Received: 31 January 2025 | Revised: 28 April 2025 | Accepted: 27 May 2025

DOI: 10.1002/alz.70424

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Joint spatial associations of amyloid beta and tau pathology in Down syndrome and preclinical Alzheimer's disease: Cross-sectional associations with early cognitive impairments

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Funding information
National Institute on Aging; National Institute of Biomedical Imaging and Bioengineering

Abstract

INTRODUCTION: Individuals with Down syndrome (DS) have elevated risks for Alzheimer's disease (AD) due to amyloid beta (Aβ) precursor protein overexpression, with nearly all developing AD pathology by age 40 at autopsy. This study examined spatial associations between Aβ and tau burden in DS and neurotypical aging.

METHODS: Data included 145 DS (25–67 years) and 191 neurotypical aging individuals (63–89 years). Regional Aβ and tau positron emission tomography outcomes were analyzed using multiset canonical correlation analysis to identify joint Aβ/tau spatial patterns, with regression models assessing associations with age and cognition.

RESULTS: For a given Aβ burden, cognitively stable DS individuals exhibited relatively higher tau burden than neurotypical aging, while DS mild cognitive impairment/AD individuals exhibited more widespread pathology. Joint Aβ/tau patterns were associated with episodic memory impairment in DS and, as the disease progresses, executive dysfunction.

DISCUSSION: DS exhibits overlapping and distinct AD-related neuropathology features, emphasizing the importance of biomarkers for early detection and intervention.

KEYWORDS
Alzheimer's disease, amyloid, Down syndrome, memory, multivariate analysis, preclinical, tau

Highlights

- There are distinct amyloid beta (Aβ) and tau spatial patterns in Down syndrome (DS): For a given level of Aβ burden, individuals with DS exhibited greater and more widespread tau burden compared to neurotypical aging, even before a clinical diagnosis of dementia.
- Aβ-associated tau burden was linked to episodic memory impairment in DS prior to dementia, with executive dysfunction emerging as the disease progressed, highlighting the sequential impact of pathology on cognition.
- The unique pattern of early striatal Aβ accumulation in DS supports its use as a potential biomarker for tracking disease progression and guiding clinical trial inclusion criteria for Alzheimer's disease interventions in DS.

1 | BACKGROUND

Most individuals with Down syndrome (DS) are at an elevated risk for Alzheimer's disease (AD), due to an extra copy of chromosome 21 (trisomy 21), which contains the amyloid beta (Aβ) precursor protein (*APP*) gene. At autopsy, nearly all individuals with DS exhibit hallmark AD neuropathology, that is, Aβ plaques and tau neurofibrillary tangles (NFTs), by age 40,[1–3] with the median age of dementia being 53.8 years.[4] Prior studies using positron emission tomography (PET) imaging, including those from the Alzheimer Biomarkers Consortium–Down Syndrome (ABC-DS), have provided key insights into aging-related, DS-specific, and AD-related changes in glucose metabolism and Aβ and tau burden.[3] Findings include a striatum-first pattern of Aβ burden unique to DS and autosomal dominant AD, which is distinct from the cortical-first pattern observed in sporadic AD;[5–8] cognitive resilience to Aβ burden in adults with DS;[9,10] and faster striatal Aβ accumulation over time in DS compared to neurotypical aging and sporadic AD, even when the global rates of Aβ accumulation are comparable.[5,7,11] Additionally, tau PET imaging has enabled the applications of the Aβ, tau, and neurodegeneration (AT[N]) framework and in vivo Braak NFT staging to the DS population.[12–15] Tau burden occurs earlier relative to Aβ burden in DS compared to sporadic and autosomal dominant AD[15–17] and is a stronger predictor of episodic memory impairment in DS before the onset of clinical dementia.[10,18–20] These findings highlight the importance of jointly examining Aβ and tau burden in relation to early cognitive impairment in DS to identify imaging biomarkers indicative of AD progression, which can inform DS-specific inclusion criteria in therapeutic trials.[21–24]

Imaging and cognitive outcomes in DS have been compared to those observed in other well-studied cohorts, including autosomal dominant and sporadic AD,[8,17] non-demented DS sibling controls,[15] and neurotypical aging populations.[8,25] Many prior studies used univariate regression analyses to evaluate the associations between PET uptake measures of Aβ and tau burden at regional or voxel levels, typically using predefined regions of interest (ROIs, e.g., cortical Aβ or entorhinal tau) to reduce the number of comparisons and the potential for inference errors. Multivariate analyses, such as multiset canonical correlation analysis (MCCA), offer an alternative by generating outcomes as weighted sums of PET uptake across multiple regions (i.e., spatial patterns), eliminating the need to predefine ROIs in the context of dimensionality reduction. MCCA is particularly effective in identifying associations between multimodal imaging datasets by decomposing data into highly correlated components. This approach has demonstrated greater statistical power and sensitivity to subtle disease-related deficits compared to univariate analyses.[26,27] Similar joint pattern analysis methods have been applied to examine spatial associations between Aβ and tau burden in aging and mild cognitive impairment (MCI), as well as relationships among Aβ burden, glucose metabolism, and brain volume in DS and AD.[28,29]

In this study, we applied MCCA to compare the joint spatial associations between Aβ and tau burden in individuals with DS and cognitively normal or stable (CS) older adults from the Harvard Aging Brain Study (HABS). The MCCA joint pattern analysis enabled the interrogation of cross-cohort similarities and differences in the expressions of joint Aβ and tau spatial patterns across multiple brain regions between DS and neurotypical aging individuals at risk of AD, providing a more nuanced view of AD-related pathology in DS relative to a large, well-characterized neurotypical aging cohort that includes individuals with preclinical AD pathology. Specifically, we investigated the joint Aβ and tau spatial patterns in cognitively stable DS individuals (DS-CS), DS individuals with MCI or AD (DS-MCI/AD), and HABS-CS individuals.

RESEARCH IN CONTEXT

1. **Systematic review**: Literature was reviewed using online databases (e.g., PubMed). While individuals with Down syndrome (DS) develop Alzheimer's disease (AD) pathology by their 40s, the joint associations between amyloid beta (Aβ) and tau burden across multiple brain regions in DS compared to neurotypical aging remains underexplored. Understanding how these pathologies interact and their associations with cognitive impairment in DS is crucial for identifying early biomarkers of disease progression and improving participant selection for clinical trials.
2. **Interpretation**: Leveraging multimodal imaging data from two large multicohort studies of DS and neurotypical aging and a multivariate analysis approach, our findings suggest that, for a given level of Aβ burden, individuals with DS exhibit a more widespread tau burden compared to neurotypical aging, even before a clinical diagnosis of dementia. Additionally, Aβ-associated tau burden was linked to episodic memory impairment in DS and, as disease progressed, to executive dysfunction. The unique striatal Aβ accumulation in DS, which was not observed in neurotypical aging, further highlights distinct neuropathological trajectories in DS-related AD.
3. **Future directions**: Future research should incorporate longitudinal data to evaluate the within-person changes in these Aβ and tau spatial patterns and their impact on cognitive decline in DS and neurotypical aging.

