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RESEARCH ARTICLE

Voxel-based dysconnectomic brain morphometry with computed tomography in Down syndrome

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Abstract

Objective: Alzheimer's disease (AD) is a major health concern for aging adults with Down syndrome (DS), but conventional diagnostic techniques are less reliable in those with severe baseline disability. Likewise, acquisition of magnetic resonance imaging to evaluate cerebral atrophy is not straightforward, as prolonged scanning times are less tolerated in this population. Computed tomography (CT) scans can be obtained faster, but poor contrast resolution limits its function for morphometric analysis. We implemented an automated analysis of CT scans to characterize differences across dementia stages in a cross-sectional study of an adult DS cohort. **Methods**: CT scans of 98 individuals were analyzed using an automatic algorithm. Voxel-based correlations with clinical dementia stages and AD plasma biomarkers (phosphorylated tau-181 and neurofilament light chain) were identified, and their dysconnectomic patterns delineated. **Results**: Dementia severity was negatively correlated with gray (GM) and white matter (WM) volumes in temporal lobe regions, including parahippocampal gyri. Dysconnectome analysis revealed an association between WM loss and temporal lobe GM volume reduction. AD biomarkers were negatively associated with GM volume in hippocampal and cingulate gyri. **Interpretation**: Our automated algorithm and novel dysconnectomic analysis of CT scans successfully described brain morphometric differences related to AD in adults with DS, providing a new avenue for neuroimaging analysis in populations for whom magnetic resonance imaging is difficult to obtain.

Introduction

Alzheimer's disease (AD) has become a major health concern for the adult population with Down syndrome (DS), particularly as life expectancy in this population has increased in recent decades.[1] AD is the leading cause of death in this group and also leads to progressive frailty, functional decline, and quality-of-life deterioration. Almost all individuals with DS will develop AD over time and at a younger age than the general population.[2–4] Thus, its early and accurate diagnosis is essential to providing effective treatment with disease-modifying or preventative therapies when these become available.[5]

Recent advances in diagnostic techniques including neuroimaging and analytical biomarkers[6–11] have improved our understanding of the pathogenesis and natural history of AD in DS. However, the diagnosis of AD in individuals with intellectual disabilities, especially those in resource-limited settings, faces unresolved challenges.[12] Furthermore, the baseline cognitive function of individuals with DS is widely variable; the more severe the intellectual disability, the less reliable neuropsychological tests become.[13] In this population, clinical judgment or the caregiver's opinion might be at least as sensitive to changes in cognition and behavior as standardized tests.

In the general population, standard diagnostic tools for AD include clinical evaluation, magnetic resonance

imaging (MRI), and lumbar puncture (LP) or positron emission tomography (PET) for AD biomarker quantification. Although MRI and LP have proven useful in the study of AD in DS adults with mild to moderate intellectual disability,[14] they require a degree of patient cooperation that individuals with more severe disability might not be able to provide. Additionally, LP biomarkers might be progressively less used, as novel plasma AD biomarkers such as phosphorylated tau and neurofilament light chain are now increasingly easy to quantify with reliable, ultrasensitive assays and have excellent diagnostic and prognostic performance in the DS population.[15] Finally, other state-of-the-art neuroimaging tools, such as amyloid- or tau-based PET, are costly and not widely available outside of research initiatives in many health care systems.

It is imperative to optimize the diagnosis of AD with widely available, better tolerated techniques in adults with DS, and computed tomography (CT) could fill this gap. CT requires less cooperation from the patient than MRI or LP and entails very few risks (with typical radiation exposure of 2mSv[16]). CTs are also significantly cheaper than MRI and are often used in clinical settings. These advantages may offset the lower contrast resolution of CT when compared to MRI in the DS population. In addition, although MRI poses significant advantages over CT when evaluating dementia in the general population by providing information on potential underlying processes (microvascular damage, white matter lesions, normal pressure hydrocephalus, etc.), this theoretical advantage is diminished in individuals with DS, where AD is the primary cause of dementia.[11]

Prior case series studies have successfully used CT to demonstrate a correlation between cerebral atrophy as measured by semi-automated image analysis methods and clinical dementia in the general population.[17–22] However, evidence of its usefulness in DS is scarce.[23–28] CTseg, an automated segmentation and nonlinear registration tool for brain CT scans, was developed by the Wellcome Centre for Human Neuroimaging (University College London, London, UK) and is openly accessible.[29] Here, we hypothesized that CTseg could be used to help identify gray and white matter differences as a function of dementia severity and would correlate with biomarkers of neurodegeneration in adults with DS.

Materials and Methods

Study design and selection criteria

This is a cross-sectional study in consecutively recruited adults with DS from the Adult Down Syndrome Unit, a specialized outpatient clinic of a tertiary care, university hospital in Madrid, Spain. A total of 120 adults were selected from all individuals who attended the unit using the following selection criteria: (a) to have a diagnosis of DS, either with a family-reported karyotype (all of which were full trisomy 21 individuals; none of the sample subjects carried a robertsonian translocation or were T21 mosaics) or a compatible typical phenotype (based on the clinical presentation of characteristic physical features associated with DS); (b) to be over 16 years old; (c) to have undergone one CT scan at the Hospital Universitario de La Princesa in Madrid for clinical reasons between 1 January 2016 and 31 December 2018; and (d) to have had donated a plasma sample to the institutional biobank with an interval of <6 months between donation and imaging study. This project was approved by the institutional IRB at the Hospital Universitario de la Princesa (registry no. 3911/2019), and informed consent was obtained from all participants.

Clinical variables

All demographic and clinical characteristics were collected retrospectively from participants' medical records. We obtained the following demographic data: age, sex, socioeconomic status (estimated from the mean income level of the district of residence), academic background, and occupation/work, if any. Family history of AD or other dementias and the following comorbidities, previously reported to be related to the development of dementia either in the general population or in individuals with DS,[30] were also collected: head trauma, prior history of general anesthesia, obstructive sleep apnea, atlantoaxial instability, thyroid disorders (and TSH level), coeliac disease, hearing loss, decreased visual acuity, venous thromboembolic disease, blood pressure, syncope, congenital heart disease, diabetes mellitus (according to American Diabetes Association diagnostic criteria[31]), hypercholesterolemia (according to ESC/EAS 2019 diagnostic criteria[32]), early menopause, and osteoarthritis, as proxy comorbidities for premature aging. Medication use at time of inclusion was also recorded for all participants.

Baseline functional status was recorded using Part 1 of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) questionnaire,[33] which evaluates speech, daily living skills, and living situation. Cognitive status was determined clinically using information provided by caregivers and data from the participant's physical examination and clinical evaluation. Individuals were then classified into the following groups, broadly in accordance with recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability: (a) cognitively stable (CS), in the absence of clinically significant cognitive decline; (b)

mild cognitive impairment (MCI), indicating that there were signs of cognitive decline beyond what would be expected with aging, without functional deterioration; (c) moderate or advanced dementia (for the current analyses, both groups were combined into a single dementia group), when there was substantial cognitive decline and severe loss of autonomy.[34,35] Symptoms associated with cognitive decline such as seizures/epilepsy, depression, behavioral disorders, and changes in sleep and/or gait were also collected.

Finally, clinically relevant hematological and biochemical parameters were collected: total blood count, renal and hepatic function, and metabolic parameters (lipid profile, glycosylated hemoglobin, and thyroid function). All of these parameters were measured as part of the standard follow-up protocol at the adult DS unit. Additionally, one 10 mL EDTA container and one 8.5 mL serological gel tube were extracted for this study and processed in the institutional biobank shortly thereafter. Samples were sorted into aliquots and stored in a freezer at −80°C.

