017b). A recent investigation, using a systems biology analytical pipeline for metabolomic data analysis, showed the association between late-onset AD and distinct metabolomic profiles that are driven by sex and *APOE* genotype. In particular, using sex and *APOE* genotype to stratify a set of ADNI cohort participants led to the identification of patient-specific serum metabolic biomarker signatures, predictive of clinical diagnosis and associated with cognitive performance. These sex- and *APOE* genotype-related metabolic profiles might help designate effective therapeutic targets for AD. Hence, a precision medicine-based operational plan, integrating metabolomic profiling and cognitive functioning evaluation, assisted by

computational network modeling, was proposed to identify pathway-based targeted therapeutic interventions for different patient clusters (Chang et al., 2023).

To summarize, it is imperative to recognize AD as a complex multifactorial disease arising from heterogeneous etiologies. This encourages the research opportunity in which a combinatorial approach of metabolomics/lipidomics data – integrated with different layers (genomics/epigenomics, transcriptomics, proteomics) of omics data (i.e. multi-omics data) – with imaging modalities, sensitive neuropsychological testing, and electronic health records (including patients' demographics, clinical measurements, clinical laboratory tests) will hopefully provide a holistic depiction of the underlying pathophysiological processes characterizing AD (Termine et al., 2021) (see Fig. 5).

4.3. The impact of Alzheimer's disease risk factors – age, sex, race, and APOE ε4 – on metabolism

Being that age, female sex, certain racial backgrounds, and *APOE ε4* allele are considerable risk factors for AD, studies were conducted to examine the impact of such risk factors on metabolism. Stratifying populations according to age, sex, race, and *APOE ε4* provides information about differences in metabolic alterations in these groups, thus supporting the concept of AD as a metabolic disease (Arnold et al., 2020).

High-throughput metabolomics analyses enabled the discovery of age-dependent differences in levels of PCs, SMs, acylcarnitines, ceramides, and amino acids (Gonzalez-Covarrubias et al., 2013; Yu et al., 2012).

Sex was shown to impact blood concentrations of several metabolites belonging to a large number of biochemical pathways. For instance, a healthy older population mostly represented by post-menopausal females exhibited higher amounts of several lipids excluding lysoPCs. Most amino acids, including BCAAs, showed more elevated concentrations in males, although glycine and serine amounts were greater in females (Krumsiek et al., 2015; Mittelstrass et al., 2011). A study using LC-MS/MS investigating the plasma lipidome of middle-aged offspring of nonagenarians from the Leiden Longevity Study reported 19 lipid species associated with familial longevity in females, especially increased values of ether PCs and SMs and decreased values of PEs, differently from males. Hence, ether PCs and SMs were indicated as novel longevity markers in females only. In summary, ageing might affect a larger range of metabolites in females than males, thus stressing the need for sex-stratified studies.

Dementia disproportionately affects the African American and Hispanic populations, with these groups being 2 and 1.5 times more likely to develop AD or other related dementias than the non-Hispanic white population, respectively ("2022 Alzheimer's disease facts and figures, ", 2022). Despite their predisposition to developing AD, these communities are typically underrepresented in AD studies. The aforementioned 10-lipid panel established by Mapstone and colleagues (2014) (Mapstone et al., 2014) was applied to a predominantly African American cohort, revealing that it was not predictive of MCI or dementia in their cohort, with an AUC of 0.607 compared to 0.827 in the original study (D. Li et al., 2017). This is not the only study that has reported differences in metabolomic/lipidomic profile between ethnic groups; a global LC-HRMS study of plasma collected from the Washington Heights, Inwood Columbia Aging Project (WHICAP) cohort found differences in the metabolomic profiles of African Americans, Caribbean Hispanics, and non-Hispanic whites (Vardarajan et al., 2020). A PLS-DA comparing all ethnic groups showed that features in the African American cohort clustered separately from the Caribbean Hispanic and non-Hispanic white cohort, with differences in arginine and proline metabolism, PUFA biosynthesis, and glutamate metabolism highlighted as significantly different pathways, among others.

Finally, common genetic variants in *APOE* were linked to blood cholesterol concentration in genome- and metabolome-wide association analyses (Shin et al., 2014; Teslovich et al., 2010). Moreover, associations with different SM concentrations were found (Long et al., 2017; Mielke et al., 2017). Recently, a stratified linear regression analysis of serum metabolites from ADNI cohort individuals indicated that variations in metabolites related to diagnosis and currently established biomarkers were affected by sex and *APOE* (performing an intertwined modulation) and were associated with altered energy homeostasis. In general, the heterogeneity in the susceptibility and severity of AD is influenced by sex-*APOE* genotype interactions and the molecular bases of this association are still unclear. The careful examination of AD metabolic heterogeneity can help establish the biomedical relevance of specific molecular pathways within definite clusters of patients, thereby outlining the way to precision medicine-based therapies (Arnold et al., 2020). In another recent study, it was found that the regulation of fatty acids and related metabolic pathways during ageing and cognitive decline depends on complex inter-relationships between *APOE ε4* genotype and sex (González-Domínguez et al., 2022).