2 | METHODS

2.1 | Participant characteristics

2.1.1 | ABC-DS

The study included 145 individuals with DS (age: 25–67 years) from the ABC-DS consortium study, which included individuals from DS cohort studies of Alzheimer's Disease Down Syndrome (ADDS) and Neurodegeneration in Aging Down Syndrome (NiAD) cohorts. All participants were classified as DS-CS, having MCI or AD (DS-MCI/AD), or undetermined based on consensus of at least three experts using caregiver-reported and direct measures of cognitive functioning, adaptive and maladaptive behavior, neurological exam, medical and psychiatric history, and recent life events (Table 1).[3] Participants underwent a comprehensive evaluation that included a cognitive assessment battery, physical/neurological exam, and caregiver questionnaires.[3] The cognitive assessment battery included measures of Down Syndrome Mental Status Examination (DSMSE) and Dementia Questionnaire for People with Learning Disabilities (DLD), functional abilities (Vineland Adaptive Behavior Scale), language (Categorical/Verbal Fluency), visuospatial construction (Block Design and Extended Block Design and Beery Buktenica Developmental Test of Visual Motor Integration [VMI]), memory (Cued Recall Task, and Rivermead Behavioral Memory Test for Children—Face & Picture Recognition), and executive function and processing speed (Stroop Dog and Cat and The Purdue Pegboard). Premorbid intellectual disability, defined as the intellectual disability level prior to a clinical status of MCI or AD, was also determined as mild, moderate, and severe.[30] The Tinetti Assessment Tool: Gait test was used to assess gait abnormalities.[31] The study protocols were approved by the local institutional review board at each participating site, and informed consent was obtained from all participants or their proxy/legally authorized representatives.

2.1.2 | HABS

The study included 191 older cognitively normal or stable adults (HABS-CS, age: 63–89 years, Table 2) from the publicly available HABS dataset (Public Release Version 2: https://habs.mgh.harvard.edu). All participants had a Clinical Dementia Rating (CDR) score of 0 at baseline, indicating no clinical signs of dementia.[32] Participants underwent standard neuropsychological assessments, including the Preclinical Alzheimer Cognitive Composite version 5 (PACC-5), Logical Memory Delayed Recall (LMDR), Free and Cued Selective Reminding Test (FCSRT), Mini-Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), and Category Fluency (CAT).[33] Clinical follow-ups were performed to assess individuals who have or have not converted to cognitive impairment (mean = 2.0 years, range: 0–5.6 years). Informed consent was obtained, and the study was approved by the Mass General Brigham Human Research Committee.

2.2 | Imaging protocols and processing

2.2.1 | ABC-DS

In this multi-site study, DS participants underwent Aβ PET imaging using [^{11}C]Pittsburgh compound B (PiB, n = 134) or [^{18}F]Florbetapir

TABLE 1 Participant characteristics in the ABC-DS cohort.

	DS-CS	DS-MCI	DS-AD	Undetermined
N	116	12	7	10
Age (years)	37.96 (8.13)	50.25 (5.31)	52 (3.83)	46.6 (8.98)
Sex	59 M, 57 F	2 M, 10 F	3 M, 4 F	6 M, 4 F
***APOE* ε4 status**	88 *APOE* ε4 negative 28 *APOE* ε4 positive	9 *APOE* ε4 negative 3 *APOE* ε4 positive	5 *APOE* ε4 negative 2 *APOE* ε4 positive	9 *APOE* ε4 negative 1 *APOE* ε4 positive
Mental status				
Premorbid intelligence disability level	61 mild, 34 moderate, 15 severe, 6 unavailable	5 mild, 3 moderate, 0 severe, 4 unavailable	4 mild, 3 moderate, 0 severe	4 mild, 4 moderate, 1 severe, 1 unavailable
DSMSE	50.77 (7.78)	45.62 (6.24)	37.07 (9.35)	38.14 (11.54)
DLD cognition	2.72 (4.7)	9.08 (5.81)	16.29 (9.74)	13.6 (11.53)
DLD social	3.03 (3.42)	6.83 (4.51)	11.71 (6.65)	16.5 (7.18)
Functional abilities				
Vineland Adaptive Behavior Scale	54.26 (17.54)	43.25 (17.16)	30 (8.67)	28.9 (14.07)
Visuospatial construction				
Extended Block Design	13.84 (2.78)	13.17 (3.35)	7.71 (5.82)	9.5 (6.26)
VMI	17.02 (3.06)	15.17 (2.95)	13.43 (4.16)	15.38 (2.67)
Memory				
Cued Recall Task	33.05 (4.5)	25.36 (7.23)	18.71 (9.46)	28.17 (8.33)
Rivermead Face & Picture Recognition	16.71 (3.72)	12.08 (3.34)	11 (1.53)	12.14 (3.13)
Executive processing and speed				
Stroop Dog and Cat	34.64 (15.01)	51.49 (22.07)	51.94 (28.46)	34.08 (36.05)
The Purdue Pegboard	6.75 (2.01)	5.27 (1.42)	4.86 (1.57)	5.14 (1.77)
PET imaging measures				
Global Aβ SUVR	1.27 (0.21)	1.66 (0.28)	2.18 (0.39)	1.47 (0.27)
Tau Entorhinal SUVR	1.13 (0.2)	1.63 (0.35)	1.63 (0.36)	1.34 (0.36)
Tau Inferior Temporal SUVR	1.17 (0.17)	1.66 (0.48)	1.9 (0.6)	1.36 (0.36)

Note: All values are expressed as mean (standard deviation) when appropriate.
Abbreviations: Aβ, amyloid beta; ABC-DS, Alzheimer Biomarkers Consortium—Down Syndrome; AD, Alzheimer's disease; *APOE*, apolipoprotein E; CS, cognitively stable; DLD, Dementia Questionnaire for People with Learning Disabilities; DS, Down syndrome; DSMSE, Down Syndrome Mental Status Examination; F, female; M, male; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratios.

(FBP, $n = 11$), tau PET imaging using [^{18}F]flortaucipir (FTP), and T1-weighted magnetic resonance (MR) imaging.[3] Image acquisition and PET reconstruction followed the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols.[3,34] A summary of the sequences used to generate the T1-weighted MR images, along with details of the participating ABC-DS sites (Harvard/Mass General Hospital, Wisconsin, Banner, Pittsburgh, Cambridge) in this study, is included in Table S1 in supporting information.

A detailed imaging processing pipeline and description of the quality control procedures can be found in Table S2 and Figure S1 in supporting information. PET frame-by-frame motion correction was performed and a mean PET image was generated using FSL (FMRIB Software library). T1-weighted MR images were bias-corrected using the Advanced Normalization Tools (ANTs).[35] Both the mean PET and MR images were skull stripped using mri_synthstrip (FreeSurfer).[36] PET images were then coregistered to the MR images using FSL, and the MR images were normalized to a publicly available DS-CS–specific MR template using ANTs.[37] Regional segmentation was performed on the DS-CS MR template using FreeSurfer (version 6, recon-all) with manual edits. After normalization, the transformation matrices were applied to the PET images for regional sampling in the template space. Visual quality control was performed at each processing step by an experienced research assistant blinded to the analysis outcomes. Standardized uptake value (SUV, g/mL) images were generated by normalizing the PET activity by body weight and injected dose.

Regional (ROI-based) PiB and FBP uptake values were quantified as standardized uptake value ratios (SUVR, 50–70 minutes post-injection) across the neocortical regions, including the frontal, lateral temporal, parietal, and retrosplenial regions, as well as the thalamus and striatum. Regional FTP uptake values were quantified as SUVR (80–100 minutes post-injection) in tau-relevant regions, including regions involved in the early (entorhinal, parahippocampus, amygdala, and hippocampus), intermediate (fusiform, inferior temporal, anterior and posterior cingulate, and insula) and late (rostral middle frontal, inferior parietal,

TABLE 2 Participant characteristics in the HABS cohort.

