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RESEARCH ARTICLE

Comparative brain metabolomics reveals shared and distinct metabolic alterations in Alzheimer's disease and progressive supranuclear palsy

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Abstract

BACKGROUND: Metabolic dysregulation is a hallmark of neurodegenerative diseases, including Alzheimer's disease (AD) and progressive supranuclear palsy (PSP). Although metabolic dysregulation is a common link between these two tauopathies, a comprehensive brain metabolic comparison of the diseases has not yet been performed.

METHODS: We analyzed 342 postmortem brain samples from the Mayo Clinic Brain Bank and examined 658 metabolites in the cerebellar cortex and the temporal cortex between the two tauopathies.

RESULTS: Our findings indicate that both diseases display oxidative stress associated with lipid metabolism, mitochondrial dysfunction linked to lysine metabolism, and an indication of tau-induced polyamine stress response. However, specific to AD, we detected glutathione-related neuroinflammation, deregulations of enzymes tied to purines, and cognitive deficits associated with vitamin B.

Richa Batra, Jan Krumsiek, and Xue Wang contributed equally to this work.

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DISCUSSION: Our findings underscore vast alterations in the brain's metabolome, illuminating shared neurodegenerative pathways and disease-specific traits in AD and PSP.

KEYWORDS
Alzheimer's disease, brain, cognitive deficit, metabolism, mitochondrial dysfunction, neuroinflammation, oxidative stress, progressive supranuclear palsy, tau-mediated stress

Highlights

- First high-throughput metabolic comparison of Alzheimer's diesease (AD) versus progressive supranuclear palsy (PSP) in brain tissue.
- Cerebellar cortex (CER) shows substantial AD-related metabolic changes, despite limited proteinopathy.
- AD impacts both CER and temporal cortex (TCX); PSP's changes are primarily in CER.
- AD and PSP share metabolic alterations despite major pathological differences.

1 | BACKGROUND

Tau protein hyperphosphorylation and its abnormal accumulation in the brain is a hallmark of several neurodegenerative diseases, including Alzheimer's disease (AD) and progressive supranuclear palsy (PSP).[1] The major clinical symptom of AD is dementia, which predominantly impairs memory,[2] whereas PSP is a Parkinsonian movement disorder.[3] Despite both representing tauopathies, these diseases have several key differences: First, AD is a dual proteinopathy, displaying deposition of both amyloid beta (Aβ) and tau tangles, whereas PSP is considered to be a pure tauopathy.[1] Second, the specific tau proteins in the two diseases differ in their protein isoforms.[4] Although AD presents neuronal tangles composed of tau of both three (3R) and four (4R) microtubule-binding repeat isoforms, shifting from 3R to 4R with disease progression,[5] PSP demonstrates different tau-inclusion patterns predominantly composed of 4R in neurons, astrocytes, oligodendrocytes, and white matter. Furthermore, although both diseases are associated with tau-encoding microtubule-associated protein tau (*MAPT*) haplotypes,[6,7] distinct genetic risk factors have been discovered for AD[8] and PSP,[7] signifying divergent genetic components contributing to these two diseases. These differences in the genetic risk, involved proteins, and tau isoforms might be the basis of the divergent molecular and clinical presentations of these two pathologies.

In a comparison of the two diseases at the molecular level, we previously reported a high overlap in transcriptomic signatures of these diseases,[9,10] including dysregulation of biological processes such as myelination. As a particularly affected cellular process, metabolic dysregulation involving mitochondrial dysfunction is a common disease pathway in neurodegenerative diseases.[11] Especially in AD pathology, such metabolic modulation is an established key component, affecting cellular processes both in the brain and in the periphery.[12–18] Moreover, our recent study on postmortem human brain tissue suggested tau as the potential driver of AD-associated metabolic alterations in the central nervous system.[15] In the context of PSP, several small-scale studies have indicated the presence of metabolic dysregulation in cerebrospinal fluid (CSF) and in blood.[19,20]

Because AD and PSP share the above-mentioned pathological features, namely, tauopathy and metabolic alterations, comparing their metabolomic profiles can help identify shared biological pathways that could be targeted for therapeutic interventions. Conducting a thorough brain metabolic comparison of the two diseases is crucial to determine the precise alterations in metabolic homeostasis, which is a hallmark of neurodegenerative diseases.[15,21] To date, there have been no brain metabolic profiling studies of PSP and no comparative metabolomic studies for these tauopathies.

To address this need, we present a human brain-based metabolic comparison derived from a sizable cohort of neuropathologically diagnosed AD, PSP, and control donors. We analyzed 342 brain samples, comprising 181 from the cerebellar cortex (CER) and 161 from the temporal cortex (TCX). These two brain regions exhibit varying degrees of proteinopathy across the two diseases, with CER being largely unaffected in both[22,23] and TCX being affected predominantly in AD.[23,24] However, proteinopathy in the CER of patients with AD seems to emerge at later stages,[25] and this region has been reported to exhibit disease-driven changes, including atrophy, diffused amyloid presence, and increased microglial activity.[26] From the perspective of PSP, proteinopathy has traditionally been reported only in the anterior CER[27]; however, a recent whole-brain magnetic resonance spectroscopy (MRS)–based study has revealed metabolic changes across various brain regions including both CER and TCX.[28] Moreover, our

previous research has identified transcriptomic alterations common to both diseases and brain regions,[9,10] suggesting that despite differences in gross pathology, widespread regulatory changes occur in both of these neurodegenerative diseases in both brain regions. Our aim here was to determine if the metabolome, similar to the transcriptome, is also affected across brain regions with varying degrees of proteinopathies and across neurodegenerative diseases—AD and PSP. An overview of the study is depicted in Figure 1.

2 | METHODS

2.1 | Cohorts, clinical data, and neuropathological data

The Mayo Clinic cohort consisted of 162 TCX and 182 CER samples. Among those samples, 138 TCX and CER samples were from the same brain donor. AD, PSP, and control donors were neuropathologically diagnosed at autopsy. AD donors met the neuropathologic criteria for definite AD according to the national institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association (NINCDS-ADRDA) criteria[29] and had a Braak score of ≥4.0. All PSP donors are from the Mayo Clinic Brain Bank and were diagnosed according to national institute of neurological disorders and stroke (NINDS) neuropathologic criteria criteria.[30] All PSP brains also met the new Rainwater criteria.[22] Control donors each had Braak neurofibrillary tangle (NFT) stage of 3.0 or less, consortium to establish a registry for Alzheimer's disease (CERAD)[31] neuritic and cortical plaque densities of 0 (none) or 1 (sparse), and lacked any of the following pathologic diagnoses: AD, Parkinson's disease (PD), dementia with Lewy bodies (DLB), vascular dementia (VaD), PSP, motor neuron disease (MND), corticobasal degeneration (CBD), Pick's disease (PiD), Huntington's disease (HD), frontotemporal lobar degeneration (FTLD), hippocampal sclerosis (HipScl), or dementia lacking distinctive histology (DLDH). These are archival brain bank samples. Information on diet, weight, and body mass index (BMI) is not available. All the donors in this study were non-Hispanic Whites of North American or European descent. Details on this cohort have also been provided in previous studies.[9,10,32]

2.2 | Metabolomics profiling

The untargeted DiscoveryHD4 metabolomics platform from Metabolon Inc. was used to measure brain metabolic profiles. Fractions of the tissue samples were used for two ultra-high performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS; positive ionization), a UPLC-MS/MS (negative ionization), and a UPLC-MS/MS polar platform (negative ionization). Based on the spectra, area under the curve (AUC) was used to quantify the peak intensities. An internal spectral database was used for compound identification. Further details can be found in File S1 and a previous publication.[15]

RESEARCH IN CONTEXT

1. **Systematic review**: Although Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) differ in genetic factors, symptoms, and proteinopathy, they share alterations in myelination and mitochondrial metabolism. Metabolic dysregulation is a hallmark of neurodegenerative diseases and a common feature of AD and PSP; however, a comprehensive brain metabolic comparison of these diseases has been missing so far.
2. **Interpretation**: We examined 658 metabolites in cerebellar cortex (CER) and temporal cortex (TCX) brain regions using 342 AD, PSP, or control brain samples from the Mayo Clinic Brain Bank. Our study shows that AD metabolically affects both CER and TCX regions, whereas PSP's impact is mostly in CER. Our study is a first step toward cataloging the common and divergent metabolic changes observed in AD and PSP.
3. **Future directions**: Future research using spatial metabolomics or induced pluripotent stem cell (iPSC)-derived cells will allow detailed comparisons of the metabolic changes in these diseases at a specific cell type level.