Plasma AD biomarkers

Neurofilament light chain (NfL) and tau phosphorylated at threonine 181 (pTau-181) were selected as plasma AD biomarkers of choice, given their better diagnostic performance compared to other plasma biomarkers (amyloid-β_{1-40}, amyloid-β_{1-42}, or total tau) in adults with DS.[7,8] NfL levels have shown good correlation with other CSF biomarkers (such as low Aβ42, high total tau, and high phosphorylated tau levels), MRI measures, and poor cognitive performance in individuals with AD with and without DS.[7,36] Plasma p-tau181 concentrations have also shown a high area under the curve for the discrimination between asymptomatic individuals with and without DS versus those in the prodromal and dementia groups, respectively.[8,37] Their concentrations were measured using the ultrasensitive single-molecule array (SIMOA) assay at the Adult Down Syndrome Memory Unit, Department of Neurology, Hospital Universitario de la Santa Creu i Sant Pau, Barcelona. All measurements were conducted by specially trained personnel in one round of experiments using one batch of reagents.

Image processing

CT images were acquired in either a Toshiba Aquilion 64-channels system at 0.4 × 0.4 × 3 mm^3 resolution, or a Siemens Sensation 64-channels system at 0.4 × 0.4 × 2.4 mm^3 resolution. Radiologist reports were first screened to exclude individuals with previous stroke or space occupying lesions. Mega cisterna magna was a relatively frequent observation (10 subjects out of 120, 8.3%) and not used as an exclusion criterion. Prior radiological studies of individuals with DS have described smaller posterior fossa, smaller cerebella, and a higher incidence of mega cisterna magna compared to nontrisomic controls.[38] In individuals with DS, the presence of mega cisterna magna is closely related to cerebellar hypoplasia. However, an isolated finding of mega cisterna magna is thought to be an anatomic variant with no clinical significance.[39] Brain CT scans were anonymized before analyses, which proceeded blind to clinical records and cognitive scores. In the case of separate posterior fossa and supratentorial acquisitions, these were merged to create one three-dimensional image per individual. Participants whose CT scans presented significant artifacts or faulty merging of supratentorial and posterior fossa acquisitions were excluded from the analysis, leaving a final sample of 98 individuals for imaging analysis.

CT scans were processed using CTseg (https://github.com/WCHN/CTseg; Wellcome Trust Centre for Neuroimaging, University College London), an automatic algorithm optimized for CT, which employs flexible Bayesian modelling to jointly spatially normalize images to standard MNI space and segment them into standard tissue classes, including gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF).[29] Segmented images were then smoothed with a Gaussian kernel of 6 mm full width at half maximum. Total intracranial volume (TIV) was obtained by summing the volumes of GM, WM, and CSF.

Statistical analysis

No estimation of the most adequate sample size was done as there was no former evidence of the utility of this algorithm in the DS population. Clinical data were processed using Stata software (Stata v15.0). Age, sex, TIV, and premorbid functionality were selected as potential confounders after using bivariate ordinal logistic regressions, with dementia severity (CS: 0, MCI: 1, dementia: 2) as the dependent variable. All statistical tests were two-tailed, establishing a p-value of 0.05 as the cutoff for statistical significance and using Bonferroni or Tukey methods when post hoc multiple comparisons were made. To rule out potential selection bias, comparisons of all baseline clinical characteristics were conducted between the 98 individuals who were included and the 22 excluded based on CT scan quality.

Whole-brain voxel-wise GM and WM volume comparisons were conducted using voxel-based morphometry (VBM) with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Smoothed and modulated GM and WM images were correlated separately with dementia severity within a general

linear model (GLM), including TIV, age, sex, and premorbid functionality as covariates of no interest. Separate GLMs correlating GM and WM images with plasma biomarkers (NfL and pTau-181) were also conducted using TIV, age, and sex as covariates of no interest. All voxel-wise results were corrected for multiple comparisons using family-wise error (FWE) correction. Potential effects of scanner type and scan resolution were tested by including scanner as a covariate (dummy coded 0 or 1).

Dysconnectome analysis

A dysconnectome analysis was conducted to examine GM volume effects in conjunction with potential upstream white matter abnormality, combining elements of two methods described previously.[40,41] The approach differs from standard disconnectome analysis—which elicits white matter tracts disconnected by a structural lesion—in identifying the connectivity of white matter tracts shown by VBM to be statistically abnormal rather than frankly lesioned. Briefly, smoothed and modulated WM images were entered into a GLM including TIV, age, and sex to remove confounding effects. The resultant residuals were thresholded at 2 standard deviations below the median for each voxel and binarized to generate masks of regions with low WM signal, plausibly corresponding to abnormal white matter. These masks were used as input for the BCBtoolkit (https://github.com/chrisfoulon/BCBToolKit)[42] thresholded at 0.5 to generate probable white matter tracts affected by the putatively abnormal regions. Finally, these tracts were smoothed at 8 mm and entered into a GLM correlating with dementia severity, with an inclusive gray matter mask, and controlling for TIV, age, sex, and premorbid functionality.

Results

Clinical characteristics of the study cohort

A total of 120 participants who met the inclusion criteria were initially selected (mean age: 48.6 ± 8.4 years, 45.8% female). Seventy-four participants were cognitively stable at the time of their evaluation, while 46 individuals showed some degree of cognitive impairment: 23 had been clinically diagnosed with dementia—5 of them in an advanced state—while the remaining 23 were diagnosed as having MCI. A summary of clinical and demographic characteristics of this cohort are presented in Table 1.

Behavioral disorders (OR 2.72; 95%CI: 1.14–6.49) and gait instability (OR 7.71; 95%CI: 2.84–21.0) were significantly associated with age-adjusted dementia severity in the preliminary ordinal logistic regression analysis (Table 2). We did not find any relevant associations between any indirect measures of cognitive reserve (prior education level, occupation, or any of the items in Part 1 of the DSQIID) and the stage of dementia, although a significant proportion of data about baseline functionality was missing (e.g., 29.2% for education).

Correlation between whole-brain VBM analysis and clinical variables

Of the initial cohort of 120 individuals, 7 were excluded based on incidental brain findings and 15 were excluded due to CT scan issues, including artifacts or failures in segmentation, leaving a final sample of 98 individuals for neuroimaging analyses (mean age: 48.0 ± 8.5 years; 45% female; 62 CS, 19 MCI, 17 dementia). No significant differences were found in baseline clinical characteristics between the included and excluded participants. Scanner type did not significantly affect any comparison, and all results are reported without scanner as a covariate.

CS individuals had larger mean total brain, GM, and WM volumes than those with MCI and dementia (CS brain volume: 893.2 cc, 95%CI: 868.2–918.2; MCI brain volume: 839.0 cc, 95%CI: 787.4–890.5; dementia brain volume: 815.8 cc, 95%CI: 764.9–866.6; CS GM: 679.8 cc, 95%CI: 661.8–697.9; MCI GM: 648.7 cc, 95%CI: 611.9–685.5; dementia GM: 626.8, 95%CI: 588.8–664.8; CS WM: 213.3 cc, 95%CI: 205.0–221.6; MCI WM: 190.3 cc, 95% CI: 171.9–208.6; dementia WM: 189.0 cc, 95%CI: 171.2–206.7). TIV was not significantly associated with dementia level when adjusted for age and sex ($F_{(2,93)} = 1.26$, $p = 0.288$), while total brain, GM, and WM volumes were negatively associated with dementia severity, adjusting for age, sex, and TIV (brain volume: $F_{(2,92)} = 41.25$, $p = 1.6 \times 10^{-13}$, $\eta_p^2 = 0.47$; GM: $F_{(2,92)} = 9.71$, $p = 1.5 \times 10^{-4}$, $\eta_p^2 = 0.17$; WM: $F_{(2,92)} = 8.00$, $p = 6.3 \times 10^{-4}$, $\eta_p^2 = 0.15$). In Tukey post hoc tests, differences were only found between CS and dementia groups for total brain and GM volumes (brain volume: CS vs. MCI: $t = 2.06$, $p = 0.103$; CS vs. dementia: $t = 2.82$, $p = 0.016$; MCI vs. dementia: $t = 0.69$, $p = 0.768$; GM: CS vs. MCI: $t = 1.64$, $p = 0.236$; CS vs. dementia: $t = 2.67$, $p = 0.024$; MCI vs. dementia: $t = 0.90$, $p = 0.639$), while WM volumes were significantly smaller in both clinical groups compared to CS individuals (CS vs. MCI: $t = 2.58$, $p = 0.031$; CS vs. dementia: $t = 2.61$, $p = 0.028$; MCI vs. dementia: $t = 0.12$, $p = 0.993$).