	Aβ−	Aβ+
N	106	85
Age (years)	75.8 (6.45)	76.84 (6.15)
Sex	45 M, 61 F	34 M, 51 F
Education (years)	15.9 (3.28)	16.36 (2.76)
APOE ε4 **status**	91 *APOE* ε4 negative 15 *APOE* ε4 positive	45 *APOE* ε4 negative 38 *APOE* ε4 positive 2 N/A
Global cognition		
Preclinical Alzheimer Cognitive Composite	0.23 (0.74)	0.08 (0.65)
Mini-Mental State Examination	29.27 (1.08)	29.13 (1)
Memory		
Logical Memory Delayed Recall	16.43 (3.7)	15.71 (3.45)
Free and Cued Selective Reminding Test—Cued	47.76 (0.67)	47.54 (1.06)
Free and Cued Selective Reminding Test—Free	32.98 (6.14)	32.56 (7.02)
Executive processing and speed		
Digit Symbol Substitution Test	47.82 (11.19)	46.82 (9.72)
Trail Making Test Part A	33.2 (10.83)	36.62 (17.07)
Trail Making Test Part B	84.05 (50.3)	83.03 (46.07)
PET imaging measures		
Global Aβ DVR	1.13 (0.04)	1.41 (0.21)
Tau entorhinal SUVR	1.08 (0.09)	1.17 (0.14)
Tau inferior temporal SUVR	1.18 (0.07)	1.23 (0.1)

Note: All values are expressed as mean (standard deviation) when appropriate. Aβ status was determined using a threshold of 1.19.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; *APOE*, apolipoprotein E; DS, Down syndrome; DVR, distribution volume ratios; F, female; HABS, Harvard Aging Brain Study; M, male; MCI, mild cognitive impairment; N/A, unavailable; PET, positron emission tomography; SUVR, standardized uptake value ratios.

lateral occipital, lingual, pericalcarine, cuneus, precentral) stages of tau spread.[38] The cerebellar gray matter was used as the reference regions for both Aβ and tau SUVR calculations.

2.2.2 | HABS

Participants underwent Aβ PET imaging using PiB and tau PET imaging using FTP and T1-weighted MR imaging. All PET data were acquired, reconstructed, and processed according to prior protocols.[39] Briefly, motion-corrected PET images were coregistered to the MR images using SPM (Coregistraton: Estimate & Write, version 8). Regional parcellations were generated using FreeSurfer (version 6, recon-all) using the MR images with manual edits and brought into the PET space. Regional PiB uptake values were quantified as distribution volume ratios (DVR, Logan graphical method), and regional FTP uptake values were quantified as SUVR (75–105 minutes post-injection). The same cerebellar gray matter reference region was used. Binary Aβ status was determined using a PiB DVR cutoff of 1.19 in the cortical composite regions, as previously described.[39]

2.3 | Statistical analyses

2.3.1 | Multivariate analyses—MCCA

Regional Aβ and tau PET data were normalized using *z* transformation relative to the DS-CS individuals in the ABC-DS cohort and relative to all HABS-CS individuals in the HABS cohort. Step-by-step details about this joint analysis approach are listed in Fu et al. and in supporting information.[26] Briefly, principal component analysis (PCA) was first performed on the normalized PET data to advise on the number of components or pairs of canonical variates for MCCA (components accounting for at least 5% of variance were retained). MCCA identified complementary or joint spatial patterns of Aβ and tau burden, maximizing the correlations across individuals. Key MCCA outcomes included: (1) spatial patterns: regional weights of Aβ and tau–relevant regions, representing each region's relative contribution to the joint Aβ and tau association; (2) subject scores or the expressions: expressions of the joint Aβ and tau spatial patterns for each individual, with high correlations between expressions of the Aβ and tau patterns.

The following equation is used to calculate the subject scores for Aβ and tau burden separately:

$$subject\ scores = \sum_{1}^{N} weight_i \times regional\ uptake_i$$

where *i* is the index for each region, *N* is the total number of regions, weight is the regional weights (spatial patterns), and regional uptake is the *z* transformed PET uptake values for each region.

Subject scores are presented as *z* scores, with positive *z* transformed values indicating individuals who strongly exhibit the spatial patterns.

Random permutation (1000 iterations) across individuals was performed separately for the Aβ and tau datasets to construct the empirical null distributions and estimate the significance of correlations between the subject scores. Leave-one-out cross-validation was performed to estimate the error bounds for regional weights. Analyses were performed separately in all DS individuals, DS-CS only, and HABS-CS individuals.

2.3.2 | Clinical correlation and group analyses

Group comparisons using analysis of covariance assessed clinical and demographic differences among DS-CS ($n = 116$), DS-MCI/AD ($n = 19$),

and HABS-CS ($n = 191$) groups. Additional comparisons evaluated Aβ and tau pattern expressions, global Aβ and early-tau burden between DS-MCI/AD and DS-CS individuals, between DS individuals with different intellectual disability levels, between Aβ+ and Aβ− HABS-CS individuals, and between HABS-CS individuals who later developed cognitive impairment and those who remained stable. Age, sex, apolipoprotein E ε4 status, and premorbid intellectual disability levels (for DS) were included as covariates. Bonferroni correction was used to control for multiple comparisons. Linear regression analyses assessed associations between Aβ and tau spatial pattern expressions, age, and clinical outcome (corrected for covariates) across individuals. Paired t tests were used to compare the overall magnitudes of spatial weights across cohorts, and linear regression analyses, followed by analyses of the residuals, were performed to assess similarities and differences in spatial patterns across cohorts. Significance was assessed at $P < 0.05$.

3 | RESULTS

3.1 | Participant characteristics

Characteristics of the participants in the ABC-DS and HABS studies are listed in Table 1 and Table 2, respectively.

3.1.1 | ABC-DS

Among the 145 individuals with DS, 116 were DS-CS, 12 were diagnosed as MCI (DS-MCI), 7 were diagnosed as AD (DS-AD), and 10 were undetermined. All participants ($n = 145$) underwent FTP tau PET, while 134 participants underwent PiB Aβ PET, and 11 participants underwent FBP Aβ PET.

Assessing DS-MCI/DS-AD versus DS-CS clinical measures, the DS-MCI (age: 50.3 ± 5.3 years) and DS-AD (age: 52.0 ± 3.8 years) individuals were significantly older compared to the DS-CS individuals (age: 38.0 ± 8.1 years, $P < 0.0001$, DS-MCI: $t = 7.2$, confidence interval [CI]: 8.7–15.9; DS-AD: $t = 8.6$, CI: 10.4–17.7). The DS-MCI and DS-AD individuals showed worse performance compared to DS-CS individuals on the DLD social ($P < 0.001$, DS-MCI: $t = 7.2$, CI: 8.7–15.9; DS-AD: $t = 8.6$, CI: 10.4–17.7) and cognition assessments ($P < 0.001$, DS-MCI: $t = 2.8$, CI: 0.9–6.7; DS-AD: $t = 3.4$, CI: 2.5–14.8). The DS-MCI and DS-AD individuals also showed worse performance compared to DS-CS individuals on assessments of memory and executive function: DSMSE memory scores ($P < 0.0001$, DS-MCI: $t = -3.4$, CI: −3.1 to −0.7; DS-AD: $t = -3.9$, CI: −3.4 to −0.8), Cued Recall Task ($P < 0.0001$, DS-MCI: $t = -3.5$, CI: −12.6 to −2.8; DS-AD: $t = -4.0$, CI: −23.1 to −5.6), Face & Picture Recognition ($P < 0.001$, DS-MCI: $t = -4.5$, CI: −6.8 to −2.4; DS-AD: $t = -8.5$, CI: −7.2 to −4.2), and Stroop Dog and Cat ($P < 0.05$, DS-MCI: $t = 2.6$, CI: 2.7 −31.0; DS-AD: $t = 1.6$, CI: 9.0–43.6). No group differences were observed in sex or premorbid intellectual disability level.