2.3 | Data preprocessing

A total of 827 metabolites were identified by the metabolomics platform. Of these, 658 metabolites with <25% missing values were used for the analysis; the remaining 169 were excluded. To correct for sample-wise variation, probabilistic quotient normalization was performed,[33] followed by $\log_2$ transformation. To impute the remaining missing values, a *k*-nearest-neighbor–based algorithm was applied as described previously.[34] The local outlier factor method was used for outlier detection,[35] identifying no samples to be excluded. Two hundred seventy-eight irregularly high or low single concentrations with absolute z-score above $q = abs(qnorm[0.0125/n])$, with n representing the number of samples, were set to missing. This formula finds the cutoff for values with less than 2.5% two-tailed probability to originate from the same normal distribution as the rest of the measurement values, after applying a Bonferroni-inspired correction factor (division by sample size). These values were then imputed using a *k*-nearest-neighbor–based algorithm.[15] All preprocessing was performed using the maplet R package.[36]

2.4 | Differential analysis of metabolites

Of 344 samples, 342 were used for the analysis; 2 with missing apolipoprotein E (*APOE*) ε4 status were excluded. To identify metabolites associated with diagnosis, two subsequent logistic regressions

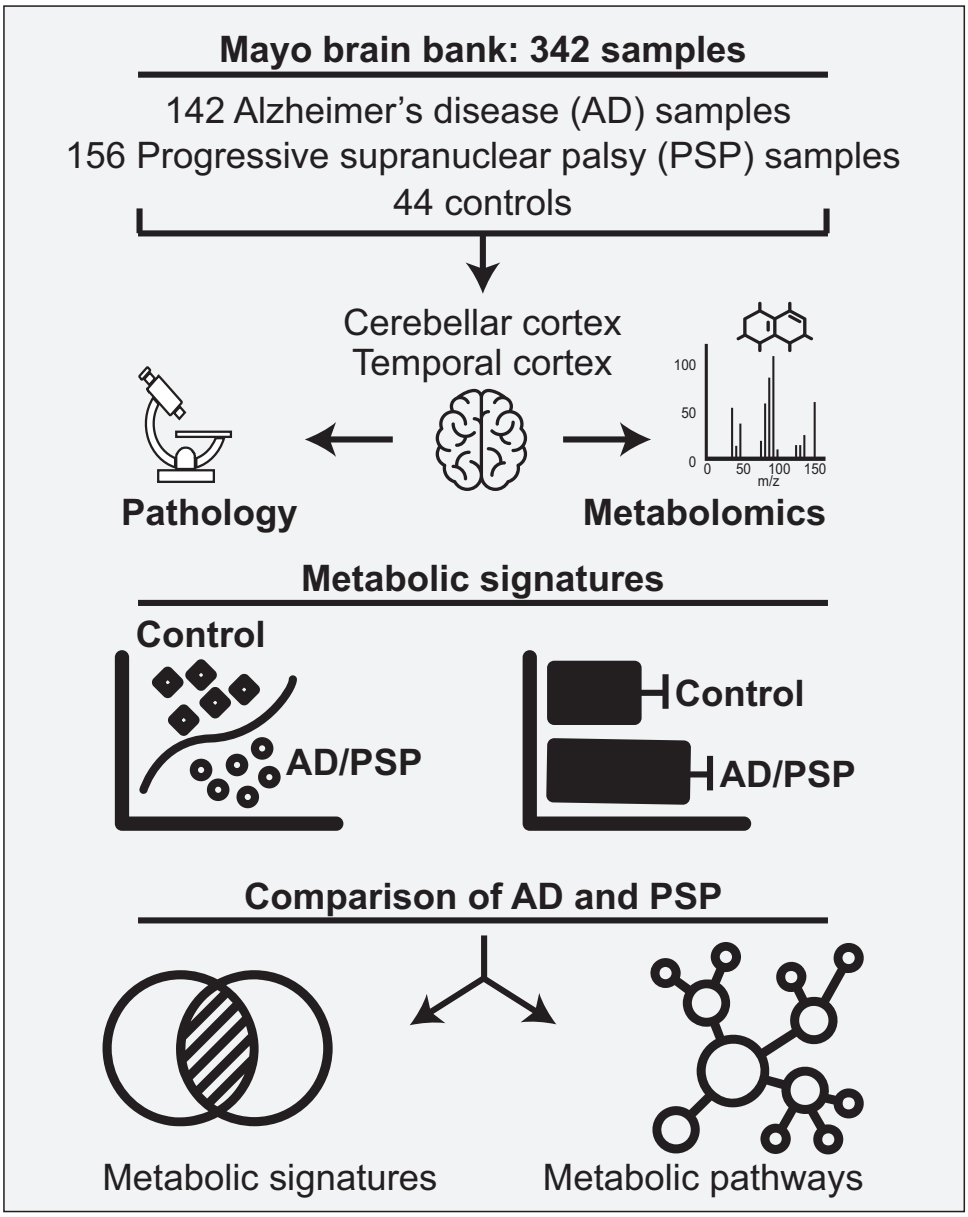

FIGURE 1 Study overview: 342 Mayo Clinic Brain Bank samples were included in this analysis. For each sample, diagnosis and demographic information were available. Metabolomic profiling was performed on samples from the cerebellar cortex (CER) and temporal cortex (TCX) regions. Metabolic signatures of each diagnosis, namely, Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) in comparison to metabolic profiles of controls without neurodegenerative disease. A comparison of the metabolic signatures of the two tauopathies was performed, highlighting the overlap in altered metabolites and metabolic pathways commonly dysregulated in the two diseases.

were used as described previously.[10,37] The first model included diagnosis as the outcome, metabolites as the predictors, but no confounding factors. *p*-Values of this model were corrected using the Benjamini–Hochberg (BH) method[38] for multiple hypothesis testing. The second logistic regression model included diagnosis as the outcome, metabolites with adjusted *p*-values < 0.25 from the first model as predictors, and sex, number of *APOE* ε4 alleles, and age at death as confounders. Metabolites with *p*-value < 0.05 in the second model were used to define the metabolic signatures of the diseases. To estimate the statistical power of the associations for each comparison, we utilized the "pwrss.z.logistic" function from the R package "pwrss." This function was employed to conduct power calculations for logistic regression at an alpha level of 0.05. We based these calculations on a range of effect sizes derived from the first model (as described above), using the maximum and minimum effect sizes observed in our results to define the upper and lower limits of this range.

To determine the effect of postmortem interval (PMI) on the associations, the association analysis was repeated including PMI as a covariate in the second model. For this analysis, 153 samples with missing PMI information were excluded. The results from the analysis are available in Tables S1–S9.

TABLE 1 Cohort overview.

	Cerebellar cortex (CER, $n = 181$)			Temporal cortex (TCX, $n = 161$)		
	AD ($n = 79$)	PSP ($n = 78$)	Control ($n = 24$)	AD ($n = 63$)	PSP ($n = 78$)	Control ($n = 20$)
Sex						
Male	32	47	11	27	46	8
Female	47	31	13	36	32	12
Age at death[a]	84 (78, 89)	74 (69, 79)	90 (87, 90)	86 (81, 90)	74 (69, 79)	90 (88, 90)
APOE ε4 allele						
0	38	66	21	28	67	17
1	36	11	3	31	10	3
2	5	1	0	4	1	0

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; IQR, interquartile range, that is, middle 50% of the value range; PSP, progressive supranuclear palsy.
[a]Median (IQR).

For a selected set of metabolites, that is, from polyamine metabolism, pairwise ratios were computed (Tables S10 and S11). The rationale is explained in Section 3.3.2 under the heading "Polyamine metabolism and tau-mediated stress." To this end, exponentials of the $\log_2$ transformed metabolic profiles were computed, ratios were generated, and then $\log_2$ transformed. The differential analysis of these ratios was performed in the same way as individual metabolites.

2.5 | Pathway analysis

For functional annotation of the significantly altered metabolites, Metabolon's sub-pathway annotations were used. For functional annotation of metabolic signatures in the CER region described in the Section 3.2, the total number of metabolites per pathway and, for each disease (AD and PSP) number of metabolites that were lower or higher compared to controls were reported. Supplementary Tables contain the complete list of annotations.

3 | RESULTS

3.1 | Metabolic signatures of the two diseases

We analyzed 342 brain samples from the Mayo Clinic Brain Bank, from AD and PSP patients as well as controls without neurodegenerative pathologic diagnoses, across two brain regions: CER and TCX. Demographic characteristics of the samples across the diagnoses and brain regions are shown in Table 1.