4.4. Pre-analytical and analytical phases of metabolomic studies

Considerable technological developments paved the way to the study of metabolites and lipids both in health and disease conditions. Although there are analyses emphasizing that metabolite and lipid concentrations may be subject to significant changes in CSF and blood, even during the preclinical stages of AD, caution is needed regarding the interpretation of the results obtained using high-throughput screening approaches for biomarker discovery, since these results need to be validated in independent cohorts. Moreover, it is not clear whether relevant metabolic/lipid signals detected in the discovery phase will persist in the following validation phases. At present, reproducibility of the results across different cohorts and laboratories is a critical challenge (Wong et al., 2017a, 2017b). The scenario is further complicated by pre-analytical factors that can impact metabolite concentrations, including biological variables (age, sex, ethnicity) and technical variables (biofluid drawing, sample collection tubes, handling procedures, transportation protocols, and conditions for sample storage, as temperature and time before further processing). Hence, the pre-analytical phase needs to be strictly controlled and monitored to avoid negative effects on the profiles of the explored metabolome; in this regard, the whole workflow needs to be strictly coordinated using standard operating procedures (SOPs), ensuring they are appropriate for sample collection for omics methods (Yin et al., 2015). Concerning the analytical phase, as multiple MS platforms can be used to detect and quantify metabolites, experimental designs necessitate a robust planning, from sample extraction to MS-based data acquisition and analysis (Yin et al., 2015). Variability in metabolic profiling is due to many factors comprising the experimental design, sample processing, platform selection, and data analysis. In human studies, experimental design can be negatively affected by the low accessibility to clinical samples, decreasing the statistical significance. In addition, samples are often not matched in terms of age, sex, and race, with some studies not including the appropriate number of male and female participants, leading to major bias by overlooking sex-specific variations. The presence of confounders, including medications, diet, environment, and whether patients fast before sample collection, can all affect an individual's metabolome; thus, these factors should be considered (Wilkins and Trushina, 2018).

In conclusion, recent breakthroughs in metabolomics platforms – including sampling and sample preparation methods, separation techniques, and ionization sources – substantially enhanced the capacity to identify candidate biomarkers for the early detection and progression of AD. In this scenario, establishment of consensus standards for sample collection and the unified application of a specific analytical workflow will be necessary to avoid multicenter variability in identifying specific metabolic signatures.