On DS-AD versus DS-CS clinical measures, the DS-AD individuals additionally showed worse performance compared to the DS-CS individuals in the DSMSE total scores ($P < 0.0001$, $t = -3.8$, CI: −22.4 to −5.0), visuospatial function, and functional ability: DSMSE visuospatial scores ($P < 0.01$, $t = -4.4$, CI: −1.9 to −0.6), VMI ($P < 0.05$, $t = -2.2$, CI: −7.4 to −0.3), Block Design test ($P < 0.0001$, $t = -2.8$, CI: −11.5 to −0.7), and Vineland ($p < 0.01$, $t = -6.2$, CI: −33.4 to −15.1).

Evaluating DS-AD versus DS-MCI clinical measures, the DS-AD individuals showed worse performance compared to the DS-MCI individuals on DLD social ($P < 0.05$, $t = 1.7$, CI: 1.5–11.3) and cognition assessments ($P < 0.05$, $t = 1.8$, CI: 2.2–16.4), memory (Cued Recall Task, $t = -1.6$, CI: −15.9 to −2.6), and visuospatial function (Block Design test, $P < 0.05$, $t = -2.3$, CI: −11.0 to −0.1).

Assessing DS-MCI/DS-AD versus DS-CS PET measures, the DS-MCI and DS-AD individuals showed higher global Aβ ($P < 10^{-6}$, DS-MCI: $t = 4.7$, CI: 0.21–0.56; DS-AD: $P < 10^{-16}$, $t = 6.1$, CI: 0.5–1.3) and tau burden in the entorhinal ($P < 10^{-10}$, DS-MCI: $t = 4.9$, CI: 0.3–0.7; DS-AD: $P < 10^{-6}$, $t = 3.6$, CI: 0.2–0.8) and inferior temporal cortex ($P < 10^{-8}$, DS-MCI: $t = 3.5$, CI: 0.2–0.8; DS-AD: $P < 10^{-10}$, $t = 3.2$, CI: 0.2–1.3) compared to the DS-CS individuals. There were no significant differences in Aβ and tau burden between the DS-MCI and DS-AD individuals. There were no significant differences in Aβ and tau burden between premorbid intellectual disability levels.

3.1.2 | HABS

Among the 191 cognitively normal older HABS-CS individuals (age: 76.3 ± 63 years), 85 were Aβ+ and all underwent FTP tau PET and PiB Aβ PET. There were no significant differences between Aβ+ and Aβ− HABS-CS individuals in age, sex, education, or cognitive outcomes at baseline. The Aβ+ individuals were significantly more likely to convert to cognitive impairment at clinical follow-ups compared to the Aβ− individuals ($P = 0.005$, $t = 2.6$, CI: 0.02–0.2) and exhibited significantly higher tau burden in the entorhinal ($P < 10^{-5}$, $t = 4.9$, CI: 0.05–0.1) and inferior temporal cortex compared to the Aβ− individuals ($P < 0.001$, $t = 3.9$, CI: 0.03–0.1).

3.2 | Multivariate analyses—associated Aβ and tau spatial patterns

3.2.1 | DS-CS individuals

In DS-CS individuals, higher Aβ weights in the temporal, parietal and frontal cortices, cingulate, and striatum was significantly associated with higher tau weights in early-tau regions ($P < 10^{-4}$, $\beta = 0.87$ [CI: 0.78–0.96], Figure 1A,B). Highest Aβ weights were observed in the striatum (weights: 0.92–0.95) and frontal cortex (weights: 0.79–0.87; Table 3), while highest tau weights were observed in the entorhinal and amygdala (weights: 0.89; Table 4). Approximately 33% of DS-CS individuals showed positive subject scores, indicating their high expression of the joint Aβ and tau spatial patterns. Higher expressions of the Aβ pattern were correlated significantly with age ($P < 10^{-8}$, $\beta = 0.50$ [CI: 0.34–0.66]), but not with cognitive outcomes. Higher expressions of the tau pattern were correlated significantly with age ($P < 10^{-8}$,