Samples were profiled using an untargeted LC-MS/MS–based metabolomics platform. This resulted in measurements of 658 metabolites from various metabolic "super-pathways" (Figure 2A, Table S1), covering lipids (44.4%), amino acids (23.3%), nucleotides (7.0%), carbohydrates (5.3%), cofactors and vitamins (3.8%), peptides (2.7%), xenobiotics (2.7%), energy-related metabolites (1.5%), and a series of uncharacterized metabolites (9.3%).

To determine the metabolic imprint of the two diseases in the brain, we performed a brain region–wise statistical comparison between disease and control samples. All models were corrected for disease-associated confounding variables, including the number of *APOE* ε4 alleles, age at death, and sex. All donors were non-Hispanic White. Of note, potentially confounding variables BMI and years of education were unavailable in this archival brain bank cohort. PMI was available only in a subset and was, therefore, not included in the main analysis. In the CER region, a total of 153 metabolites were associated with AD; 35 were associated with PSP (Figure 2B), of which 27 were commonly associated with both diseases (Figure 2C). In the TCX region, 63 metabolites were associated with AD, only two were associated with PSP (Figure 2B), and none were shared between the two diseases (Figure 2D). Detailed statistical results from the two brain regions can be found in Tables S2–S5. A comparison of the effect sizes across diseases within the same brain region and across the brain regions in the same disease is shown in Figure S1. A visual representation of the power analysis of these associations are available in Figure S2. Statistical results in the subset of samples with PMI can be found in Table S6–S9.

Overall, AD-related metabolic alterations were observed in both brain regions, whereas PSP-related alterations had a regional preference for CER and were less pronounced compared to AD-related alterations. Of note, the sample sizes were comparable for both brain regions as well as diseases (Table 1), suggesting that statistical power was unlikely to cause this discrepancy. In the following, we focused on the CER region for a detailed comparison of AD and PSP, as this region had commonly perturbed metabolites between these two diseases, whereas TCX had none.

3.2 | Comparison of AD and PSP metabolic signatures in CER

To compare the metabolic signatures of the two diseases in CER, each metabolite was categorized using a "sub-pathway" annotation. One

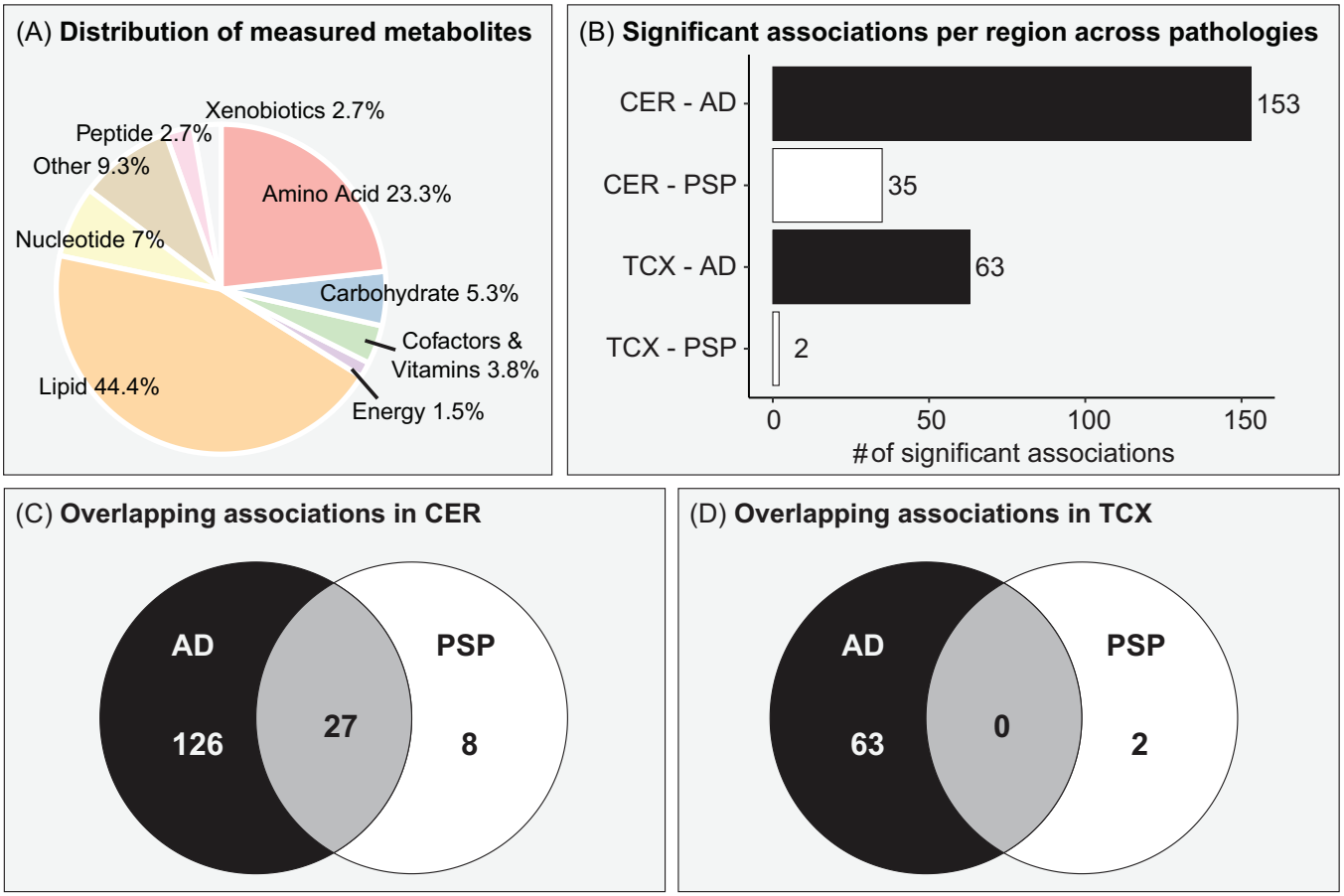

FIGURE 2 Overview of metabolites and their associations with Alzheimer's disease (AD) and progressive supranuclear palsy (PSP). (A) Distribution of metabolites detected by metabolomics platform across metabolic classes. (B) Number of metabolic associations for each brain region and each disease. (C) Overlap of metabolic associations between the two diseases in cerebellar cortex samples. (D) Overlap of metabolic associations between the two diseases in temporal cortex samples.

hundred fifty-three metabolites were significantly associated with AD, 136 of these 153 were annotated with 53 pathways, and the remaining 17 metabolites were MS peaks without any identifiable characteristics and thus were excluded from further analysis. Similarly, 35 metabolites were significantly associated with PSP, 30 of which were annotated with 19 pathways, and the remaining 5 metabolites were uncharacterized and thus were excluded from further analysis. Overall, 35 pathways were exclusively dysregulated in AD, 1 pathway was exclusive to PSP, and 18 pathways were shared across the two diseases. These pathways were distributed across all eight super-pathways, with amino acids and lipids representing the groups with the most changes (Figure 3).

Pathways exclusively dysregulated in AD

A total of 35 pathways were dysregulated in AD but not in PSP. Among these, various amino acid pathways were negatively associated with AD including the urea cycle, alanine and aspartate, tyrosine, and branched-chain amino acid (BCAA) metabolism, whereas glutathione metabolism was positively associated. In addition, the metabolism of vitamins B1, B2, and B6 was negatively associated with AD, whereas vitamin C metabolism was positively associated. Moreover, several pathways belonging to the metabolic groups of peptides, carbohydrates, energy metabolites, and nucleotide metabolism were dysregulated only in AD.

Pathways exclusively dysregulated in PSP

Dicarboxylate metabolism was the only pathway uniquely dysregulated in PSP. However, within this pathway, only one of the seven metabolites, the fatty acid 3-hydroxyadipate, was significantly lower in PSP as compared to controls, whereas changes in the remaining six metabolites were insignificant. Thus, there is limited evidence to support the dysregulation of this pathway in PSP.