Whole-brain VBM analyses revealed that dementia level negatively correlated with GM volume in the bilateral parahippocampal gyri, extending into the hippocampus and amygdala, with a peak minimum in the left parahippocampal gyrus (MNI: −28 −30 −22, $Z = 6.39$, $t = 7.19$, whole-brain FWE-corrected $p < 0.01$; Fig. 1A,B). WM

Table 1. Baseline characteristics of the study sample population.

	Cognitively stable (n = 74)	Mild cognitive impairment (n = 23)	Dementia (n = 23)	One-way ANOVA or χ^2 results
Age (years) ± standard deviation	45.4 ± 8.3	51.8 ± 4.5	55.9 ± 5.5	$F_{(2,117)} = 21.25$ $p = 2.2 \times 10^{-9}$*
Sex				
Male	41 (55.4%)	15 (65.2%)	9 (39.1%)	$\chi^2_{(2)} = 3.27$
Female	33 (44.6%)	8 (34.8%)	14 (60.9%)	$p = 0.195$
Family history of dementia				
No	52 (70.3%)	21 (91.3%)	19 (82.6%)	$\chi^2_{(2)} = 4.90$
Yes	22 (29.7%)	2 (8.7%)	4 (17.4%)	$p = 0.086$
Income level				
Low	26 (35.1%)	9 (39.1%)	10 (43.5%)	$\chi^2_{(4)} = 8.91$
High	27 (36.5%)	2 (8.7%)	8 (34.8%)	$p = 0.063$
Education				
None	5 (6.8%)	2 (8.7%)	5 (21.7%)	$\chi^2_{(4)} = 9.31$
Special	42 (56.8%)	14 (60.9%)	10 (43.5%)	$p = 0.075$
Baseline occupation				
None	9 (12.2%)	4 (17.4%)	7 (30.4%)	$\chi^2_{(4)} = 6.82$
Occupational center	51 (68.9%)	14 (60.9%)	13 (56.5%)	$p = 0.162$
Labor integration	8 (10.8%)	0	1 (4.3%)	
Living situation				
Family home	52 (70.3%)	13 (56.5%)	14 (60.9%)	$\chi^2_{(4)} = 3.90$
Residence	18 (24.3%)	10 (43.5%)	8 (34.8%)	$p = 0.384$
Congenital heart disease				
No	67 (90.5%)	20 (87.0%)	22 (95.7%)	$\chi^2_{(2)} = 1.06$
Yes	7 (9.5%)	3 (13.0%)	1 (4.3%)	$p = 0.607$
High blood pressure				
No	70 (94.6%)	22 (95.7%)	22 (95.7%)	$\chi^2_{(2)} = 0.07$
Yes	4 (5.4%)	1 (4.3%)	1 (4.3%)	$p = 1.000$
Hypercholesterolemia				
No	23 (31.1%)	10 (43.5%)	8 (34.8%)	$\chi^2_{(2)} = 1.20$
Yes	51 (68.9%)	13 (56.5%)	15 (65.2%)	$p = 0.548$
Prediabetes/diabetes mellitus				
No	52 (70.3%)	20 (87.0%)	13 (56.5%)	$\chi^2_{(2)} = 5.19$
Yes	22 (29.7%)	3 (13.0%)	10 (43.5%)	$p = 0.075$
Sleep apnea				
No	56 (75.7%)	20 (87.0%)	19 (82.6%)	$\chi^2_{(4)} = 1.76$
Yes	9 (12.2%)	2 (8.7%)	2 (8.7%)	$p = 0.902$
Thyroid disorders				
None	28 (37.8%)	11 (47.8%)	6 (26.1%)	$\chi^2_{(4)} = 4.16$
Hypothyroidism	45 (60.8%)	11 (47.8%)	17 (73.9%)	$p = 0.324$
Hyperthyroidism	1 (1.4%)	1 (4.3%)	0	
Hearing loss				
No	64 (86.5%)	19 (82.6%)	14 (60.9%)	$\chi^2_{(2)} = 7.49$
Yes	10 (13.5%)	4 (17.4%)	9 (39.1%)	$p = 0.033$**
Vision impairment				
No	53 (71.6%)	16 (69.6%)	14 (60.9%)	$\chi^2_{(2)} = 0.95$
Yes	21 (28.4%)	7 (30.4%)	9 (39.1%)	$p = 0.621$
Behavioral changes				
None	61 (82.4%)	13 (56.5%)	13 (56.5%)	$\chi^2_{(2)} = 9.55$
Yes	13 (17.6%)	10 (43.5%)	10 (43.5%)	$p = 0.008$*
Depression				
No	67 (90.5%)	18 (78.3%)	20 (87.0%)	$\chi^2_{(2)} = 2.43$
Yes	7 (9.5%)	5 (21.7%)	3 (13.0%)	$p = 0.258$

(*Continued*)

Table 1 Continued.

	Cognitively stable (n = 74)	Mild cognitive impairment (n = 23)	Dementia (n = 23)	One-way ANOVA or χ^2 results
Sleep disorder				
No	58 (78.4%)	18 (78.3%)	15 (65.2%)	$\chi^2_{(2)} = 1.75$
Yes	16 (21.6%)	5 (21.7%)	8 (34.8%)	$p = 0.417$
Gait				
No change	68 (91.9%)	16 (69.6%)	7 (30.4%)	$\chi^2_{(6)} = 43.37$
Instability present	6 (8.1%)	7 (30.4%)	12 (52.2%)	$p < 0.001$*
Use of antiepileptic drugs				
No	72 (97.3%)	19 (82.6%)	18 (78.3%)	$\chi^2_{(2)} = 9.95$
Yes	2 (2.7%)	4 (17.4%)	5 (21.7%)	$p = 0.004$**
Use of benzodiazepines				
No	71 (95.9%)	19 (82.6%)	22 (95.7%)	$\chi^2_{(2)} = 5.26$
Yes	3 (4.1%)	4 (17.4%)	1 (4.3%)	$p = 0.096$

Comparisons between groups were performed using one-way ANOVAs for quantitative variables and chi-square tests for categorical ones. Statistical significance for multiple comparisons was corrected using a Bonferroni approach. Percentages may not add up to 100% due to missing values.

*Indicates statistical significance maintained after correcting for multiple comparisons, except when comparing mild cognitive impairment and dementia groups.

**Indicates statistical differences only found when comparing cognitively stable and dementia groups.

Table 2. Association between baseline characteristics and dementia level.