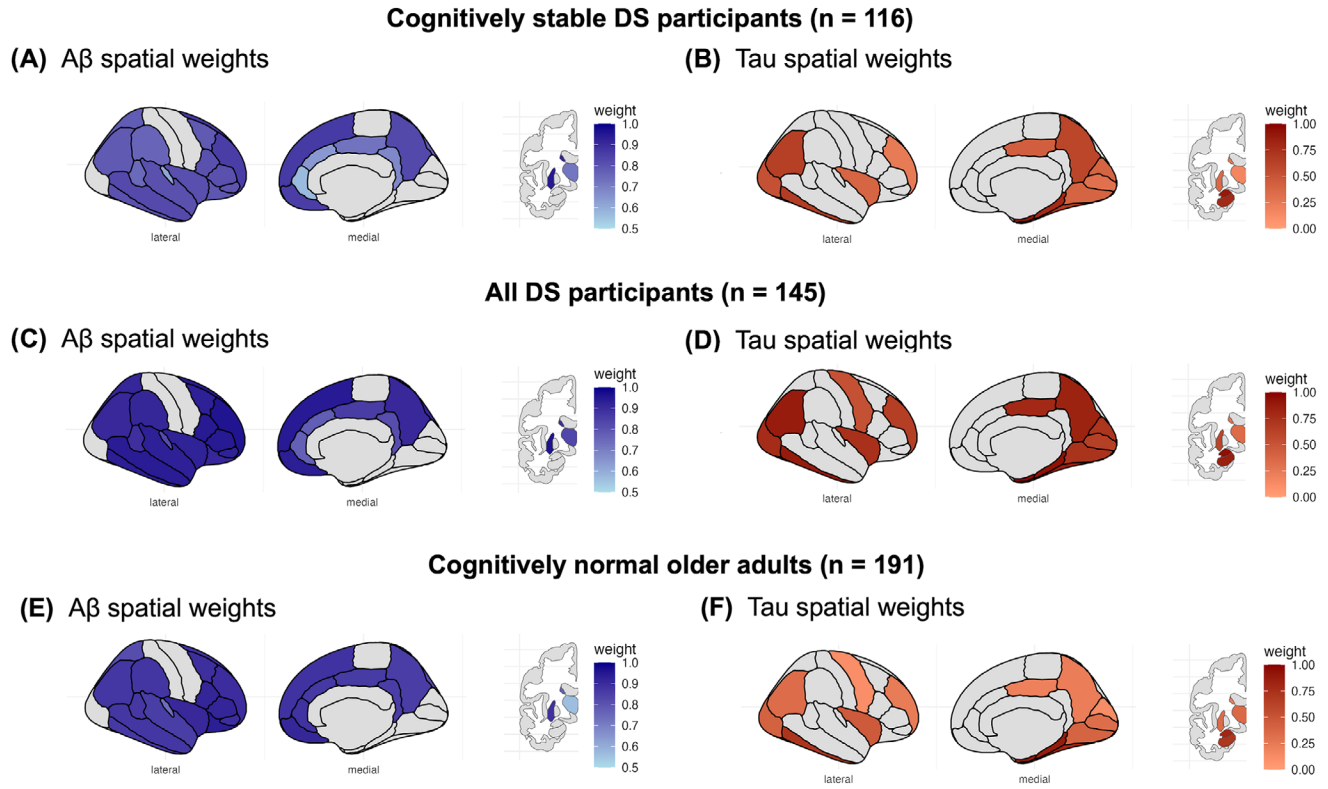

FIGURE 1 MCCA-derived joint spatial patterns of Aβ and tau deposition. A,B, Across DS-CS individuals, elevated cortical and striatal Aβ burden (highest weights in the striatum and frontal cortex) was associated with elevated tau burden in early-to-intermediate tau regions, with highest weights in early-tau regions (e.g., entorhinal). C,D, Across all individuals with DS, elevated cortical and striatal Aβ burden (highest weights in the striatum and frontal cortex) was associated with elevated tau burden in early-to-late tau regions (highest weights in early tau regions). E,F, Across cognitively unimpaired HABS-CS individuals, elevated cortical Aβ burden (highest weights in the frontal cortex) was associated with elevated tau burden in early-tau regions, with the Aβ pattern exhibiting lower weights in the striatum compared to DS. * Regional weights were estimated for bilateral regions; however, for visualization purposes, only regional weights for the right hemisphere were displayed. Aβ, amyloid beta; CS, cognitively stable; DS, Down syndrome; HABS, Harvard Aging Brain Study; MCCA, multiset canonical correlation analysis

β = 0.53 [CI: 0.37–0.68]), and worse episodic memory (Cued Recall Task; $P < 0.05$, $\beta = -0.20$ [CI: −0.35 to −0.04]). There were no significant differences in pattern expressions in sex and premorbid intellectual disability levels.

3.2.2 | All DS individuals

Among all individuals with DS (116 DS-CS, 19 DS-MCI/AD, 10 undetermined), higher Aβ weights in the temporal, parietal and frontal cortices, cingulate, and striatum was significantly associated with higher tau weights in all tau-relevant regions (P$p < 0.0001$, β = 0.88 [CI: 0.81–0.96], Figure 1C,D). Highest Aβ weights were observed in the striatum (weights: 0.89- 0.96) and frontal cortex (weights: 0.91–0.96; Table 3), and highest tau weights were observed in early-tau regions, such as the entorhinal cortex, parahippocampus, amygdala, hippocampus, and inferior temporal (weights: 0.86–0.96; Table 4). Approximately 27% of DS individuals showed positive subject scores, indicating their high expression of the joint Aβ and tau spatial patterns. Higher expressions of the DS-related Aβ and tau spatial patterns were significantly correlated with age ($P < 10^{-13}$, Aβ pattern: $\beta = 0.63$ [CI: 0.50–0.76], tau pattern: $\beta = 0.57$ [CI: 0.44–0.71]), worse episodic memory (Cued Recall Task; corrected $P < 10^{-7}$, Aβ pattern: $\beta = -0.38$ [CI: −0.51 to −0.36], tau pattern: $\beta = -0.49$ [CI: −0.62 to −0.36]), and executive function (Stroop Cat and Dog; corrected $P < 0.05$, Aβ pattern: $\beta = 0.14$ [CI: 0.01–0.27], tau pattern: $\beta = 0.16$ [CI: 0.02–0.29], Figure 2A,B). The Aβ ($P < 0.001$, DS-MCI: $t = 4.6$, CI: 0.7–2.0; DS-AD: $t = 4.7$, CI: 1.2–3.6) and tau ($P < 0.001$, DS-MCI: $t = 4.0$, CI: 0.7–2.3; DS-AD: $t = 4.3$, CI: 0.9–3.2) pattern expressions were significantly higher in DS-MCI/AD than DS-CS. There were no significant differences in pattern expressions between the DS-MCI and DS-AD individuals and in sex and premorbid intellectual disability levels. There were no significant differences in MCCA subject scores between the different ABC-DS participating sites, suggesting that site-specific factors did not significantly influence the results.

3.2.3 | Cognitively normal older adults

Among the HABS-CS participants, higher Aβ weights in cortical regions were associated with higher tau weights in early-tau regions ($P < 0.0001$, $\beta = 0.49$ [CI: 0.37–0.62], Figure 1E,F). Highest Aβ weights

TABLE 3 MCCA-derived regional weights [95% CI] for the Aβ spatial patterns across the three cohorts, ranked from highest to lowest by region in each cohort.

All DS		DS-CS		HABS-CS	
Putamen	**0.96 [0.95–0.97]**	**Putamen**	**0.95 [0.93–0.96]**	**Lateral orbitofrontal**	**0.94 [0.92–0.95]**
Rostral Middle Frontal	0.96 [0.94–0.97]	Ventral striatum	0.95 [0.92–0.96]	Parsopercularis	0.92 [0.89–0.94]
Parstriangularis	0.95 [0.92–0.96]	Caudate	0.92 [0.89–0.95]	Parstriangularis	0.92 [0.89–0.94]
Parsopercularis	0.95 [0.92–0.96]	Superior frontal	0.87 [0.81–0.91]	Medial orbitofrontal	0.91 [0.89–0.93]
Superior frontal	0.94 [0.92–0.96]	Medial orbitofrontal	0.86 [0.8–0.9]	Insula	0.91 [0.88–0.93]
Ventral striatum	0.94 [0.92–0.96]	Rostral middle frontal	0.86 [0.8–0.9]	Rostral Middle Frontal	0.9 [0.87–0.92]
Middle temporal	0.94 [0.92–0.96]	Precuneus	0.83 [0.76–0.88]	Parsorbitalis	0.89 [0.86–0.92]
Medial orbitofrontal	0.94 [0.91–0.95]	Middle temporal	0.82 [0.75–0.87]	Caudal Middle Frontal	0.89 [0.86–0.92]
Inferior temporal	0.93 [0.91–0.95]	Insula	0.81 [0.74–0.87]	Putamen	0.89 [0.85–0.91]
Superior temporal	0.93 [0.9–0.95]	Parsopercularis	0.81 [0.73–0.86]	Rostral anterior cingulate	0.89 [0.85–0.91]
Caudal middle frontal	0.93 [0.9–0.95]	Parstriangularis	0.81 [0.73–0.86]	Superior frontal	0.88 [0.85–0.91]
Parsorbitalis	0.93 [0.9–0.95]	Superior temporal	0.81 [0.73–0.86]	Supramarginal	0.88 [0.84–0.91]
Insula	0.93 [0.9–0.95]	Inferior temporal	0.8 [0.73–0.86]	Middle temporal	0.87 [0.84–0.9]
Superior parietal	0.92 [0.88–0.94]	Parsorbitalis	0.8 [0.72–0.86]	Inferior parietal	0.87 [0.83–0.9]
Supramarginal	0.91 [0.88–0.94]	Lateral orbitofrontal	0.79 [0.72–0.85]	Bankssts	0.87 [0.83–0.9]
Lateral Orbitofrontal	0.91 [0.88–0.93]	Inferior parietal	0.79 [0.71–0.85]	Caudal Anterior Cingulate	0.87 [0.83–0.9]
Precuneus	0.91 [0.88–0.93]	Caudal middle frontal	0.79 [0.71–0.85]	Inferior temporal	0.87 [0.83–0.9]
Inferior parietal	0.91 [0.87–0.93]	Superior parietal	0.78 [0.7–0.84]	Posterior cingulate	0.87 [0.82–0.9]
Caudate	0.89 [0.85–0.92]	Supramarginal	0.76 [0.67–0.83]	Superior temporal	0.86 [0.81–0.89]
Bankssts	0.89 [0.85–0.92]	Bankssts	0.75 [0.66–0.82]	Isthmus cingulate	0.86 [0.81–0.89]
Posterior cingulate	0.86 [0.81–0.9]	Posterior cingulate	0.73 [0.63–0.8]	Precuneus	0.86 [0.81–0.89]
Thalamus	0.83 [0.78–0.88]	Thalamus	0.72 [0.62–0.8]	Ventral striatum	0.85 [0.8–0.88]
Transverse temporal	0.82 [0.76–0.87]	Isthmus cingulate	0.68 [0.57–0.77]	Superior parietal	0.82 [0.76–0.86]
Isthmus cingulate	0.82 [0.75–0.86]	Caudal anterior cingulate	0.64 [0.52–0.74]	Caudate	0.77 [0.71–0.83]
Caudal anterior cingulate	0.78 [0.71–0.84]	Transverse temporal	0.61 [0.48–0.71]	Transverse temporal	0.74 [0.67–0.8]
Rostral anterior cingulate	0.77 [0.7–0.83]	Rostral anterior cingulate	0.57 [0.43–0.68]	Thalamus	0.56 [0.46–0.65]
Cerebral white matter	0.62 [0.51–0.71]	Cerebral white matter	0.36 [0.19–0.51]	Cerebral white matter	0.3 [0.17–0.42]