Pathways commonly dysregulated in both diseases

Eighteen pathways were commonly perturbed in AD and PSP. These pathways were mainly from the amino acid and lipid groups. Within the amino acid group, creatine, glutamate, and lysine metabolism were positively associated with both diseases, whereas polyamine, glycine, and histidine metabolism were negatively associated. Within

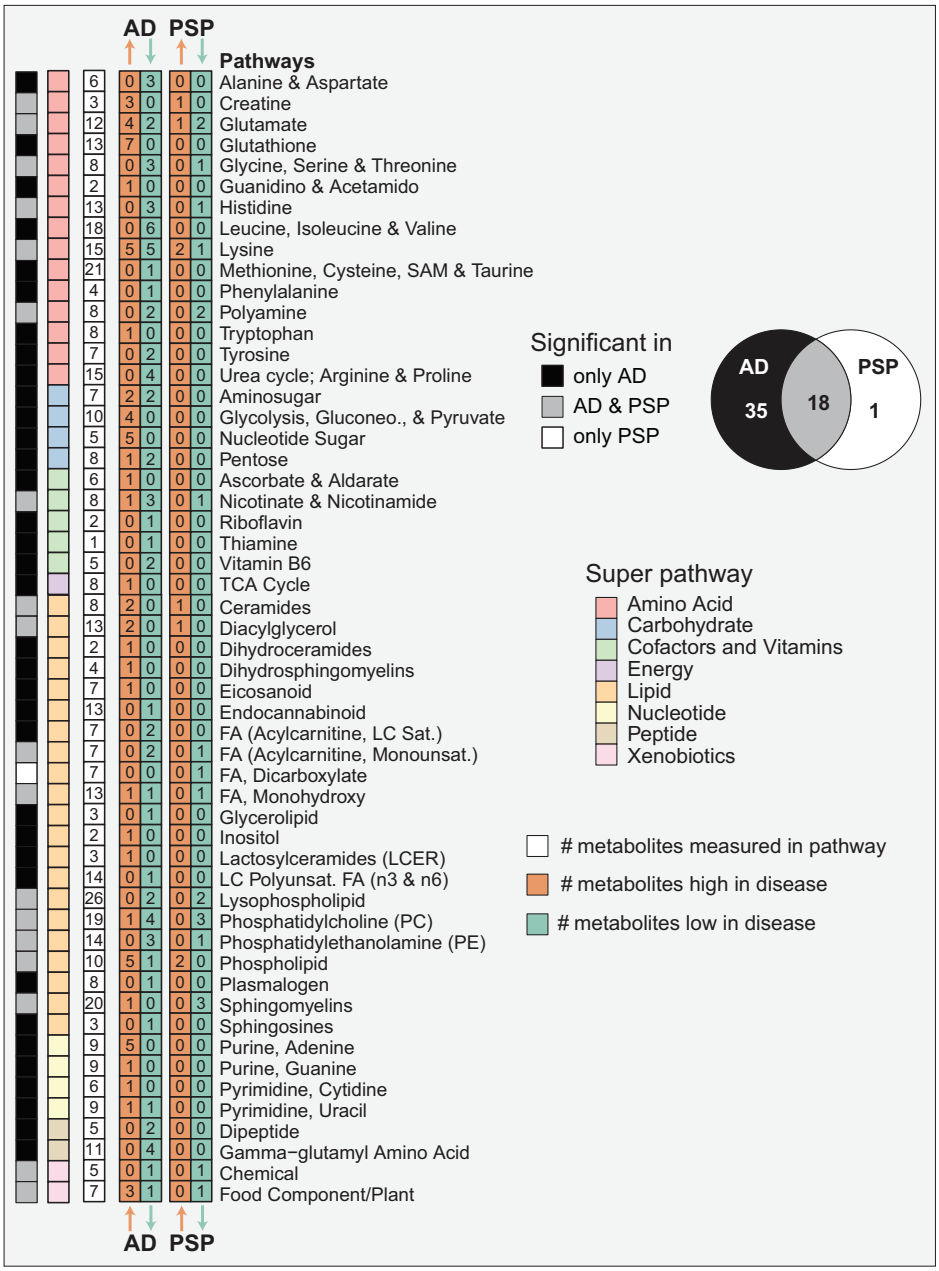

FIGURE 3 Functional annotation of metabolic signatures in the cerebellar cortex (CER) region. Within the CER region, for each disease and pathway, the number of positively or negatively associated metabolites is shown in orange and green boxes, respectively. These pathways are further annotated by super-pathways. The significance of these pathways in one or both diseases is shown per pathway. Venn diagram depicts the overlap of the number of significant pathways in the two diseases. FA, fatty acid; LC, long chain.

the lipid group, ceramides, diacylglycerol, and phospholipids were positively associated with both diseases, whereas sphingomyelin, lysophospholipid, phosphatidylcholine, phosphoethanolamine, and Fatty Acid (acylcarnitine, monounsaturated) were negatively associated.

Overall, in the two diseases, common metabolic perturbations were better captured at the functional level of pathways (18/54 changed, 33.34%) than at the individual metabolite level (27/161 changed, 16.77%).

3.3 | Functional insights into unique and shared metabolic dysregulation in AD and PSP in CER

As outlined earlier, in the CER region, 35 metabolic pathways were exclusively dysregulated in AD, only 1 pathway was exclusively dysregulated in PSP, and 18 pathways were shared across the diseases (Figure 4). In the following, we discuss functional insights into the commonalities and differences of metabolic dysregulation in the two diseases based on selected pathways.

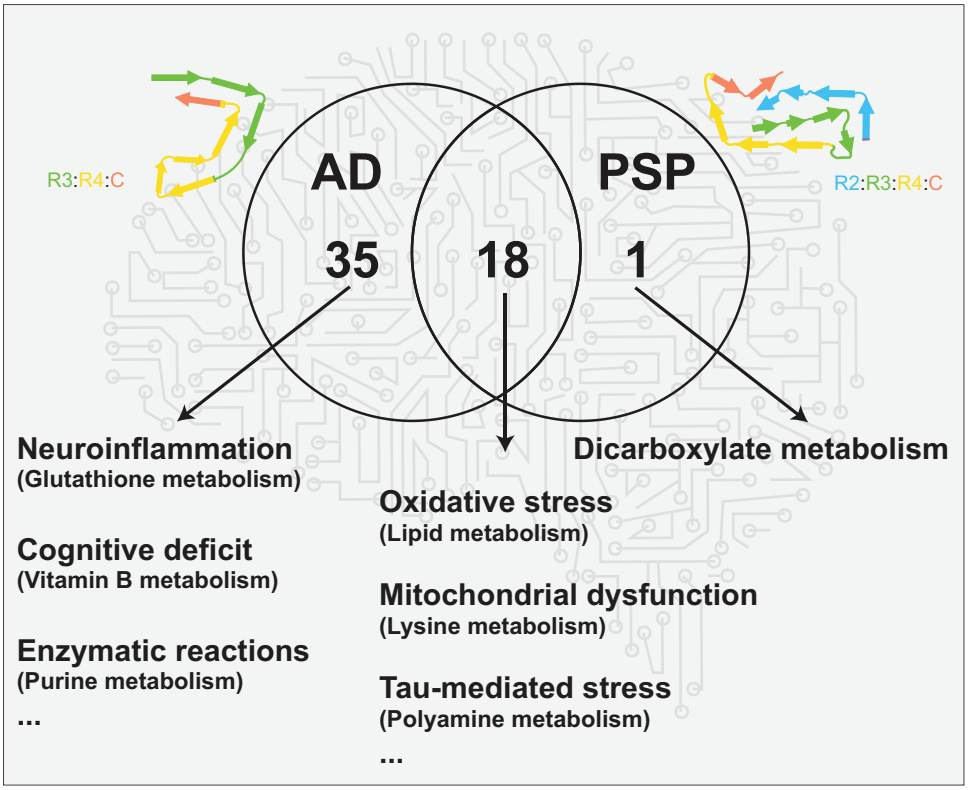

FIGURE 4 Comparison of deregulated pathways in the two diseases. Within the cerebellar cortex region, 35 pathways were exclusively dysregulated in Alzheimer's disease (AD), 18 pathways were shared between the two diseases, and 1 pathway was dysregulated exclusively in progressive supranuclear palsy (PSP). The labeled processes indicate selected pathways discussed in the text. Included for illustrative purposes are stylistic representations of the tau isoform associated with each tauopathy. Within these protein structures, residues in R1–R4 and in the C-terminal domain are colored purple, blue, green, gold, and orange, respectively.[24]

3.3.1 | Metabolic pathways altered exclusively in AD in CER

Within the CER region, 35 metabolic pathways were dysregulated exclusively in AD. Based on the number of metabolites altered, we highlight the three most perturbed pathways from three different metabolic groups in the following.

Glutathione metabolism and neuroinflammation

Neuroinflammation is central to AD pathogenesis and is marked by the release of pro-inflammatory molecules as well as reactive oxygen species.[39] Antioxidants such as glutathione play a key role in combating oxidative stress resulting from neuroinflammation.[40] Neuroinflammation and oxidative stress in the brain are believed to mediate neuronal dysfunction and death.[39] In our data, 7 of 13 metabolites from glutathione metabolism were higher in AD as compared to controls. Of these seven, glutathione disulphide bond glutathione molecule (GSSG), ophthalmate, and 4-hydroxy-nonenal-glutathione are known biomarkers of oxidative stress.[41–43] Of note, based on genomic and transcriptomic data, we have demonstrated previously that this pathway is disrupted in AD.[44]

Purine metabolism and enzymatic reactions

Purine bases serve as cofactors for various biochemical reactions and are thus crucial for many metabolic processes.[30] Moreover, adenosine has been implicated in the modulation of cognition and memory, as well as the permeability of the blood–brain barrier.[45] In our data, five metabolites from adenine metabolism and one from guanine metabolism were higher in AD as compared to controls. Purine metabolism has been shown to be perturbed in AD; however, effect directions were inconsistent between CSF and brain regions.[13,45,46] Overall, our findings indicate a dysregulation of purines in AD brains, which has the potential to alter various brain functions.