	OR	95% confidence interval	p-value
Female sex	1.76	0.76–4.04	0.184
Family history of dementia	0.34	0.11–1.00	0.050
Low income	2.25	0.78–6.55	0.135
Special education	0.79	0.19–3.29	0.746
Labor integration	0.23	0.02–3.41	0.288
Supervised housing	0.26	0.02–4.29	0.349
High blood pressure	0.68	0.11–4.28	0.684
Hypercholesterolemia	0.81	0.35–1.89	0.623
Diabetes mellitus	1.26	0.06–29.0	0.884
Sleep apnea	1.07	0.24–4.71	0.927
Hypothyroidism	1.05	0.45–2.43	0.909
Hearing loss	2.30	0.87–6.05	0.092
Vision impairment	1.10	0.47–2.60	0.823
Behavioral changes	2.72	1.14–6.49	0.024*
Depression	2.08	0.69–6.25	0.192
Sleep disorder	0.95	0.36–2.51	0.916
Gait instability	7.71	2.84–21.0	<0.001**
Use of antiepileptic drugs	1.88	0.82–4.31	0.137
Use of benzodiazepines	0.96	0.27–3.40	0.948

Odds ratios (OR) were obtained using bivariate ordinal logistic regression analysis, adjusting for age.

*$p < 0.05$;

**$p < 0.001$.

volume was negatively associated with dementia level in the bilateral parietal and occipitotemporal regions, with right-lateralization in the superior and inferior longitudinal fasciculi (peak minimum MNI: 46 −46 24, $Z = 7.12$, $t = 8.14$, FWE-corrected $p < 0.01$; Fig. 1C,D). No significant associations were found between baseline DSQIID scores and total or region-specific gray or white matter volume.

GM volume loss associated with WM dysconnection

GM volume decrease associated with increasing dementia level was masked with the outcome of the dysconnectome analysis. This revealed several foci of effects in the right lateral temporal lobe (Fig. 2).

Correlation between clinical variables, whole-brain VBM analysis, and AD plasma biomarkers

Plasma pTau-181 and NfL values were available for 87 of the 98 individuals included in neuroimaging analyses (mean age: 48.2 ± 8.3 years; 47% female; 55 CS, 17 MCI, 15 dementia). Older age was significantly associated with higher biomarker levels in CS individuals (pTau-181: $F_{(1,52)} = 11.49$, $p = 0.0013$, $\eta_p^2 = 0.18$; NfL: $F_{(1,52)} = 25.59$, $p = 5.6 \times 10^{-6}$, $\eta_p^2 = 0.33$), but only with NfL in those with dementia ($F_{(1,12)} = 5.55$, $p = 0.036$, $\eta_p^2 = 0.32$; Fig. 3A). A one-way ANOVA revealed that pTau-181 and NfL levels were significantly higher with increasing dementia severity (pTau-181: $F_{(2,82)} = 15.21$, $p = 2.4 \times 10^{-6}$, $\eta_p^2 = 0.27$; NfL: $F_{(2,82)} = 4.61$, $p = 0.013$, $\eta_p^2 = 0.10$; Fig. 3B,C) after adjusting for age and sex. A

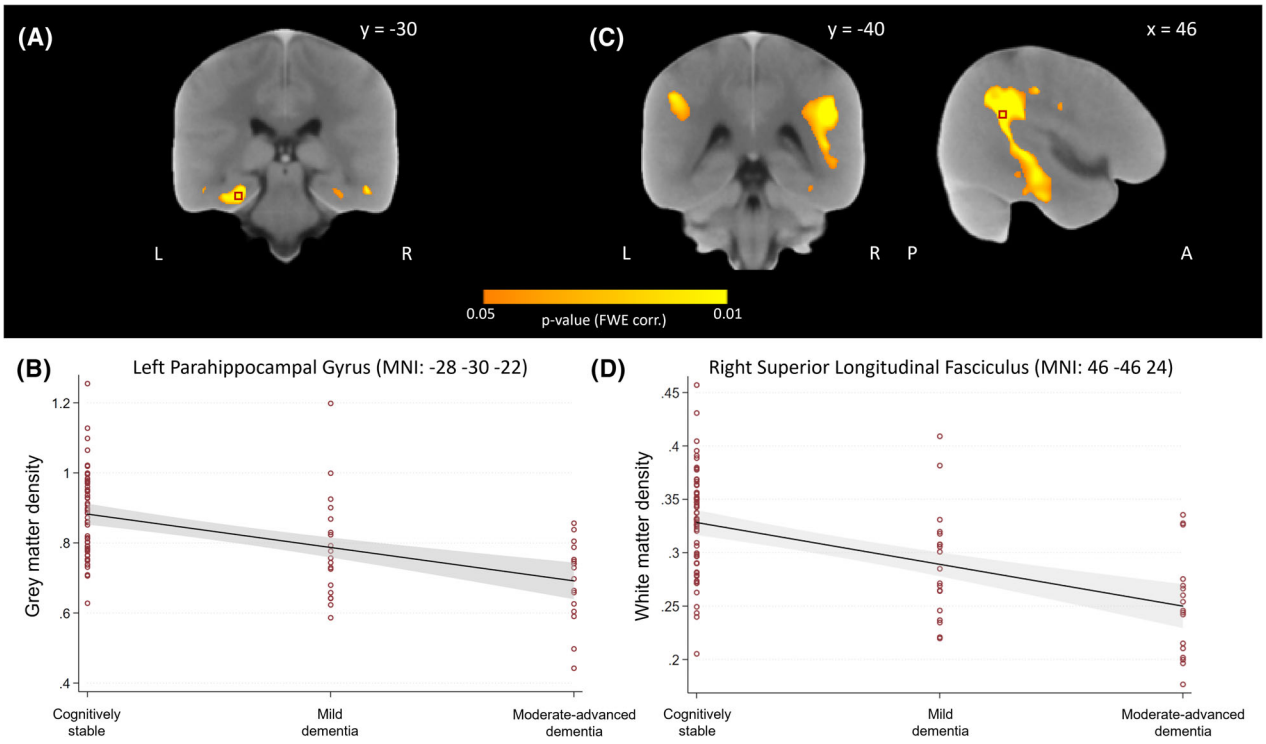

Figure 1. VBM analysis of gray and white matter from CT scans demonstrates a significant negative association between dementia level and tissue volume in individuals with Down syndrome. (A) Individuals with higher dementia levels have lower gray matter volume in the bilateral parahippocampal gyri extending to the hippocampus and amygdala. (B) Gray matter volume values from the global peak voxel (indicated by the red box in (A), MNI: −28 −30 −22), plotted against dementia level (0: cognitively stable; 1: mild cognitive impairment; 2: moderate dementia; 3: advanced dementia). (C) Higher dementia levels are associated with lower white matter volume in bilateral superior longitudinal fasciculi, with right-lateralized extension into the inferior longitudinal fasciculus. (D) White matter volume values from the global peak voxel (indicated by the red box in (C), MNI: 46 −46 24) plotted against dementia level. Color bar indicates the whole-brain family-wise error (FWE)-corrected *p*-value. Clusters are significant at $p < 0.05$, FWE-corrected. Both comparisons were corrected for age, sex, and total intracranial volume.