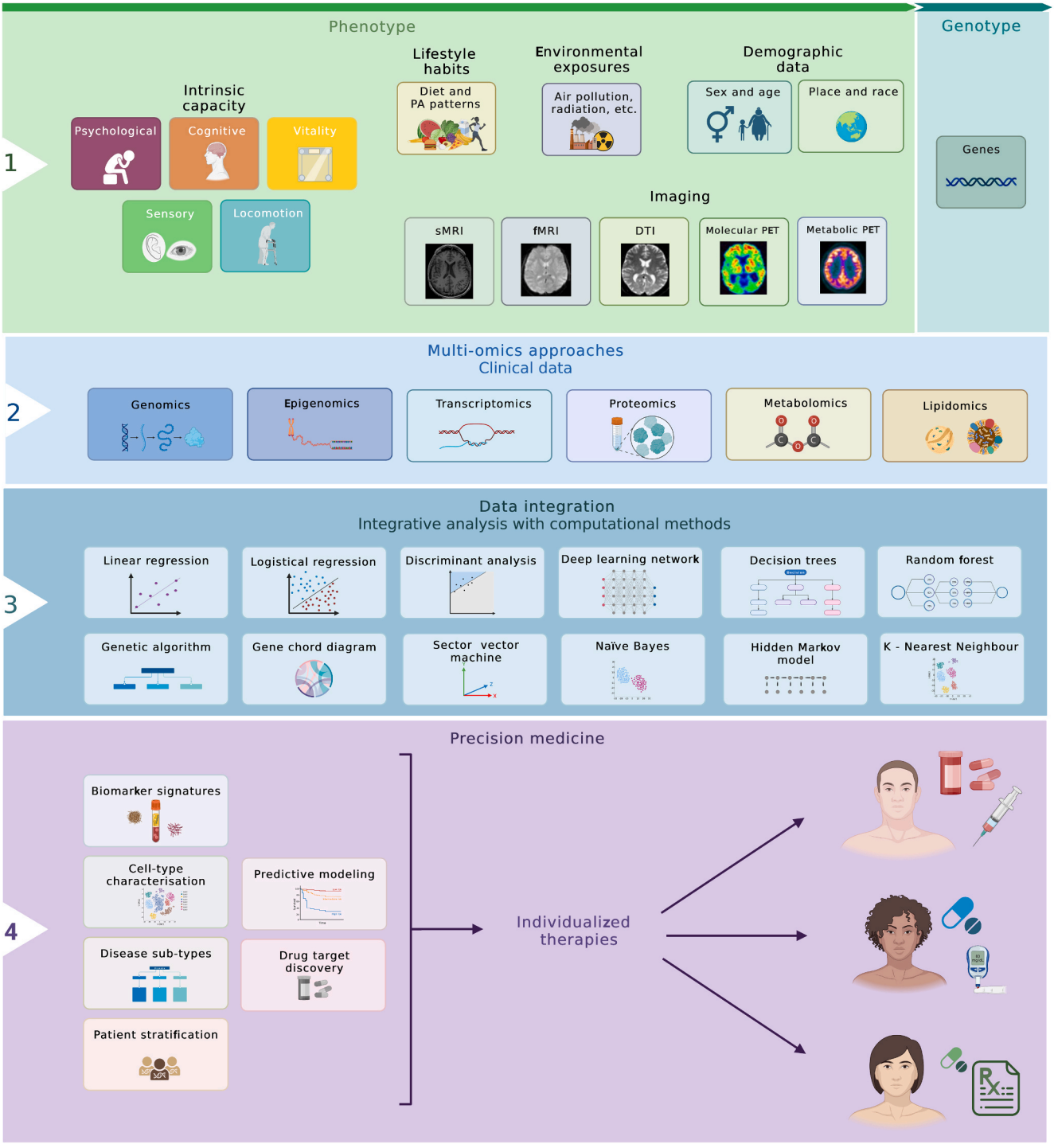

Fig. 5. Integration of multi-dimensional data for the holistic depiction of AD pathophysiology. The integration of unbiased exploratory omics sciences – including genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics – leads to generate diverse patients' biological data (genetic/epigenetic, RNA, protein/peptide, and metabolic/lipid). Advanced statistical/computational tools will enable the integrative analysis of such biological data with patients' non-omics data. These can include socio-demographic data as well as information on lifestyle habits and environmental exposure; data on the dimensions (psychological, cognitive, vitality, sensory, locomotion) of the intrinsic capacity concept; data obtained using imaging modalities (sMRI, fMRI, DTI, molecular PET, metabolic PET); data on patients' genotype. The combined analysis of these multi-dimensional data will allow – under a precision medicine framework – identifying unique biomarker signatures, facilitating cell type discovery and characterization (and accurately defining cell type signatures), establishing disease sub-types and improving the stratification of patients, developing relevant prediction models of the disease, and discovering novel potential therapeutic targets. This approach is expected to facilitate the holistic assessment of AD pathophysiology and to optimize the development of effective individualized therapies. *Abbreviations*: AD, Alzheimer's disease; DTI, diffusion tensor imaging; e-health, electronic health; fMRI, functional magnetic resonance imaging; PA, physical activity; PET, positron emission tomography; sMRI, structural magnetic resonance imaging.

4.5. Metabolic interventions in Alzheimer's disease

AD patients often exhibit brain glucose hypometabolism and are more susceptible to develop type 2 diabetes or insulin resistance compared with age-matched controls. This suggests the existence of a link between the two pathologies. The most studied metabolic interventions in AD are represented by the use of high-fat, low-carbohydrate diets, known as ketogenic diets. A key mechanism of this treatment is thought to be the generation of ketones, which provide neurons with an energy source that is more efficient than glucose, resulting in beneficial downstream metabolic changes (Augustin et al., 2018).

A single-blind, 12-week, cross-over, randomized study in 26 AD patients provided some encouraging results (Phillips et al., 2021). Twenty-one patients (81%) completed the ketogenic diet with only one withdrawal was attributed to the ketogenic diet. While on the ketogenic diet, patients achieved sustained ketosis with mean β-hydroxybutyrate levels of 0.95 ± 0.34 mmol/L. Compared with usual diet, patients on the ketogenic diet significantly improved functionality as measured with the ADCS-ADL scale (AD Cooperative Study - Activities of Daily Living: + 3.13 ± 5.01 points) and quality of life as measured with QOL-AD (Quality of Life in AD: + 3.37 ± 6.86 points) scores. Changes in cardiovascular risk factors were mostly favorable, and adverse effects were mild (Phillips et al., 2021). A 26-week double-blind, placebo-controlled study of a ketogenic drink containing medium chain triglyceride in 79 individuals with MCI individuals showed significant improvements vs placebo on cognition evaluated with the free and cued recall, verbal fluency, Boston Naming Test and the Trail-Making Test (Fortier et al., 2021). On the other hand, a large 26-week, double-blind, placebo-controlled study on a proprietary ketogenic product (Tricaprilin or AC-1204) in 413 mild-to-moderate AD participants produced negative results (Henderson et al., 2020). A recent review concluded that the strongest evidence of ketogenic diets for cognitive improvement are in individuals with MCI and in non-*APOE ε4* AD carriers (Bohnen et al., 2023). When closely supervised by medical experts and well-tolerated by patients, the ketogenic diet can be deemed a valuable strategy for individuals in the early stages of dementia. As we continue to explore more effective treatments for AD, it is crucial to conduct extensive, large-scale studies on the potential benefits of the ketogenic diet.