Abbreviation: Aβ, amyloid beta; CI, confidence interval; DS, Down syndrome; DS-CS , cognitively stable Down syndrome individuals; HABS-CS, cognitively normal/stable older adults in the Harvard Aging Brain Study cohort; MCCA, multiset canonical correlation analysis.

were observed in the frontal cortex (weights: 0.88–0.94), with lower Aβ weights observed in the striatum (weights: 0.77–0.89; Table 3). Highest tau weights were observed in early-tau regions (weights: 0.71–0.88; Table 4). The expressions of the Aβ pattern were not significantly correlated with age or cognitive outcomes. Approximately 41% of DS individuals showed positive subject scores, indicating their high expression of the joint Aβ and tau spatial patterns. Higher expressions of the tau pattern were correlated significantly with age ($P < 0.001$, $\beta = 0.26$ [CI: 0.13–0.40]), and worse global cognition (PACC-5: corrected $P < 0.05$, $\beta = -0.18$ [CI: −0.33 to −0.03], MMSE total scores: corrected $P < 0.01$, $\beta = -0.22$ [CI: −0.36 to −0.08]), and episodic memory (Free and Cued Selective Reminding Test, age-corrected $P < 0.01$, $\beta = -0.26$ [CI: −0.39 to −0.12]). The Aβ+ individuals showed significantly higher expressions of both Aβ ($P < 10^{-16}$, $t = 11.6$, CI: 1.1–1.6) and tau ($P < 10^{-6}$, $t = 5.2$, CI: 0.5–1.0) patterns compared to the Aβ− individuals. The expressions of the Aβ ($P < 0.001$, $t = 4.3$, CI: 0.7–2.0) and tau ($P < 0.001$, $t = 4.1$, CI: 0.9–2.9) patterns were significantly higher in HABS-CS individuals who progressed to MCI/AD compared to those who remained cognitively normal. Associations between pattern expressions and clinical outcomes in each cohort are shown in Figure S2 in supporting information.

3.2.4 | Comparisons of Aβ and tau spatial patterns across cohorts

For Aβ spatial patterns, strong similarity was observed between patterns obtained with all DS and DS-CS individuals ($R^2 = 0.85$), with the largest regional difference in the caudate and higher overall spatial weights in the pattern obtained with all DS ($t = 10.3$, CI: 0.10–0.14,

TABLE 4 MCCA-derived regional weights [95% CI] for the tau spatial patterns across the three cohorts, ranked from highest to lowest by region in each cohort.

All DS		DS-CS		HABS-CS	
Entorhinal	0.96 [0.94–0.97]	Entorhinal	0.89 [0.85–0.92]	Parahippocampal	0.88 [0.84–0.91]
Amygdala	0.94 [0.92–0.96]	Amygdala	0.89 [0.84–0.92]	Entorhinal	0.87 [0.83–0.9]
Parahippocampal	0.93 [0.9–0.95]	Hippocampus	0.79 [0.71–0.85]	Fusiform	0.82 [0.76–0.86]
Inferior temporal	0.89 [0.84–0.92]	Parahippocampal	0.79 [0.71–0.85]	Amygdala	0.81 [0.76–0.86]
Inferior parietal	0.88 [0.83–0.91]	Fusiform	0.67 [0.56–0.76]	Inferior temporal	0.73 [0.65–0.79]
Hippocampus	0.86 [0.82–0.9]	Inferior temporal	0.67 [0.56–0.76]	Hippocampus	0.71 [0.64–0.78]
Fusiform	0.86 [0.81–0.9]	Inferior parietal	0.65 [0.53–0.74]	Insula	0.47 [0.35–0.57]
Precuneus	0.84 [0.78–0.88]	Precuneus	0.6 [0.47–0.71]	Cerebral white matter	0.45 [0.33–0.56]
Posterior cingulate	0.8 [0.73–0.85]	Lateral occipital	0.52 [0.38–0.64]	Lateral occipital	0.42 [0.29–0.53]
Lateral occipital	0.78 [0.71–0.84]	Posterior cingulate	0.43 [0.27–0.57]	Lingual	0.4 [0.27–0.51]
Cerebral white matter	0.77 [0.69–0.83]	Lingual	0.4 [0.24–0.54]	Thalamus	0.36 [0.23–0.48]
Insula	0.75 [0.67–0.81]	Cuneus	0.4 [0.23–0.54]	Putamen	0.34 [0.21–0.46]
Lingual	0.74 [0.65–0.8]	Insula	0.39 [0.23–0.54]	Inferior parietal	0.34 [0.2–0.46]
Cuneus	0.72 [0.63–0.79]	Putamen	0.37 [0.2–0.51]	Pericalcarine	0.33 [0.19–0.45]
Rostral middle frontal	0.66 [0.56–0.74]	Cerebral white matter	0.33 [0.16–0.48]	Rostral middle frontal	0.24 [0.1–0.37]
Pericalcarine	0.65 [0.55–0.74]	Pericalcarine	0.31 [0.13–0.46]	Precuneus	0.23 [0.09–0.36]
Putamen	0.61 [0.5–0.71]	Caudate	0.25 [0.07–0.42]	Caudate	0.22 [0.08–0.35]
Precentral	0.53 [0.4–0.63]	Rostral middle frontal	0.25 [0.07–0.41]	Posterior cingulate	0.21 [0.07–0.34]
Anterior cingulate	0.46 [0.32–0.58]	Thalamus	0.17 [−0.01–0.34]	Cuneus	0.12 [−0.02–0.26]
Thalamus	0.35 [0.2–0.49]	Precentral	−0.04 [−0.22–0.14]	Precentral	0.11 [−0.03–0.25]
Caudate	0.28 [0.13–0.43]	Anterior cingulate	−0.08 [−0.25–0.11]	Anterior cingulate	0.09 [−0.05–0.23]

Abbreviation: CI, confidence interval; DS, Down syndrome; DS-CS, cognitively stable Down syndrome individuals; HABS-CS, cognitively normal/stable older adults in the Harvard Aging Brain Study cohort; MCCA, multiset canonical correlation analysis.