Vitamin B metabolism and cognitive deficit

Multiple B vitamins are considered protective against cognitive decline.[47] In our data, thiamine (vitamin B1), riboflavin (vitamin B2), and pyridoxine (vitamin B6) were found to be lower in AD compared to controls. Thiamine-dependent enzymes play central roles in glucose metabolism.[48] In AD brains, a reduction in thiamine levels has been associated with the diminished activity of thiamine-dependent enzymes, including transketolase from the pentose phosphate pathway and 2-ketoglutarate dehydrogenase complex from the tricarboxylic

acid (TCA) cycle.[48,49] Riboflavin and pyridoxine in their co-enzymatic forms are involved in one-carbon metabolism.[50] Riboflavin acts as a cofactor in the folate cycle, whereas pyridoxine is involved in the transsulphuration pathway.[50] Overall, these vitamins are essential for a well-functioning metabolism, and reduction in their levels has been associated with a decline in cognitive functions.[47,51]

Of note, all the above-mentioned AD-related metabolic dysregulations identified in the CER region were also detected in our previous findings in the dorsolateral prefrontal cortex region of the religious order study and memory aging project (ROS/MAP) cohort.[15]

3.3.2 | Metabolic pathways altered in both diseases

Within the CER region, 18 metabolic pathways were dysregulated in both diseases. In the following, we highlight pathways from the two biggest metabolic classes, lipids and amino acids.

Lipid metabolism and oxidative stress

In neurodegenerative diseases, lipid metabolism has been implicated widely in disease pathogenesis, including in amyloid beta (Aβ)-associated lipid rafts, increased lipid peroxidation,[52] altered cholesterol and lipid homeostasis,[53] as well as phospholipase-2-mediated lipid cleavage.[54] In our data, lipids from various lipid classes were dysregulated, with 15 lipids dysregulated in AD and 8 of those 15 also dysregulated in PSP.

Oxidative stress, a hallmark of neurodegenerative diseases, induces lipid peroxidation, which leads to increased phospholipase activity.[55,56] The breakdown of phospholipids by phospholipases leads to compromised membrane integrity,[57] which affects neuronal excitability.[55] In our data, several phosphatidylcholines (PCs), the major membrane phospholipids, were lower in both diseases compared to controls. Phospholipases degrade PCs into lyso-PCs, which get further broken down into glycerophoshorylcholine (GPC) and fatty acids.[58] GPC was high in both diseases as compared to controls in our study.

Moreover, oxidative stress is also known to increase ceramide production, which in turn may trigger synaptic dysfunction and neuronal death.[59] Ceramides play an important role in many cellular processes, including lipid signaling, metabolic homeostasis, and mitochondria-linked apoptosis.[60] In our data, ceramide levels were positively associated with both diseases with varying degrees. *N*-stearoyl-sphingadienine (d18:2/18:0)* was high in both diseases compared to controls, whereas lactosyl-*N*-stearoyl-sphingosine (d18:1/18:0)*, a lactosylceramide, and *N*-stearoyl-sphinganine (d18:0/18:0)*, a dihydroceramide, were high only in AD compared to controls. Moreover, the myelin sheath that assists in signal transduction across neurons is composed of ceramides.[60] Notably, in our previous transcriptome-based studies, we observed myelination dysregulation in both AD and PSP.[9,61]

Lysine metabolism and mitochondrial dysfunction

Lysine is an essential amino acid that can be catabolized by two pathways: the saccharopine pathway in mitochondria and the pipecolate pathway in cytosol.[62] In our data, 10 metabolites from lysine metabolism were dysregulated. Of these, all 10 were perturbed in AD, whereas only 3 metabolites were altered in PSP. One of the 10 metabolites was saccharopine, which was high in both AD and PSP as compared to controls. Previous studies in *Caenorhabditis elegans* and mice have argued that saccharopine accumulation leads to mitochondrial dysfunction.[63] Our results are thus another potential piece of evidence in support of mitochondrial dysregulation in the pathogenesis of tauopathies.[64]

Polyamine metabolism and tau-mediated stress

In our study, two of the eight metabolites from polyamine metabolism, spermidine and spermine, were significantly lower in both tauopathies compared to controls. Polyamines are known for their neuroprotective effects, such as the clearance of apoptotic cells via efferocytosis[65] and autophagy[66]; both mechanisms are affected in AD and other neurodegenerative diseases.[67] Moreover, mouse-based studies have speculated a complex interaction between polyamines and tau neuropathology.[68,69] Specifically, it has been hypothesized that spermidine and spermine reduce tau fibrillization, oligomerization, and tau seeding/propagation, whereas tau can lead to polyamine stress response.[68] The polyamine stress response is defined as an alteration in the brain polyamine metabolism that is stimulated by a stressor leading to an increase in putrescine level, while levels of spermine and spermidine decrease or remain unchanged.[70,71] Notably, in our data, putrescine levels were unchanged. Previous metabolomic studies have reported that metabolite ratios may serve as proxies for enzymatic activity, in particular when two metabolites correspond to the immediate substrates and products of an enzymatic transformation.[72] Therefore, we performed a ratio analysis for the metabolites in the polyamine metabolite pathway because putrescine is the substrate to produce spermidine, which in turn is the substrate to produce spermine in a reversible reaction. (Tables S10 and S11). In our analysis, ratios of putrescine/spermidine and putrescine/spermine were higher in both tauopathies as compared to controls, indicating relatively higher levels of putrescine compared to the other polyamines.

4 | DISCUSSION

The two tauopathies AD and PSP exhibit several shared and unique characteristics. They differ in the genetic risk factors involved, tau-isoforms, main symptoms, and type of proteinopathy, with PSP being a pure tauopathy and AD exhibiting deposition of Aβ along with tau.[1] At the molecular level, the two diseases display similarities, particularly in the alterations of biological processes including myelination[9] and mitochondrial metabolism.[10] However, prior to this study, the comparative analysis of metabolic alterations, a key feature of neurodegeneration,[21] between AD and PSP had not been explored. To address this gap, we conducted a comprehensive assessment using a sizable cohort of 342 samples of AD, PSP, and control donors from the Mayo Clinic Brain Bank. We profiled 658 metabolites across CER and TCX brain regions and provided a detailed comparative account of metabolic alterations in AD and PSP. Of the 658 metabolites, 200

(30.4%) were significantly associated with at least one of the diseases in at least one of the regions. In the following, we discuss the key findings of our study.

Our results show that AD-related metabolic alterations encompass both regions, namely, CER and TCX. We identified 153 AD-associated metabolic alterations within the CER region and 63 alterations within the TCX region. Remarkably, we found a larger number of metabolic alterations in CER compared to TCX. This was unexpected, as CER is relatively devoid of significant gross neuropathology in AD.[23] We speculate that the metabolic alterations observed in CER may be due to the presence of either neuropathology in late-phase AD[25] or toxic Aβ/tau oligomer species[73] transported from other brain regions due to the functional and structural connectivity between CER and other brain regions including the hippocampus, which is affected early in AD.[74] Alternatively, the metabolic changes seen in CER could reflect the modulation of CER because of the pathological changes in other regions of the brain, for example, due to altered neural network connectivity.[75] The greater number of metabolic alterations in the CER compared to the TCX could indicate the varying metabolic needs of these regions and how these needs shift with age or during neurodegeneration.[76] Furthermore, our results indicate that PSP-related metabolic alterations were scarce in TCX (two metabolites), whereas some metabolic alterations were observed in CER (35 metabolites). Because TCX has limited neuropathology in PSP,[24] our results were in line with what may be expected from this relatively unaffected region. Although the CER generally shows minimal significant neuropathology in PSP,[22] it may still be susceptible to metabolic alterations for the above-mentioned reasons.

Within the CER region, AD and PSP differed significantly in the number of metabolic alterations (153 in AD and 35 in PSP). As opposed to our previous speculation that tau is the potential driver of AD-associated metabolic alterations in the dorsolateral prefrontal cortex,[15] the current results stipulate that tau may not be the sole driver of metabolic alterations in the CER. Based on these results, it can be inferred that various factors differentiating these diseases may have contributed to the differences in their metabolic imprint. Furthermore, although our analysis adjusted for age as a covariate, the observed differences in age could potentially contribute to the variance in the number of metabolic alterations identified within AD and PSP brains. The median age at death of PSP donors was lower than that of AD donors, and controls were older than both AD and PSP cases.