5. Conclusions

As AD has been documented as a "network" disorder, not merely circumscribed to defined brain regions, there has been an increase in studies that inspect AD pathophysiology at the systemic level. The accurate examination of metabolomic and lipidomic biomarker profiles clearly shows the complexity of AD pathophysiology, where lipid dyshomeostasis is a fundamental piece.

From a systems biology perspective, the inspection of metabolic pathways and networks – accounting for the metabolism of amino acids, fatty acids, and lipids, as well as for metabolic glucose and energy consumption – will bolster existing knowledge about underlying AD pathomechanisms. Given that metabolic alterations correlated with the evolution of AD can occur before the development of clinical signs, metabolomics – either applied individually or in tandem with the existing accessible biomarkers used for AD screening and diagnosis – may denote an innovative strategy to: (I) develop novel candidate metabolomic-based biomarker signatures, especially in blood (plasma/serum); (II) optimize both AD diagnosis and prognosis; and (III) enhance personalized pharmacological treatment efficacy monitoring. However, the clinical translatability of metabolomics findings is currently limited to the lack of proper validation studies in large and independent cohorts, which are mandatory for assessing the real utility of metabolites as candidate biomarkers. In this respect, it should also be noted that many authors have repeatedly reported inconsistent results and unsatisfactory validation of metabolomics-based biomarkers for AD and cognitive decline. For instance, the previously discussed work by Mapstone and colleagues (2014) described a 10-lipid signature that could accurately predict the conversion of cognitively normal individuals into AD (Mapstone et al., 2014). Despite several subsequent studies showing similar findings for individual lipids or combination of lipids in the panel, no study to date has replicated the entire 10-lipid panel in external validation (Casanova et al., 2016; Costa et al., 2019; D. Li et al., 2017). Similarly, Low and colleagues (2019) identified a serum signature of 22 diet-related metabolites associated with subsequent cognitive decline in a prospective cohort (Low et al., 2019). Further analyses in other populations shown alterations in metabolites that are involved in the same metabolic pathways and/or derived from the consumption of the same food products, but individual metabolites were not successfully replicated (González-Domínguez et al., 2021b). In this respect, growing evidence suggests that biomarker validation in metabolomics is mainly challenged by intra- and inter-individual variability factors arising from genetic (e.g. sex), temporal (e.g. circadian rhythm), environmental (e.g. dietary habits) and microbial (e.g. eubiosis/dysbiosis) factors (Beebe and Kennedy, 2016). Thus, a growing number of authors emphasized, in recent years, the great potential of metabolomics to comprehensively investigate biological pathways and to decipher the molecular mechanisms underlying the human phenotype, but also the extreme difficulty of using specific metabolites as robust clinical biomarkers (Johnson et al., 2016).

Application of metabolomics in clinical practice also requires implementation of strict experimental guidelines and the development of robust and easy-to-implement analytical platforms and major effort is underway in these areas. Increased availability of large, high-quality metabolomics and lipidomics datasets of relevance to AD, combined with high-level data analysis and modeling methods and innovation in analytical platforms is expected to have major impact on AD understanding, prevention, therapy, and diagnostics.

CRediT authorship contribution statement

Simone Lista: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Raúl González-Domínguez, Susana López-Ortiz, Álvaro González-Domínguez, Héctor Menéndez, Juan Martín-Hernández, Alejandro Lucia, Enzo Emanuele, Diego Centonze, Bruno P. Imbimbo, Viviana Triaca, Luana Lionetto, Maurizio Simmaco, Miroslava Cuperlovic-Culf, Jericha Mill, Lingjun Li**: Writing – original draft, Writing – review & editing. **Mark Mapstone**: Supervision, Writing – original draft, Writing – review & editing. **Alejandro Santos-Lozano**: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Robert Nisticò**: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

EE is the unique owner of 2E Science, a for-profit private scientific company. Neither EE nor 2E Science have any commercial interest or financial tie in relation with this article. BPI is an employee at Chiesi Farmaceutici. He is listed among the inventors of a number of Chiesi Farmaceutici's patents of anti-Alzheimer drugs. SL, RG-D, SL-O, AG-D, HM, JM-H, AL, DC, VT, LL, MS, MC-C, JM, LL, MM, AS-L, and RN declare that they have no conflict of interest.

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