$P < 10^{-9}$). A weaker similarity was found between DS-CS and HABS-CS ($R^2 = 0.42$), with notable differences in the striatum and cingulate regions and slightly higher overall spatial weights in HABS-CS ($t = 3.3$, CI: 0.02–0.11, $P = 0.003$). Comparisons between the patterns obtained with all DS and HABS-CS individuals showed moderate similarity ($R^2 = 0.57$), with regional differences concentrated in the cingulate cortex and higher overall spatial weights in the pattern obtained with all DS ($t = 3.1$, CI: 0.02–0.09, $P = 0.005$).

For tau spatial patterns, strong similarity was observed between patterns obtained with all DS and DS-CS individuals ($R^2 = 0.72$), with differences mainly in regions with low tau weights (e.g., caudate, thalamus), and higher overall spatial weights in the pattern obtained with all DS ($t = 8.1$, CI: 0.20–0.34, $P < 10^{-7}$). Moderate similarity was found between DS-CS and HABS-CS ($R^2 = 0.67$), with the largest regional differences in the precuneus and inferior parietal cortex; however, there was no significant difference in overall tau spatial weight (P = n.s.). Comparisons between the patterns obtained with all DS and HABS-CS individuals revealed weaker similarity ($R^2 = 0.45$), with the largest regional differences in the thalamus, caudate, precuneus, inferior parietal, and posterior cingulate, and significantly higher overall spatial weights in the pattern obtained with all DS ($t = 6.8$, CI: 0.20–0.38, $P < 10^{-5}$).

4 | DISCUSSION

This study provides further evidence that individuals with DS exhibit AD neuropathology (Aβ and tau) with both overlapping and distinct features compared to neurotypical aging. By leveraging multimodal imaging and cognitive data from ABC-DS and HABS research cohorts, this study offers a direct comparison of the Aβ and tau associations between DS and neurotypical aging individuals exhibiting preclinical AD pathology. A multivariate joint pattern analysis, MCCA, was applied to PET uptake values in 27 Aβ-relevant and 21 tau-relevant regions to provide a more informative evaluation of the Aβ and tau spatial associations beyond a global or regional composite (e.g., aggregate regions based on Braak NFT staging). Our results suggest that DS-CS individuals exhibited lower cortical Aβ but higher tau burden compared to neurotypical aging individuals also exhibited Aβ and tau burden. On the other hand, DS individuals with MCI or AD (DS-MCI/AD) exhibited more widespread Aβ and tau burden. The Aβ-associated tau burden was significantly linked to episodic memory impairment in both DS-CS and HABS-CS, even prior to clinical dementia. Moreover, executive function impairments emerged later as DS advanced. These findings are further supported by other findings consistent with prior studies, as discussed below.

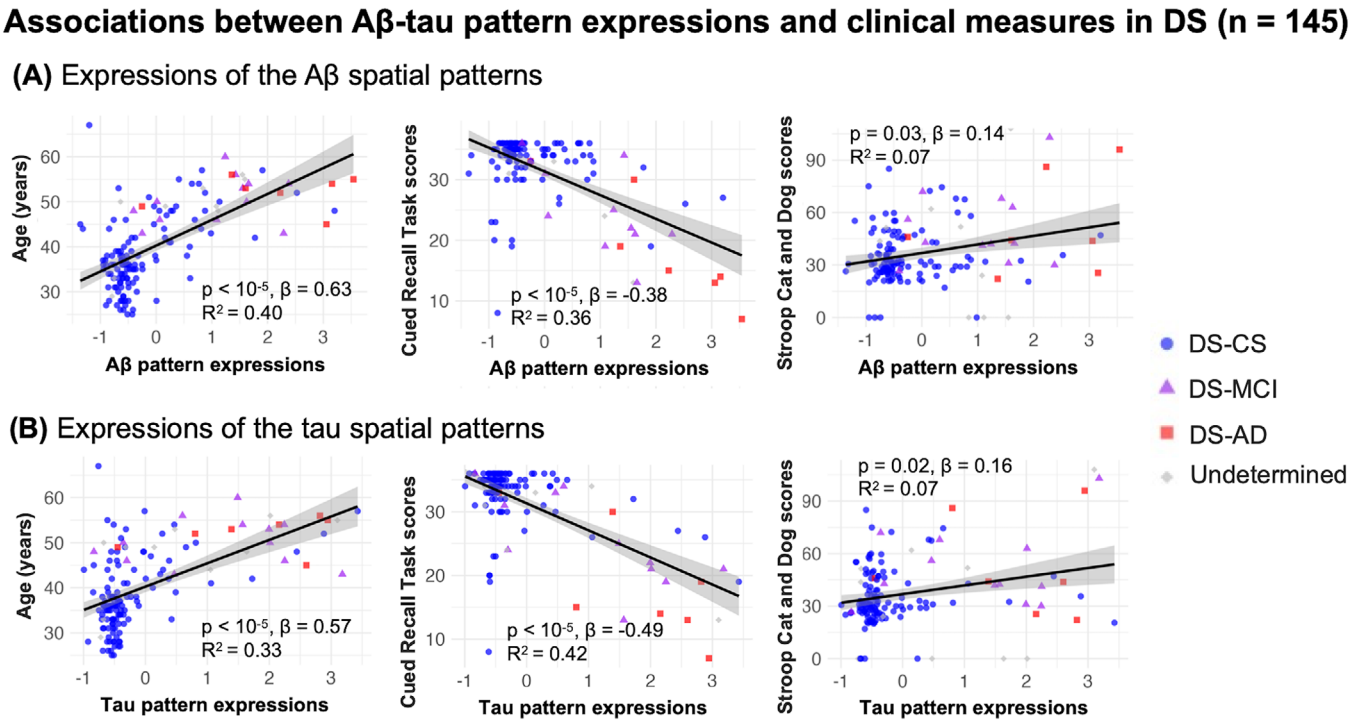

FIGURE 2 Associations between joint Aβ and tau pattern expressions (subject scores) and clinical outcomes across all DS individuals. Higher expressions of the DS-related Aβ (A) and tau (B) patterns expressions were correlated significantly with older age and worse episodic memory (Cued Recall Task scores) and executive function (Stroop Dog and Cat scores). Aβ, amyloid beta; AD, Alzheimer's disease; CS, cognitively stable; DS, Down syndrome; MCI, mild cognitive impairment

Strong associations between relatively higher cortical Aβ (especially in the frontal cortex) and tau burden in early-tau regions were observed in both neurotypical aging and DS populations, even prior to a clinical diagnosis of MCI/AD. The Aβ-associated tau burden was most pronounced in early-tau regions, including the entorhinal cortex and amygdala. Higher expressions of these spatial patterns at baseline were predictive of future conversion to MCI/AD in the HABS neurotypical aging cohort, suggesting that these patterns reflect preclinical AD deficits. These findings align with prior Aβ and tau PET studies in DS[12,14–17,40–42] and support the "amyloid cascade hypothesis" in DS, which posits that Aβ accelerates tau burden, driving neurodegeneration and cognitive decline.[43–47]

Despite these shared features, key differences emerged between neurotypical aging and DS. In DS, relatively higher striatal Aβ burden was most strongly associated with relatively higher early tau burden, persisting across both CS and cognitively impaired stages. This is consistent with prior studies in DS and autosomal dominant AD, further supporting the potential of early striatal Aβ burden as an imaging biomarker for tracking disease progression and informing clinical trial inclusion in DS.[5,7,25,48]