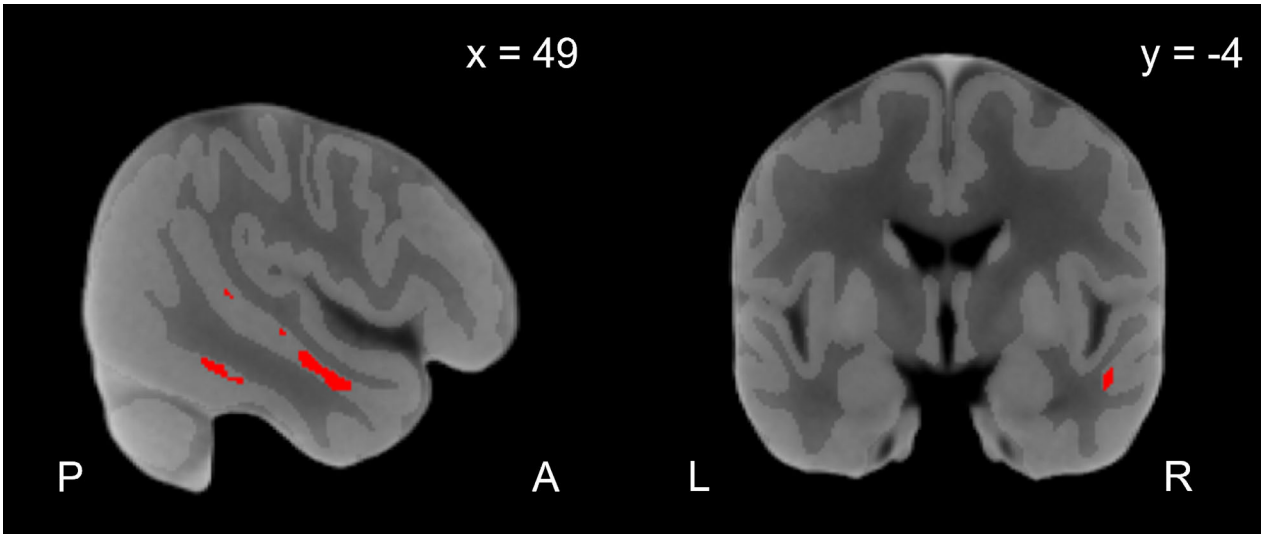

Figure 2. Lower gray matter density associated with dementia level in the right lateral temporal lobe is related to white matter deterioration based on dysconnectome analysis. Red clusters indicate overlapping regions of significant gray matter results from conventional gray matter VBM and from white matter dysconnectome analyses, at $p < 0.05$ FWE-corrected. Results are overlaid on an average gray matter mask for visualization.

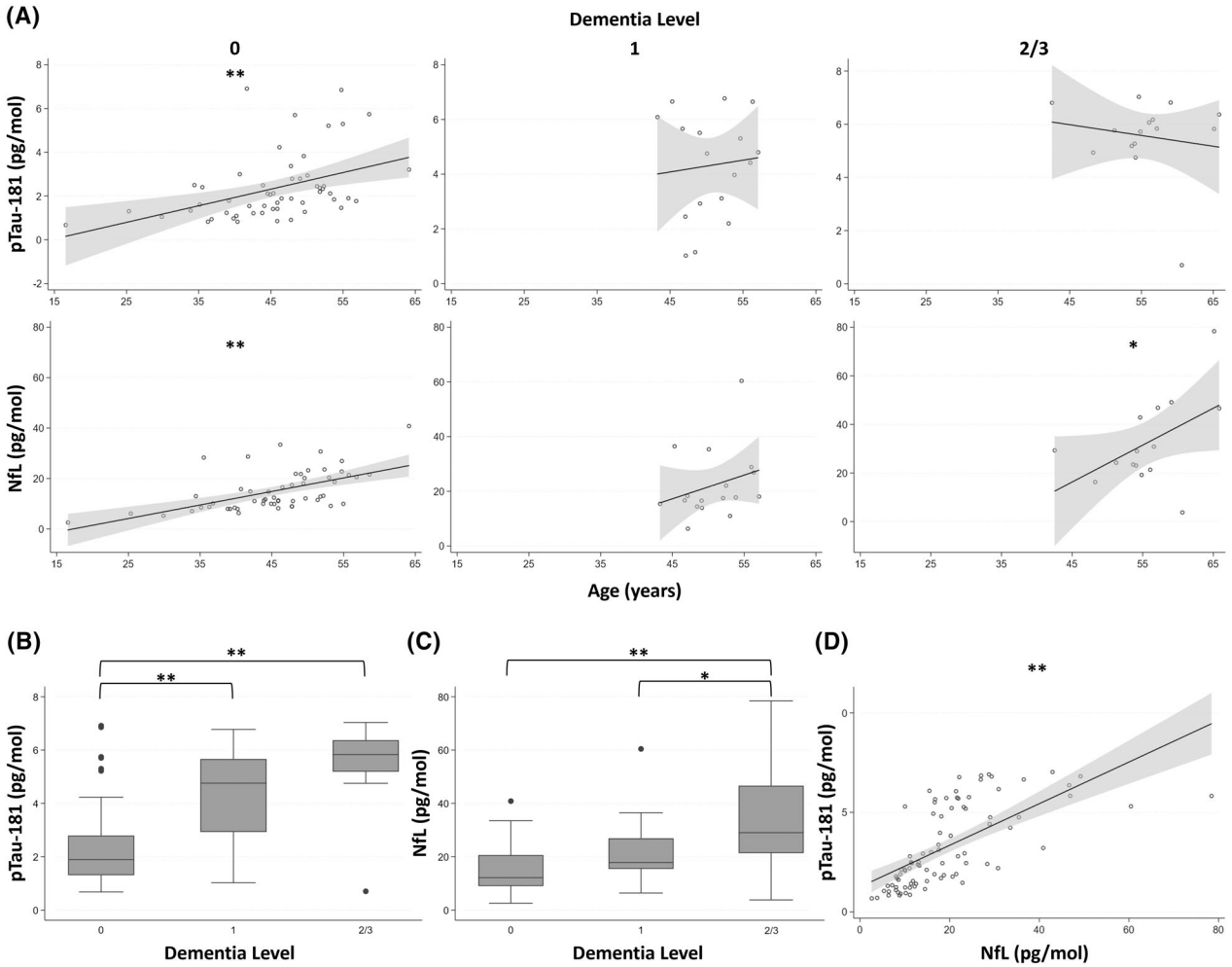

Figure 3. Blood phosphorylated tau 181 (pTau-181) and neurofilament light chain (NfL) levels are significantly correlated with age, dementia level, and each other. (A) Individuals with cognitive impairment (dementia levels >0) have significantly higher levels of pTau-181 and NfL than cognitively stable individuals, when adjusted for age and sex. Age is significantly associated with both biomarker levels in cognitively stable individuals, and with NfL levels in moderate-advanced dementia (dementia level 2/3). (B) pTau-181 levels are significantly higher in mild cognitive impairment and dementia compared to cognitively stable individuals, whereas (C) NfL levels are significantly higher in dementia compared to both mild cognitive impairment and cognitively stable individuals. (D) pTau-181 levels are significantly associated with NfL levels after adjusting for age, sex, and dementia level. *$p < 0.05$, **$p < 0.001$.

Tukey post hoc test showed significantly different pTau-181 levels between CS and both MCI and dementia, but not between MCI and dementia (pTau-181: CS vs. MCI: $t = 4.50$, $p = 6.4 \times 10^{-5}$; CS vs. dementia: $t = 6.95$, $p = 2.5 \times 10^{-9}$; MCI vs. dementia: $t = 2.19$, $p = 0.08$; Fig. 3B). Meanwhile, NfL levels were significantly different in dementia compared with both CS and MCI, but not between CS and MCI (NfL: CS vs. MCI: $t = 2.28$, $p = 0.06$; CS vs. dementia: $t = 5.29$, $p = 2.9 \times 10^{-6}$; MCI vs. dementia: $t = 2.56$, $p = 0.03$; Fig. 3C). pTau-181 and NfL levels were significantly associated with each other, after controlling for age, sex, and dementia level ($F_{(1,82)} = 20.37$, $p = 2.1 \times 10^{-5}$, $\eta_p^2 = 0.20$; Fig. 3D).

Significant negative correlations were also found between both blood biomarkers and total brain volume (pTau-181: $F_{(1,82)} = 19.19$, $p = 3.5 \times 10^{-5}$, $\eta_p^2 = 0.19$; NfL: $F_{(1,82)} = 9.53$, $p = 0.0028$, $\eta_p^2 = 0.10$) and total GM volume (pTau-181: $F_{(1,82)} = 6.47$, $p = 0.013$, $\eta_p^2 = 0.07$; NfL: $F_{(1,82)} = 15.97$, $p = 0.00014$, $\eta_p^2 = 0.16$), whereas total WM volume was only negatively associated with pTau-181 (pTau-181: $F_{(1,82)} = 4.53$, $p = 0.036$, $\eta_p^2 = 0.05$; NfL: $F_{(1,82)} = 0.25$, $p = 0.622$) after adjusting for age, sex, and TIV.