Despite the differences in the two tauopathies, common metabolic processes were altered across the two diseases. Pathway analysis of the altered metabolites in the CER region indicated a higher overlap in affected biological processes (33.34%) across the pathologies as compared to individual metabolites (16.77%). We found metabolic alterations shared between the two tauopathies in various pathways and highlighted the specifics of several selected pathways. We speculate that these similarities in the two diseases can result from either common metabolic rewiring to combat the neurodegenerative processes or common perturbation of the metabolism due to the neurodegenerative process. AD showed more unique alterations, whereas PSP shared most of its altered processes with AD. We found that lipid metabolism–mediated oxidative stress, lysine metabolism-associated mitochondrial dysfunction, and tau-mediated polyamine stress were shared processes between the two diseases. Meanwhile, glutathione metabolism–mediated oxidative stress and neuroinflammation, purine-linked enzymatic deregulations, and vitamin B–associated cognitive deficits were unique to AD.

Our study had several limitations. First, confounding variables including BMI, years of education, and PMI were unavailable either in all or a subset of donors in this cohort. Thus, we could not adjust for potential differences in certain metabolites that may be due to these factors. Second, the measured metabolites could be further influenced by factors such as medication and supplement use,[15] diet, the gut microbiome,[77,78] and comorbidities, potentially affecting some of our results. Third, although both our transcriptomics-based and metabolomics-based studies identified substantial PSP-associated molecular alterations in the brain regions currently examined, our study design lacks a brain region substantially affected by neuropathology in PSP. Fourth, in our hypothesis-generating analysis, we have used a less-conservative false discovery rate threshold of 25%, as compared to the traditional threshold of 5% accepting, the possibility that up to one in four metabolites might be a false positive in our results. Fifth, bulk tissue profiling as used in this study lacks resolution at the single-cell level that might be necessary to distinguish the contribution of various cell fractions. Differential proportions of cell types or differences in microenvironment could affect bulk levels of metabolites in various ways. (1) Significant differences in cell proportion could alter the levels of metabolites in the bulk sample.[79] (2) Neuropathology could reprogram certain cell types to produce different levels of metabolites. For instance, tau accumulation within neurons could reprogram their metabolism, leading to aberrations at both the metabolome and transcriptome levels.[9] (3) The cellular microenvironment could influence the metabolic profiles of certain cell types. For example, pathology leads to the activation of microglial cells,[80] which could have a different metabolic profile than a microglial cell in a steady state. In summary, one or more of these mechanisms may drive the changes in metabolic profiles at the cell type–specific level. Future studies need to focus on single-cell or spatial metabolic profiling approaches to delineate these mechanisms. To our knowledge, this is the first study to conduct a comparative metabolome analysis between AD and PSP, and also in two brain regions. Consequently, our findings are based on statistical associations from a single cohort. Nevertheless, the discovery of metabolic pathways commonly perturbed in both AD and PSP in this study - along with prior metabolomic and transcriptomic studies that support associations of some of these pathways with AD and/or PSP, including lipid metabolism[52–54]; oxidative stress,[55,56] ceramides[9,60,61] and mitochondrial metabolism[64] - highlight the robust and replicable nature of our findings.

In summary, we presented the first large-scale metabolic comparison of two tauopathies—AD and PSP—focusing on two different brain regions. Our study is a step toward cataloging the common and divergent metabolic changes observed in these two diseases. Our findings support the hypothesis that many metabolic changes are common to neurodegeneration (both AD and PSP) and reflect

molecular disruptions that are not driven by gross pathology, since most perturbations occur in CER, which has limited neuropathology in both diseases. Future studies on experimental model systems, such as induced pluripotent stem cell (iPSC) cell lines or mouse models of tauopathy, ß-amyloidosis, or both could further support our findings and enable longitudinal assessment of metabolomic changes. One specific example would be targeting enzymes from polyamine metabolism (spermidine synthase (SRM) or spermine synthase (SMS)) as a therapeutic strategy. Through genetic (e.g., CRISPR) or pharmacological means, altering these enzymes in advanced cell lines like human iPSC 4R tauopathy models[81] could shed light on their role in tau pathology and cell health, offering insights into novel ways to combat tauopathies. Likewise, blood and CSF metabolome studies of longitudinally followed human cohorts can reveal the temporal progression of these changes and align them to brain tau, Aß, and neurodegeneration when combined with neuroimaging.[82] Follow-up studies in additional postmortem cohorts are needed to investigate the specific metabolic pathways commonly implicated in these and other neurodegenerative diseases. Moreover, the contribution of specific cell types toward the observed metabolic changes remains to be determined. Future studies with specific cell populations, using either spatial metabolomics or iPSC-derived cell type populations, will enable a precise comparison of the metabolic changes in the two diseases at the cell type–specific level.

AUTHOR CONTRIBUTIONS

Richa Batra, Jan Krumsiek, Xue Wang, Nilüfer Ertekin-Taner, and Rima Kaddurah-Daouk designed the study and analytic approaches. Richa Batra and Jan Krumsiek designed the computational and statistical methods, performed the analysis, interpreted the results, and drafted the manuscript. Mariet Allen, Matthias Arnold, and Gabi Kastenmüller contributed to scientific discussions. Nilüfer Ertekin-Taner, Xue Wang, and Mariet Allen provided samples and phenotypic data on the Mayo Clinic cohort, interpreted the results, and edited the manuscript. Colette Blach curated and managed data. Nilüfer Ertekin-Taner acquired funding, and provided supervision and overall direction for the Mayo Clinic cohort. Rima Kaddurah-Daouk acquired funding and is the overall principal investigator of the Alzheimer's Disease Metabolomics Consortium. All authors read and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

R.K-D., M.Arnold, G.K. are (through their institutions) inventors on key patents in the field of metabolomics, including applications for Alzheimer's disease. R.K-D. holds equity in Metabolon Inc., a metabolomics technologies company. This platform was used in the current analyses. R.K-D. formed Chymia LLC and PsyProtix, a Duke University biotechnology spinout aiming to transform the treatment of mental health disorders. M.Arnold and G.K. hold equity in Chymia LLC and IP in PsyProtix. J.K. holds equity in Chymia LLC, IP in PsyProtix, and equity in iollo. N.E.T. is an inventor on a patent through Mayo Clinic in PSP therapeutics. R.B., X.W., M.Allen, and C.B., have no conflicts. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Metabolomics as well as clinical data for the Mayo Clinic cohorts are available via the AD Knowledge Portal. The AD Knowledge Portal is a platform for accessing data, analyses, and tools generated by the Accelerating Medicines Partnership (AMP-AD) Target Discovery Program and other National Institute on Aging (NIA)–supported programs to enable open-science practices and accelerate translational learning. The data, analyses, and tools are shared early in the research cycle without a publication embargo on a secondary use. Data are available for general research use according to the following requirements for data access and data attribution (https://adknowledgeportal.org/DataAccess/Instructions). For access to the metabolomics data used in this manuscript see: https://www.synapse.org/#!Synapse:syn26446587

An interactive view of AD associations from this study can be found at https://krumsieklab.shinyapps.io/tauopathies/

All R scripts to generate the tables and figures of this paper are available at https://github.com/krumsieklab/ad-mayo-tauopathies

ETHICS STATEMENT

This study was approved by the appropriate Mayo Clinic Institutional Review Board.

CONSENT STATEMENT

All participants or next-of-kin provided consent.