Beyond the common cortical Aβ and early tau burden patterns, MCCA revealed more nuanced differences in Aβ and tau spatial associations between DS and neurotypical aging by analyzing the joint spatial patterns of Aβ and tau burden across multiple brain regions rather than relying on predefined regional composites. In particular, relatively lower cortical Aβ burden but relatively higher tau burden in more widespread tau-relevant regions were observed in DS-CS compared to neurotypical aging. The lower cortical Aβ burden in DS-CS may partially reflect partial volume effects in PET quantification, driven by greater cortical atrophy or brain volume loss in DS relative to neurotypical aging. Another potential confound is the use of a DS-specific template to extract PET regional outcomes instead of individual-specific segmentations. Future studies will incorporate MR-based volumetric measures in the analyses and individual-specific FreeSurfer segmentations to formally assess the impact of potential confounds on these results. In DS-CS individuals who exhibited relatively higher striatal and cortical Aβ burden, tau burden extended beyond early-tau regions to intermediate-to-advanced tau regions (e.g., precuneus and inferior parietal), whereas in neurotypical aging, tau burden remained restricted to early-tau regions despite similarly elevated cortical Aβ burden. This suggests that, for the same level of Aβ burden, individuals with DS may exhibit higher and more widespread tau burden compared to neurotypical aging, even before a clinical diagnosis of MCI/AD. Similar findings have been reported in DS compared to autosomal dominant AD as well as shorter latency between Aβ+ onset and early tau burden (2.5 years) relative to sporadic AD (5–10 years).[15–17] Our results provide a more direct comparison of the Aβ and tau association between DS and neurotypical aging individuals exhibiting preclinical AD pathology, further supporting that tau pathology in DS may follow a distinct trajectory from that observed in neurotypical aging.

When including DS-MCI/AD individuals, relatively higher cortical Aβ burden associated with relatively higher and more widespread

tau burden were observed compared to both DS-CS and neurotypical aging. While striatal Aβ weights remained similar to that observed in DS-CS, the elevated cortical Aβ weights in DS-MCI/AD likely reflects disease progression, despite the expected influence of more pronounced cortical atrophy and partial volume effect in DS-MCI/AD. For DS individuals with relatively higher striatal and cortical Aβ burden, more widespread tau was observed; however, the highest tau weights remained localized to early-tau regions. This suggests that tau burden in early-tau regions may not have reached a plateau in our sample. Further studies with larger DS-MCI/AD cohorts are needed to comprehensively evaluate Aβ and tau burden patterns as the disease progresses.

The evaluation of the joint spatial associations between Aβ and tau burden revealed Aβ-associated tau spatial patterns, whose expressions were associated with early episodic memory impairment in both neurotypical aging and DS, prior to a clinical diagnosis of dementia. This suggests that individuals with elevated Aβ and early tau burden already exhibit subtle cognitive impairment, with tau burden playing a significant role. These results were adjusted for expected age-related increases in Aβ and tau burden.[49–51] These findings align with previous cross-sectional and longitudinal studies reporting similar associations between regional tau burden and episodic memory decline, reinforcing the idea that episodic memory impairment may serve as an early indicator of cognitive impairment in DS.[18–20,52] Given that the HABS neurotypical aging cohort is ≈ 30 years older than the DS cohort, the similar associations between Aβ-associated early tau burden and episodic memory impairment in both groups may reflect accelerated aging and preclinical AD deficits in DS. As the disease progressed, DS individuals with relatively higher Aβ burden and more widespread tau burden exhibited additional impairments in executive function. This progression likely reflects the spatial spread of AD-related neuropathology from memory-related regions to regions involved in decision making and planning, such as the frontal-striatal pathway. These findings further highlight the potential sequential impact of Aβ and tau on distinct cognitive domains over time.

There are several methodological considerations in this study. First, the PET imaging data were acquired and analyzed using different acquisition and preprocessing protocols. In the HABS dataset, PET analyses were performed in the native space using FreeSurfer segmentations with manual edits, and Aβ burden was quantified as DVR using dynamic PiB PET data. These steps were consistent with prior HABS studies using the same data.[39,53] In the ABC-DS dataset, PET analyses were performed in a template space using FreeSurfer segmentations with manual edits, instead of using segmentations in the native space. This used a DS-specific MR template, previously validated against individual-based MR segmentations.[37] Second, two Aβ PET radioligands (FBP and PiB) were used in the ABC-DS dataset. While both provided comparable global Aβ burden estimates, regional differences were noted, particularly in detecting early striatal Aβ accumulation, likely due to differences in binding characteristics to Aβ subtypes.[7,54,55] Sensitivity analyses using only PiB PET data yielded consistent results (not shown). To address differences in acquisition protocols and radioligands, we used *z* transformation instead of the Centiloid scale to quantify regional Aβ burden across the cortex, enabling more detailed regional analyses rather than relying on a global Aβ measure. A key strength of this study is the use of multivariate analysis, specifically MCCA, to jointly evaluate Aβ and tau uptake across multiple brain regions. This approach mitigates issues related to multiple comparisons and is less affected by protocol differences, as MCCA identifies spatial patterns based on relative relationships between regions.

Important study limitations include the relatively small number of DS individuals with MCI or AD (DS-MCI/AD: $n = 19$), which limits the ability to comprehensively evaluate spatial associations between Aβ and tau burden and cognitive impairment in later disease stages. Future studies with larger DS-MCI/AD samples are needed to address this gap. Additionally, the ABC-DS and HABS cohorts used different cognitive assessment protocols; however, both included episodic memory measures through recall tasks, allowing for some comparability. The cross-sectional design of this study precludes analysis of the spatiotemporal relationships between Aβ and tau burden. Longitudinal studies are necessary to clarify these dynamics and their relationship to cognitive decline in DS and aging populations. Future research should also include sibling controls of individuals with DS to provide a deeper understanding of the genetic and environmental factors influencing AD pathology in DS.

In conclusion, the study underscores both overlapping and distinct features of AD-related neuropathology in DS and neurotypical aging. By jointly analyzing Aβ and tau burden across multiple brain regions, our results suggest that for a given level of Aβ burden, tau pathology was more widespread in DS compared to neurotypical aging, even prior to a clinical diagnosis of dementia. Moreover, Aβ-associated tau burden patterns were linked to impairment in episodic memory and executive function in DS, reflecting the progressive impact of AD-related neuropathology on cognition. These findings highlight the importance of biomarker-driven strategies for early detection and intervention in DS.

ACKNOWLEDGMENTS

The authors disclosed receipt of the following financial support: 3U19AG068054-03S3, K99AG081457, P01AG036694, R01AG046396, P41EB030006, and P41EB015896.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The ABC-DS cohort study was approved by the local institutional review board at each participating site, and informed consent was obtained from all participants or their proxy/legally authorized representatives. The HABS cohort study was approved by the Mass General Brigham Human Research Committee, and informed consent was obtained from all participants.

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SUPPORTING INFORMATION

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

How to cite this article: Fu JF, Garimella A, Lapointe A, et al. Joint spatial associations of amyloid beta and tau pathology in Down syndrome and preclinical Alzheimer's disease: Cross-sectional associations with early cognitive impairments. *Alzheimer's Dement*. 2025;21:e70424. https://doi.org/10.1002/alz.70424