When correlated with GM volume using whole-brain VBM, pTau-181 was found to be negatively associated with GM volume in bilateral hippocampus (left

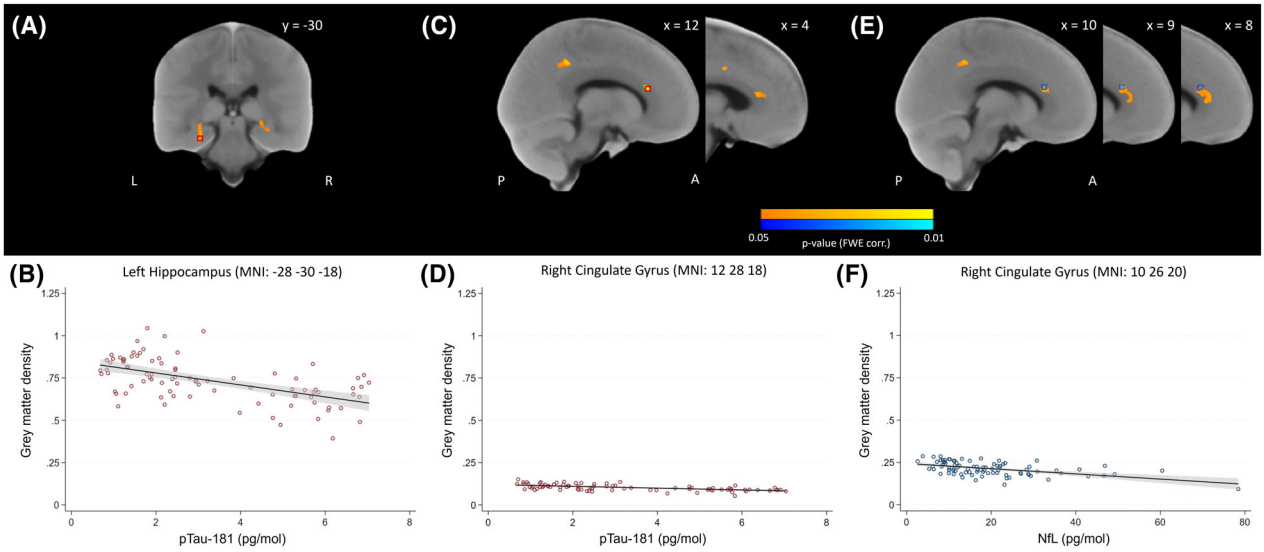

Figure 4. VBM analysis of gray matter from CT scans demonstrates a significant negative association between blood biomarkers and tissue volume in individuals with Down syndrome. Higher levels of blood phosphorylated tau 181 (pTau-181) are significantly associated with lower gray matter volume in (A) the bilateral hippocampi as shown in (B) at the local peak voxel (indicated by the red box in (A), MNI: −28 −30 −18), and in (C) the right anterior and posterior cingulate cortices. (D) Gray matter volume at the global peak voxel (indicated by the red box in (C), MNI: 12 28 18) plotted against pTau-181. (E) Higher blood neurofilament light chain (NfL) levels were significantly associated with lower gray matter volume in the right anterior cingulate cortex, overlapping with the pTau-181 peak cluster (NfL cluster in blue, pTau-181 clusters in orange; the color bars indicate the whole-brain family-wise error (FWE)-corrected *p*-value for each effect in their respective colors). (F) Gray matter volume at the global peak voxel (indicated by the blue box in (E), MNI: 10 26 20) plotted against NfL. Clusters are significant at $p < 0.05$, FWE-corrected. All comparisons were corrected for age, sex, and total intracranial volume.

hippocampus cluster peak: MNI: −28 −30 −18, $Z = 5.14$, $t = 5.60$, FWE-corrected $p = 0.014$; right hippocampus cluster peak: MNI: 24 −34 −10, $Z = 5.05$, $t = 5.49$, FWE-corrected $p = 0.021$; Fig. 4A,B), and in the right anterior and posterior cingulate cortices (anterior cingulate cortex (ACC) cluster peak: MNI: 12 28 18, $Z = 5.82$, $t = 6.49$, FWE-corrected $p < 0.001$; posterior cingulate cortex (PCC) cluster peak: MNI: 14 −44 42, $Z = 5.40$, $t = 5.94$, FWE-corrected $p = 0.002$; Fig. 4C,D). NfL levels were negatively correlated with GM volume in the right ACC (MNI: 10 26 20, $Z = 5.38$, $t = 5.91$, FWE-corrected $p = 0.005$), overlapping with the pTau-181 global peak cluster (Fig. 4E,F). No significant voxel-wise effects were found between biomarker levels and WM volume.

Discussion

In DS adults with and without AD-type dementia, CTseg, a novel open-source automated brain CT segmentation tool, was employed to identify how GM and WM volumes are related to the clinical stage of dementia and to plasma biomarkers of neurodegeneration. Increasing dementia severity was associated with reduced GM volume in the medial temporal lobe, in keeping with MRI-based reports of hippocampal and amygdala volumes in adults with DS being particularly compromised in those with dementia.[43] The same test on WM revealed volume loss in the superior longitudinal fasciculus, primarily right-sided, and associated with dysconnection of lateral temporal GM. Plasma pTau-181 levels correlated negatively with GM volume in hippocampus, and both pTau-181 and NfL levels were inversely associated with anterior cingulate GM volume.

Our findings align with those of Teipel et al., who observed regional GM volume decreases with advancing age in bilateral parietal and frontal cortices and the right parahippocampal gyrus using VBM analysis.[44] Interestingly, these reductions were unrelated to general cognitive function. GM volume was relatively preserved in the anterior cingulate gyrus in adults with DS without dementia in their study. However, when analyzing this region in patients with mild cognitive decline and symptomatic dementia, we found that its GM volume is particularly related to pTau-181 and NfL levels and dementia severity. A similar observation was also reported by Sabbagh et al., who documented higher florbetapir SUVRs in the DS population than in controls specifically in the vicinity of posterior and anterior cingulate, precuneus, parietal, temporal, frontal, and striatal regions,[45] all of which are

findings that hold a similar pattern to those observed in the clinical and preclinical stages of autosomal dominant AD in previously published reports.[46] In a detailed MRI study of changes in cortical thickness and subcortical volumes in biomarker-defined DS groups ([11C]-Pittsburgh compound B (PIB)-positive versus PIB-negative subjects), Annus et al. observed cortical thinning in adults with PIB-positive DS, particularly marked in the right hemisphere, at the level of the lateral parieto-temporo-occipital cortex and in the medial posterior cingulate and precuneal cortices, analogous to that observed in sporadic and familial AD,[47] which is consistent with the most affected areas in the dysconnectome analysis in our study. Finally, our results also concur with recent MRI-based studies in adults with DS, which identified significant volumetric reductions in the substantia innominata region of the basal forebrain, hippocampus, lateral temporal cortex, and left arcuate fasciculus.[48] Hence, though a direct comparison between CT and MRI voxel-based morphometry is still lacking, we have observed a significant and consistent concordance between our findings and those of previous MRI-based studies.