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REFERENCES

1. Uversky VN. Intrinsically disordered proteins and their (disordered) proteomes in neurodegenerative disorders. *Front Aging Neurosci*. 2015;7:18. doi:10.3389/fnagi.2015.00018
2. Knopman DS, Amieva H, Petersen RC, et al. Alzheimer disease. *Nat Rev Dis Primer*. 2021;7(1):33. doi:10.1038/s41572-021-00269-y
3. Kurz C, Ebersbach G, Respondek G, Giese A, Arzberger T, Höglinger GU. An autopsy-confirmed case of progressive supranuclear palsy with predominant postural instability. *Acta Neuropathol Commun*. 2016;4:120. doi:10.1186/s40478-016-0391-7
4. Wagshal D, Sankaranarayanan S, Guss V, et al. Divergent CSF τ alterations in two common tauopathies: Alzheimer's disease and progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry*. 2015;86(3):244-250. doi:10.1136/jnnp-2014-308004
5. Uchihara T. Neurofibrillary changes undergoing morphological and biochemical changes—How does tau with the profile shift of from four repeat to three repeat spread in Alzheimer brain? *Neuropathol Off J Jpn Soc Neuropathol*. 2020;40(5):450-459. doi:10.1111/neup.12669
6. Allen M, Kachadoorian M, Quicksall Z, et al. Association of MAPT haplotypes with Alzheimer's disease risk and MAPT brain gene expression levels. *Alzheimers Res Ther*. 2014;6(4):39. doi:10.1186/alzrt268
7. Chen JA, Chen Z, Won H, et al. Joint genome-wide association study of progressive supranuclear palsy identifies novel susceptibility loci and genetic correlation to neurodegenerative diseases. *Mol Neurodegener*. 2018;13(1):41. doi:10.1186/s13024-018-0270-8
8. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. 2022;54(4):412-436. doi:10.1038/s41588-022-01024-z
9. Allen M, Wang X, Burgess JD, et al. Conserved brain myelination networks are altered in Alzheimer's and other neurodegenerative diseases. *Alzheimers Dement*. 2018;14(3):352-366. doi:10.1016/j.jalz.2017.09.012
10. Wang X, Allen M, İş Ö, et al. Alzheimer's disease and progressive supranuclear palsy share similar transcriptomic changes in distinct brain regions. *J Clin Invest*. 2022;132(2). doi:10.1172/JCI149904
11. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*. 2006;443(7113):787-795. doi:10.1038/nature05292
12. Nho K, Kueider-Paisley A, MahmoudianDehkordi S, et al. Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: relationship to neuroimaging and CSF biomarkers. *Alzheimers Dement*. 2019;15(2):232-244. doi:10.1016/j.jalz.2018.08.012
13. Kaddurah-Daouk R, Zhu H, Sharma S, et al. Alterations in metabolic pathways and networks in Alzheimer's disease. *Transl Psychiatry*. 2013;3:e244. doi:10.1038/tp.2013.18
14. Arnold M, Nho K, Kueider-Paisley A, et al. Sex and APOE ε4 genotype modify the Alzheimer's disease serum metabolome. *Nat Commun*. 2020;11(1):1148. doi:10.1038/s41467-020-14959-w
15. Batra R, Arnold M, Wörheide MA, et al. The landscape of metabolic brain alterations in Alzheimer's disease. *Alzheimers Dement*. 2023;19(3):980-998. doi:10.1002/ALZ.12714
16. Toledo JB, Arnold M, Kastenmüller G, et al. Metabolic network failures in Alzheimer's disease: a biochemical road map. *Alzheimers Dement*. 2017;13(9):965-984. doi:10.1016/j.jalz.2017.01.020
17. Mahajan UV, Varma VR, Griswold ME, et al. Dysregulation of multiple metabolic networks related to brain transmethylation and polyamine pathways in Alzheimer disease: a targeted metabolomic and transcriptomic study. *PLoS Med*. 2020;17(1):e1003012. doi:10.1371/JOURNAL.PMED.1003012
18. MahmoudianDehkordi S, Arnold M, Nho K, et al. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-An emerging role for gut microbiome. *Alzheimers Dement*. 2019;15(1):76-92. doi:10.1016/j.jalz.2018.07.217
19. Mori A, Ishikawa KI, Saiki S, et al. Plasma metabolite biomarkers for multiple system atrophy and progressive supranuclear palsy. *PloS ONE*. 2019;14(9):e0223113. doi:10.1371/journal.pone.0223113
20. Takahashi K, Iwaoka K, Takahashi K, et al. Cerebrospinal fluid levels of oxidative stress measured using diacron-reactive oxygen metabolites and biological antioxidant potential in patients with Parkinson's disease and progressive supranuclear palsy. *Neurosci Lett*. 2021;757:135975. doi:10.1016/j.neulet.2021.135975
21. Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. *Cell*. 2023;186(4):693-714. doi:10.1016/j.cell.2022.12.032
22. Roemer SF, Grinberg LT, Crary JF, et al. Rainwater charitable foundation criteria for the neuropathologic diagnosis of progressive supranuclear palsy. *Acta Neuropathol*. 2022;144(4):603-614. doi:10.1007/s00401-022-02479-4
23. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259. doi:10.1007/BF00308809
24. Kovacs GG, Lukic MJ, Irwin DJ, et al. Distribution patterns of tau pathology in progressive supranuclear palsy. *Acta Neuropathol*. 2020;140(2):99-119. doi:10.1007/s00401-020-02158-2
25. Hampel H, Hardy J, Blennow K, et al. The amyloid-β pathway in Alzheimer's disease. *Mol Psychiatry*. 2021;26(10):5481-5503. doi:10.1038/s41380-021-01249-0
26. Larner AJ. The cerebellum in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1997;8(4):203-209. doi:10.1159/000106632
27. Burciu RG, Ofori E, Shukla P, et al. Distinct patterns of brain activity in progressive supranuclear palsy and Parkinson's disease. *Mov Disord*. 2015;30(9):1248-1258. doi:10.1002/mds.26294
28. Klietz M, Mahmoudi N, Maudsley AA, et al. Whole-brain magnetic resonance spectroscopy reveals distinct alterations in neurometabolic profile in progressive supranuclear palsy. *Mov Disord*. doi:10.1002/mds.29456
29. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group⋆ under the auspices of department of health and human services task force on alzheimer's disease. *Neurology*. 1984;34(7):939-944. doi:10.1212/wnl.34.7.939
30. Hauw JJ, Daniel SE, Dickson D, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology*. 1994;44(11):2015-2015. doi:10.1212/WNL.44.11.2015
31. Mirra SS, Gearing M, McKeel DW, et al. Interlaboratory comparison of neuropathology assessments in Alzheimer's disease: a study of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). *J Neuropathol Exp Neurol*. 1994;53(3):303-315. doi:10.1097/00005072-199405000-00012