The relationship between dementia severity and GM volume is further supported by their correlation to pTau-181 and NfL levels, which have already been shown to correlate with clinical stage of dementia by Fortea et al. and Lleó et al. in previous cross-sectional and longitudinal evaluations of cohorts of adults with DS.[8,14,49]

In addition, CTseg enabled the study of WM integrity in adults with DS. The greater regional WM abnormality observed in both parietal and occipitotemporal regions, with right-lateralization in the superior and inferior longitudinal fasciculi is consistent with previous diffusion tensor imaging-based reports in adults with DS with and without AD.[50] WM measures derived from diffusion-weighted MRI are related to amyloid levels in nondemented individuals with DS.[51] In DS individuals with MCI and dementia, fractional anisotropy and mean diffusivity were reduced relative to nondemented individuals, with effects primarily localized to frontal and cingulate tracts.[34] This contrasts with the more posterior WM effects we observed with increasing dementia level in our cohort. DS patients are known to have prominent cerebral amyloid angiopathy (CAA) due to the excessive production of Aβ.[5] In non-DS CAA, postmortem and imaging studies show a posterior lobar predominance (parietooccipital) of CAA-related vascular pathology.[52,53] In view of the posterior predominance of the white matter volume reductions observed here in DS dementia, we suggest that this could be attributable to CAA. In support of this suggestion, nonhemorrhagic brain injury in CAA includes white matter hyperintensities, cerebral microinfarcts, and structural disconnection.[54,55] In keeping with the latter, our dysconnectome analysis indicated that gray matter volume loss in the right lateral temporal cortex can be explained by white matter dysconnection.

Our study has several strengths. Ours is one of the largest published cohorts dedicated to the study of AD in DS, even after accounting for losses in the final analysis, with the advantage that we evaluated adults along the entire spectrum of intellectual disability, who are generally not included in research studies because they require some degree of collaboration from the participants. This feature should increase the power and external validity of the study. In addition, objective variables such as plasma biomarker levels have been used to complement the subjective assessment made by clinicians. The results of CT analysis have also been obtained in an automated and objective manner, with minimal intervention and dispensing with visual scales. Moreover, we have sought to control for possible confounding variables by using a multivariate statistical analysis in all cases. Our results may be particularly valuable to people with DS and their families in resource-limited settings, where access to CT might be easier or cheaper than to MRI. They may also be applicable to individuals who cannot collaborate with the strict positional requirements of MRI, as CT is significantly quicker and less demanding in this regard. We acknowledge that CT could be considered a source of additional, non-negligible external irradiation; however, it should be noted that the incidence of AD only starts to increase after the age of 40 and that the incidence of solid tumors in the adult DS population is extremely low, and significantly lower than that of the general population.[56] It is our hope that these reasons may help outweigh the potential concerns raised due to the risk of irradiation associated with this technique. Finally, although the etiology of cognitive decline in other developmental disorders may pose a broader differential diagnosis than in the DS population, we believe that our results lend support to promoting research into the validity of this tool in other populations for which obtaining MRI imaging might prove equally challenging.

While our findings open the path to several potential applications of CT in the evaluation of cognitive decline, both in adults with DS and in other vulnerable populations, some limitations warrant consideration and preliminary steps need to be taken before this tool is more widely implemented. First, we acknowledge that a head-to-head, noninferiority study against MRI would be necessary to validate our preliminary findings. A longitudinal evaluation of adults with DS using both techniques further strengthened using plasma AD biomarkers would clarify the potential prognostic value of our results. Ours was a cross-sectional, single-center study, which should not be used to reach generalizable conclusions, but rather

to generate new hypotheses and confirm the validity of this line of research. Given the retrospective nature of the study, classification of dementia was done without the most specific clinical tools, although in the analysis we found a good correlation between dementia severity and plasma biomarker levels. Furthermore, many individuals lacked information on their baseline functionality and/or degree of intellectual disability, so we had to rely on indirect caregiver reports. It would have been interesting to include some variables not collected in the medical records, such as hand dominance, whose relationship with the lateralization of WM findings in the VBM analysis could have been explored. Lastly, more than 18% of the initially selected participants had to be excluded due to faulty scans, which could lead to selection bias; however, no significant differences were observed in the characteristics of the excluded individuals from those who were included in the analysis.

In summary, our results show that a volumetric assessment of CT scans using CTseg has potential utility for characterizing AD morphometric changes in adults with DS, a difficult group to study with other imaging techniques due to practical limitations. Any diagnostic aid would obviously require normative volumetric values for comparison or require longitudinal study to detect atrophy in regions shown to discriminate between individuals with dementia vs. those without. GM volume in the bilateral parahippocampal gyri, extending into hippocampus and amygdalae, and parietal and occipito temporal WM reductions, right-lateralized in the superior and inferior longitudinal fasciculi were significantly negatively correlated with clinical stage of dementia. These findings open an avenue for potential new applications of CT in the evaluation of brain atrophy, both in DS and other vulnerable populations, or in resource-limited settings where CT is more readily available than other imaging modalities.

Author Contributions

Manuscript concept and design: BSM, BAS, PN, DRA. Data collection: BSM, GM, FM, DRA. Data analysis and interpretation: LZ, BAS, BSM, DRA, MB, JA, PN. Manuscript drafting and revision: LZ, BAS, BSM, DRA. Approval of the final version: All.

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Conflict of Interest

Nothing to report.

References

1. Real de Asúa D, Quero M, Moldenhauer F, Suárez C. Clinical profile and main comorbidities of Spanish adults with Down syndrome. Eur J Intern Med. 2015;26(6): 385-391.
2. Iulita MF, Garzón Chavez D, Klitgaard Christensen M, et al. Association of Alzheimer disease with life expectancy in people with Down syndrome. JAMA Netw Open. 2022;5:e2212910. doi:10.1001/jamanetworkopen.2022.12910
3. McCarron M, McCallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. J Intellect Disabil Res. 2017;61:843-852.
4. Lautarescu BA, Holland AJ, Zaman SH. The early presentation of dementia in people with Down syndrome: a systematic review of longitudinal studies. Neuropsychol Rev. 2017;27:31-45.
5. Ballard C, Mobley W, Hardy J, Williams G, Corbett A. Dementia in Down's syndrome. Lancet Neurol. 2016;15 (6):622-636.
6. Lott IT, Head E. Dementia in Down syndrome: unique insights for Alzheimer disease research. Nat Rev Neurol. 2019;15:135-147.
7. Fortea J, Carmona-Iragui M, Benejam B, et al. Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet Neurol. 2018;17:860-869.
8. Lleó A, Zetterberg H, Pegueroles J, et al. Phosphorylated tau181 in plasma as a potential biomarker for Alzheimer's disease in adults with Down syndrome. Nat Commun. 2021;12(1):4304.
9. Neale N, Padilla C, Mascarenhas Fonseca L, et al. Neuroimaging and other modalities to assess Alzheimer's disease in Down syndrome. Neuroimage Clin. 2018;17:263-271.
10. Head E, Helman AM, Powell D, Schmitt FA. Down syndrome, beta-amyloid and neuroimaging. Free Radic Biol Med. 2018;114:102-109.
11. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with

Down syndrome: a genetic form of dementia. Lancet Neurol. 2021;20:930-942.
12. Hithersay R, Hamburg S, Knight B, Strydom A. Cognitive decline and dementia in Down syndrome. Curr Opin Psychiatry. 2017;30:102-107.
13. Benejam B, Videla L, Vilaplana E, et al. Diagnosis of prodromal and Alzheimer's disease dementia in adults with Down syndrome using neuropsychological tests. Alzheimers Dement (Amst). 2020;12:e12047. doi:10.1002/dad2.12047
14. Carmona-Iragui M, Santos T, Videla S, et al. Feasibility of lumbar puncture in the study of cerebrospinal fluid biomarkers for Alzheimer's disease in subjects with Down syndrome. J Alzheimers Dis. 2017;55(4):1489-1496.
15. Fortea J, Vilaplana E, Carmona-Iragui M, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet. 2020;395(10242):1988-1997.
16. McCollough CH, Bushberg JT, Fletcher JG, Eckel LJ. Answers to common questions about the use and safety of CT scans. Mayo Clin Proc. 2015;90(10):1380-1392.
17. Rose M, Scharf S. Is there any role for computed tomography measurements of medial temporal lobe atrophy in dementia? A review of the literature and case series from a memory clinic. Intern Med J. 2008;38:136-139.
18. Zhang Y, Londos E, Minthon L, et al. Usefulness of computed tomography linear measurements in diagnosing Alzheimer's disease. Acta Radiol. 2008;1:91-97.
19. Olesen PJ, Guo X, Gustafson D, et al. A population-based study on the influence of brain atrophy on 20-year survival after age 85. Neurology. 2011;76:879-886.
20. Bin Zahid A, Mikheev A, Srivatsa N, Babb J, Samadani U, Rusinek H. Accelerated brain atrophy on serial computed tomography: potential marker of the progression of Alzheimer disease. J Comput Assist Tomogr. 2016;40(5):827-832.
21. Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelsø C. Estimated ventricle size using Evans index: reference values from a population-based sample. Eur J Neurol. 2017;24(3):468-474.
22. Del Brutto OH, Mera RM, Zambrano M, Costa AF. The value of the Evans and bicaudate indices for predicting poor cognitive performance and central atrophy. Results from the Atahualpa Project. J Clin Neurosci. 2019;59:245-247.
23. Lawlor BA, McCarron M, Wilson G, McLoughlin M. Temporal lobe-oriented CT scanning and dementia in Down's syndrome. Int J Geriatr Psychiatry. 2001;16:427-429.
24. Lott IT, Lai F. Dementia in Down's syndrome: observations from a neurology clinic. Appl Res Ment Retard. 1982;3:233-239.
25. Devinsky O, Sato S, Conwit RA, Schapiro MB. Relation of EEG alpha background to cognitive function, brain atrophy, and cerebral metabolism in Down's syndrome. Age-specific changes. Arch Neurol. 1990;47:58-62.
26. Pearlson GD, Warren AC, Starkstein SE, et al. Brain atrophy in 18 patients with Down syndrome: a CT study. Am J Neuroradiol. 1990;11(4):811-816.
27. Schapiro MB, Haxby JV, Grady CL. Nature of mental retardation and dementia in down syndrome: study with PET, CT, and neuropsychology. Neurobiol Aging. 1992;13(6):723-734.
28. Schapiro MB, Luxenberg JS, Kaye JA, Haxby JV, Friedland RP, Rapoport SI. Serial quantitative CT analysis of brain morphometrics in adult Down's syndrome at different ages. Neurology. 1989;39(10):1349-1353.
29. Brudfors M, Balbastre Y, Flandin G, Nachev P, Ashburner J. Flexible Bayesian modelling for nonlinear image registration. Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part III. 2020:253-263. doi:10.1007/978-3-030-59716-0_25
30. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-446.
31. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes. Diabetes Care. 2021;44:S15-S33. doi:10.2337/dc21-S002
32. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
33. Deb S, Hare M, Prior L, Bhaumik S. Dementia screening questionnaire for individuals with intellectual disabilities. Br J Psychiatry. 2007;190:440-444. doi:10.1192/bjp.bp.106.024984
34. Rosas HD, Hsu E, Mercaldo ND, et al. Alzheimer-related altered white matter microstructural integrity in Down syndrome: a model for sporadic AD? Alzheimers Dement (Amst). 2020;12:e12040. doi:10.1002/dad2.12040
35. Burt DB, Aylward EH. Test battery for the diagnosis of dementia in individuals with intellectual disability. Working group for the establishment of criteria for the diagnosis of dementia in individuals with intellectual disability. J Intellect Disabil Res. 2000;44(Pt 2):175-180.
36. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. JAMA Neurol. 2019;76(7):791-799.
37. Moscoso A, Grothe MJ, Ashton NJ, et al. Longitudinal associations of blood phosphorylated Tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. JAMA Neurol. 2021;78(4):396-406.
38. Bodensteiner JB, Gay CT, Marks WA, Hamza M, Bradley Schaefer G. Mega cisterna magna: a marker for

maldevelopment of the brain? Pediatr Neurol. 1988;4:284-286.
39. Lai TH, Cheng YM, Chang FM. Prenatal diagnosis of trisomy 21 in a fetus with an enlarged cisterna magna. Ultrasound Obstet Gynecol. 2002;20:413-416.
40. Jha A, Teotonio R, Smith AL, et al. Metabolic lesion-deficit mapping of human cognition. Brain. 2020;143 (3):877-890.
41. Thiebaut de Schotten M, Foulon C, Nachev P. Brain disconnections link structural connectivity with function and behaviour. Nat Commun. 2020;11(1):1-8.
42. Foulon C, Cerliani L, Kinkingnéhun S, et al. Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. Gigascience. 2018;7(3):1-17.
43. Pearlson GD, Breiter SN, Aylward EH, et al. MRI brain changes in subjects with Down syndrome with and without dementia. Dev Med Child Neurol. 1998;40 (5):326-334.
44. Teipel SJ, Alexander GE, Schapiro MB, Möller HJ, Rapoport SI, Hampel H. Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. Brain. 2004;127(Pt 4):811-824.
45. Sabbagh MN, Chen K, Rogers J, et al. Florbetapir PET, FDG PET, and MRI in Down syndrome individuals with and without Alzheimer's dementia. Alzheimers Dement. 2015;11(8):994-1004.
46. Fleisher AS, Chen K, Quiroz YT, et al. Florbetapir PET analysis of amyloid-β deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study. Lancet Neurol. 2012;11 (12):1057-1065.
47. Annus T, Wilson LR, Acosta-Cabronero J, et al. The Down syndrome brain in the presence and absence of fibrillar β-amyloidosis. Neurobiol Aging. 2017;53: 11-19.
48. Pujol J, Fenoll R, Ribas-Vidal N, et al. A longitudinal study of brain anatomy changes preceding dementia in Down syndrome. Neuroimage Clin. 2018;18:160-166.
49. Carmona-Iragui M, Alcolea D, Barroeta I, et al. Diagnostic and prognostic performance and longitudinal changes in plasma neurofilament light chain concentrations in adults with Down syndrome: a cohort study. Lancet Neurol. 2021;20(8):605-614.
50. Powell D, Caban-Holt A, Jicha G, et al. Frontal white matter integrity in adults with Down syndrome with and without dementia. Neurobiol Aging. 2014;35(7):1562-1569.
51. Bazydlo AM, Zammit MD, Wu M, et al. White matter microstructure associations to amyloid burden in adults with Down syndrome. Neuroimage Clin. 2022;33:102908. doi:10.1016/j.nicl.2021.102908
52. Nelson PT, Pious NM, Jicha GA, et al. APOE-ε2 and APOE-ε4 correlate with increased amyloid accumulation in cerebral vasculature. J Neuropathol Exp Neurol. 2013;72(7):708-715.
53. Thanprasertsuk S, Martinez-Ramirez S, Pontes-Neto OM, et al. Posterior white matter disease distribution as a predictor of amyloid angiopathy. Neurology. 2014;83 (9):794-800.
54. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw S. Cerebral amyloid angiopathy and Alzheimer disease—one peptide, two pathways. Nat Rev Neurol. 2019;16(1):30-42.
55. Reijmer YD, Fotiadis P, Martinez-Ramirez S, et al. Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. Brain. 2015;138(1):179-188.
56. Baksh RA, Pape SE, Chan LF, et al. Multiple morbidity across the lifespan in people with Down syndrome or intellectual disabilities: a population-based cohort study using electronic health records. Lancet Public Health. 2023;8(6):e453-e462.