32. Allen M, Carrasquillo MM, Funk C, et al. Human whole genome genotype and transcriptome data for Alzheimer's and other neurodegenerative diseases. *Sci Data*. 2016;3:160089. doi:10.1038/sdata.2016.89
33. Dieterle F, Ross A, Schlotterbeck G, Senn H. Probabilistic quotient normalization as robust method to account for dilution of complex biological mixtures. Application in1H NMR metabonomics. *Anal Chem*. 2006;78(13):4281-4290. doi:10.1021/ac051632c
34. Do KT, Wahl S, Raffler J, et al. Characterization of missing values in untargeted MS-based metabolomics data and evaluation of missing data handling strategies. *Metabolomics*. 2018;14(10):128. doi:10.1007/s11306-018-1420-2
35. Breunig MM, Kriegel HP, Ng RT, Sander J.. LOF: identifying density-based local outliers. *Proc 2000 ACM SIGMOD Int Conf Manag Data—SIGMOD*. 2000;29(2):93-104. doi:10.1145/342009.335388
36. Chetnik K, Benedetti E, Gomari DP, et al. Maplet : an extensible R toolbox for modular and reproducible metabolomics pipelines. *Bioinformatics*. 2022;38(4):1168-1170. doi:10.1093/bioinformatics/btab741
37. Zehetmayer S, Posch M. False discovery rate control in two-stage designs. *BMC Bioinformatics*. 2012;13:81. doi:10.1186/1471-2105-13-81
38. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57(1):289-300. doi:10.1111/J.2517-6161.1995.TB02031.X
39. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3):157-172. doi:10.1038/s41582-020-00435-y
40. Rose S, Melnyk S, Pavliv O, et al. Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. *Transl Psychiatry*. 2012;2(7):e134. doi:10.1038/tp.2012.61
41. Dello SAWG, Neis EPJG, de Jong MC, et al. Systematic review of ophthalmate as a novel biomarker of hepatic glutathione depletion. *Clin Nutr*. 2013;32(3):325-330. doi:10.1016/j.clnu.2012.10.008
42. Chen JJ, Thiyagarajah M, Song J, et al. Altered central and blood glutathione in Alzheimer's disease and mild cognitive impairment: a meta-analysis. *Alzheimers Res Ther*. 2022;14(1):1-17. doi:10.1186/S13195-022-00961-5/TABLES/4
43. Dalleau S, Baradat M, Guéraud F, Huc L. Cell death and diseases related to oxidative stress: 4-hydroxynonenal (HNE) in the balance. *Cell Death Differ*. 2013;20(12):1615-1630. doi:10.1038/cdd.2013.138
44. Allen M, Zou F, Chai HS, et al. Glutathione S-transferase omega genes in Alzheimer and Parkinson disease risk, age-at-diagnosis and brain gene expression: an association study with mechanistic implications. *Mol Neurodegener*. 2012;7(1):13. doi:10.1186/1750-1326-7-13
45. Ansoleaga B, Jové M, Schlüter A, et al. Deregulation of purine metabolism in Alzheimer's disease. *Neurobiol Aging*. 2015;36(1):68-80. doi:10.1016/j.neurobiolaging.2014.08.004
46. Kaddurah-Daouk R, Rozen S, Matson W, et al. Metabolomic changes in autopsy-confirmed Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):309-317. doi:10.1016/j.jalz.2010.06.001
47. Morris MC, Schneider JA, Tangney CC. Thoughts on B-vitamins and dementia. *J Alzheimers Dis*. 2006;9(4):429-433.
48. Gibson GE, Hirsch JA, Fonzetti P, Jordon BD, Cirio RT, Elder J. Vitamin B1 (thiamine) and dementia. *Ann NY Acad Sci*. 2016;1367(1):21-30. doi:10.1111/nyas.13031
49. Gibson GE, Sheu KF, Blass JP, et al. Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease. *Arch Neurol*. 1988;45(8):836-840. doi:10.1001/archneur.1988.00520320022009
50. Porter K, Hoey L, Hughes CF, Ward M, McNulty H. Consequences and public health implications of low b-vitamin status in ageing. *Nutrients*. 2016;8(11):725. doi:10.3390/nu8110725
51. An Y, Feng L, Zhang X, et al. Dietary intakes and biomarker patterns of folate, vitamin B6, and vitamin B12 can be associated with cognitive impairment by hypermethylation of redox-related genes NUDT15 and TXNRD1. *Clin Epigenetics*. 2019;11(1):139. doi:10.1186/s13148-019-0741-y
52. Gómez-Ramos A, Díaz-Nido J, Smith MA, Perry G, Avila J. Effect of the lipid peroxidation product acrolein on tau phosphorylation in neural cells. *J Neurosci Res*. 2003;71(6):863-870. doi:10.1002/jnr.10525
53. Adibhatla RM, Hatcher JF. Role of lipids in brain injury and diseases. *Future Lipidol*. 2007;2(4):403-422. doi:10.2217/17460875.2.4.403
54. Sun GY, Xu J, Jensen MD, Simonyi A. Phospholipase A2 in the central nervous system: implications for neurodegenerative diseases. *J Lipid Res*. 2004;45(2). doi:10.1194/jlr.R300016-JLR200
55. Hermann PM, Watson SN, Wildering WC. Phospholipase A2 – nexus of aging, oxidative stress, neuronal excitability, and functional decline of the aging nervous system? Insights from a snail model system of neuronal aging and age-associated memory impairment. *Front Genet*. 2014;5:419. https://www.frontiersin.org/articles/10.3389/fgene.2014.00419
56. Niedzielska E, Smaga I, Gawlik M, et al. Oxidative stress in neurodegenerative diseases. *Mol Neurobiol*. 2016;53(6):4094-4125. doi:10.1007/s12035-015-9337-5
57. Dias C, Nylandsted J. Plasma membrane integrity in health and disease: significance and therapeutic potential. *Cell Discov*. 2021;7(1):4. doi:10.1038/s41421-020-00233-2
58. Klein J. Membrane breakdown in acute and chronic neurodegeneration: focus on choline-containing phospholipids. *J Neural Transm*. 2000;107(8-9):1027-1063. doi:10.1007/s007020070051
59. Cutler RG, Kelly J, Storie K, et al. Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc Natl Acad Sci USA*. 2004;101(7):2070-2075. doi:10.1073/pnas.0305799101
60. Pant DC, Aguilera-Albesa S, Pujol A. Ceramide signalling in inherited and multifactorial brain metabolic diseases. *Neurobiol Dis*. 2020;143:105014. doi:10.1016/j.nbd.2020.105014
61. Wang X, Allen M, Li S, et al. Deciphering cellular transcriptional alterations in Alzheimer's disease brains. *Mol Neurodegener*. 2020;15(1):38. doi:10.1186/s13024-020-00392-6
62. Hallen A, Jamie JF, Cooper AJL. Lysine metabolism in mammalian brain: an update on the importance of recent discoveries. *Amino Acids*. 2013;45(6):1249-1272. doi:10.1007/s00726-013-1590-1
63. Zhou J, Wang X, Wang M, et al. The lysine catabolite saccharopine impairs development by disrupting mitochondrial homeostasis. *J Cell Biol*. 2019;218(2):580-597. doi:10.1083/jcb.201807204
64. Pérez MJ, Jara C, Quintanilla RA. Contribution of tau pathology to mitochondrial impairment in neurodegeneration. *Front Neurosci*. 2018;12:441. doi:10.3389/fnins.2018.00441
65. Yurdagul A, Subramanian M, Wang X, et al. Macrophage metabolism of apoptotic cell-derived arginine promotes continual efferocytosis and resolution of injury. *Cell Metab*. 2020;31(3):518-533.e10. doi:10.1016/j.cmet.2020.01.001
66. Freitag K, Sterczyk N, Wendlinger S, et al. Spermidine reduces neuroinflammation and soluble amyloid beta in an Alzheimer's disease mouse model. *J Neuroinflammation*. 2022;19(1):172. doi:10.1186/s12974-022-02534-7
67. Boada-Romero E, Martinez J, Heckmann BL, Green DR. The clearance of dead cells by efferocytosis. *Nat Rev Mol Cell Biol*. 2020;21(7):398-414. doi:10.1038/s41580-020-0232-1
68. Sandusky-Beltran LA, Kovalenko A, Placides DS, et al. Aberrant AZIN2 and polyamine metabolism precipitates tau neuropathology. *J Clin Invest*. 2021;131(4):e126299. doi:10.1172/JCI126299
69. Sandusky-Beltran LA, Kovalenko A, Ma C, et al. Spermidine/spermine-N1-acetyltransferase ablation impacts tauopathy-induced polyamine stress response. *Alzheimers Res Ther*. 2019;11:58. doi:10.1186/s13195-019-0507-y

70. Gilad GM, Gilad VH. Overview of the brain polyamine-stress-response: regulation, development, and modulation by lithium and role in cell survival. *Cell Mol Neurobiol*. 2003;23:637-649.
71. Hayashi Y, Tanaka J, Morizumi Y, Kitamura Y, Hattori Y. Polyamine levels in brain and plasma after acute restraint or water-immersion restraint stress in mice. *Neurosci Lett*. 2004;355(1):57-60. doi:10.1016/j.neulet.2003.10.027
72. Gieger C, Geistlinger L, Altmaier E, et al. Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. *PLOS Genet*. 2008;4(11):e1000282. doi:10.1371/journal.pgen.1000282
73. Puangmalai N, Bhatt N, Montalbano M, et al. Internalization mechanisms of brain-derived tau oligomers from patients with Alzheimer's disease, progressive supranuclear palsy and dementia with Lewy bodies. *Cell Death Dis*. 2020;11(5):314. doi:10.1038/s41419-020-2503-3
74. Bernard JA. Cerebello-hippocampal interactions in the human brain: a new pathway for insights into aging. *Cerebellum Lond Engl*. doi:10.1007/s12311-024-01670-5
75. Zhou J, Seeley WW. Network dysfunction in Alzheimer's disease and frontotemporal dementia: implications for psychiatry. *Biol Psychiatry*. 2014;75(7):565-573. doi:10.1016/j.biopsych.2014.01.020
76. Tomasi D, Wang GJ, Volkow ND. Energetic cost of brain functional connectivity. *Proc Natl Acad Sci USA*. 2013;110(33):13642-13647. doi:10.1073/pnas.1303346110
77. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nat 2013 5007464*. 2013;500(7464):541-546. doi:10.1038/nature12506
78. Bell LK, Edwards S, Grieger JA. The relationship between dietary patterns and metabolic health in a representative sample of adult Australians. *Nutrients*. 2015;7(8):6491. doi:10.3390/NU7085295
79. Kim T, Lim CS, Kaang BK. Cell type-specific gene expression profiling in brain tissue: comparison between TRAP, LCM and RNA-seq. *BMB Rep*. 2015;48(7):388-394. doi:10.5483/BMBRep.2015.48.7.218
80. Streit WJ, Xue QS, Tischer J, Bechmann I. Microglial pathology. *Acta Neuropathol Commun*. 2014;2(1):142. doi:10.1186/s40478-014-0142-6
81. Parra Bravo C, Giani AM, Perez JM, et al. Human iPSC 4R tauopathy model uncovers modifiers of tau propagation. *Cell*. 2024;187(10):2446-2464.e.22. doi:10.1016/j.cell.2024.03.015
82. Veitch DP, Weiner MW, Aisen PS, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement*. 2019;15(1):106-152. doi:10.1016/j.jalz.2018.08.005

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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