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Florbetapir PET, FDG PET, and MRI in Down syndrome individuals with and without Alzheimer's dementia

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Abstract

Introduction: Down syndrome (DS) is associated with amyloid b (Ab) deposition.
Methods: We characterized imaging measurements of regional fibrillar Ab burden, cerebral metabolic rate for glucose (rCMRgl), gray matter volumes (rGMVs), and age associations in 5 DS with dementia (DS/AD1), 12 DS without dementia (DS/AD2), and 9 normal controls (NCs).
Results: There were significant group differences in mean standard uptake value ratios (SUVRs) for florbetapir with DS/AD1 having the highest, followed by DS/AD2, followed by NC. For [18F]-fluorodeoxyglucose positron emission tomography, posterior cingulate rCMRgl in DS/AD1 was significantly reduced compared with DS/AD2 and NC. For volumetric magnetic resonance imaging (vMRI), hippocampal volumes were significantly reduced for the DS/AD1 compared with DS/AD2 and NC. Age-related SUVR increases and rCMRgl reductions were greater in DS participants than in NCs.
Discussion: DS is associated with fibrillar Ab, rCMRgl, and rGMV alterations in the dementia stage and before the presence of clinical decline. This study provides a foundation for the studies needed to inform treatment and prevention in DS.

Keywords: Down syndrome; Florbetapir; FDG-PET; PET; Dementia; Alzheimer's disease; Imaging

1. Introduction

Down syndrome (DS) is characterized by partial to complete trisomy of chromosome 21, developmental delay, and other developmental abnormalities. DS is also associated with a significant increase in the risk of Alzheimer's disease (AD) [1]. This increased AD risk is generally believed to be because of trisomy of the amyloid precursor protein (APP) gene, which resides on the distal arm of chromosome 21. Presumably, the possession of an extra copy of the APP gene induces APP overexpression, accounting for the virtually universal presence of fibrillar amyloid β (Aβ) peptide neuropathology in autopsied DS patients over the age of 35 years [2,3].

Conflicts of Interest: All authors declare that they have no material conflicts of interest with respect to the present study, as defined by the ICMJE guidelines.

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AD dementia occurs in approximately 10% to 25% of persons with DS in their 40s, 20% to 50% of those in their 50s, and 60% to 75% of those over the age of 60 years [2–4]. Due especially to improvements in the treatment of DS-related cardiac anomalies, more persons with DS are living to older ages [5]. Given their increased risk for AD, there is a critical and largely unmet need to characterize the clinical and biomarker changes associated with the preclinical and clinical stages of AD in DS individuals.

To date, the best established brain imaging methods for the preclinical and clinical evaluation of AD include positron emission tomography (PET) measurements of fibrillar Aβ burden, reductions in regional PET measurements of the cerebral metabolic rate for glucose (CMRgl), and magnetic resonance imaging (MRI) measurements of regional and whole-brain volumes. These imaging techniques have been used successfully in a small number of studies to detect and track characteristic brain alterations in DS [6–17]. To our knowledge, although, no reported studies have yet characterized all three measurements in the assessment of DS patients, and only one has reported findings in DS individuals with (DS/AD+) and without AD dementia (DS/AD−) [6].

The primary objective in this small cross-sectional study was to use PET measurements of fibrillar Aβ burden, PET measurements of regional CMRgl, and MRI measurements of hippocampal and regional gray matter volumes to identify age-related brain imaging alterations associated with preclinical and clinical AD dementia in individuals with DS. Clinical, functional, and neuropsychological findings provided secondary outcomes of interest. These findings could establish a cohort for the longitudinal research of AD biomarker assessments in DS and help set the stage for the evaluation of interventions to treat and prevent AD dementia in this at-risk population.

2. Methods

2.1. Subjects

Five DS participants with the clinical diagnosis of Alzheimer's dementia (DS/AD+), 12 DS participants without the clinical diagnosis of Alzheimer's dementia (DS/AD−), and 9 normal controls (NCs) were enrolled in the study (Table 1). Participants and/or their caregivers/legal guardians provided informed consent, and the participants were studied under protocols approved by our organization's Institutional Review Board. DS/AD+ participants met *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)* and National Institute on Aging (NIA)-Alzheimer's Association diagnostic criteria for AD dementia by informant report of progressive cognitive decline with clear historical evidence of functional decline from premorbid abilities [18]. DS/AD− participants had neither evidence of progressive cognitive nor functional decline.

"Although the standard diagnostic criteria from the *DSM-IV* are not modified specifically for individuals with intellectual disability, it is stated within these criteria that change from a previous level of function is required for a diagnosis. Specifically, "The cognitive deficits in Criteria A1 and A2 (memory, language, executive functioning, etc.) each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning". The study lead here is a neurologist with a large number of patients in his practice and is familiar with premorbid deficits in DS (on average). We were careful to query parents/caregivers about noted changes in their daily life, much like is emphasized in a number of dementia screeners for ID currently in development (NTG screener from the National Task Group on Intellectual Disabilities and Dementia Practices—not available at the start of this study)."

The DS/AD+ and DS/AD− subjects had no history of epilepsy or seizures and their neurological examinations were nonfocal. NC participants were cognitively normal, without trisomy 21, and matched for age to the DS/AD− group. All DS subjects were confirmed by chromosome testing to have trisomy 21. Exclusion criteria included a lifetime history of another neurodegenerative disease, vascular dementia, or psychiatric disorders. Except as noted later, a medical history, physical examination, clinical evaluation, functional and neuropsychological testing, chromosome testing, and brain imaging were performed in all subjects. One DS/AD− participant withdrew consent after florbetapir PET scan and was not subsequently assessed by MRI. An additional DS/AD+ subject, who was severely impaired and agitated during imaging procedures, was excluded from the study due to extremely poor PET and MRI imaging quality. All other participants were evaluated with both florbetapir PET and MRI.

2.2. Clinical, functional and neuropsychological tests

All participants completed the Dementia Questionnaire for People with Learning Disabilities (DLD) [19], the Mini-Mental State Examination (MMSE) [20], the Brief Praxis Test [21], the severe impairment battery (SIB) [22], and the Vineland Adaptive Behavior Scale, second edition (see Table 1) [23]. Premorbid IQ estimation was not available from records, nor was it assessed as part of the study.

2.3. [18F] Florbetapir PET acquisition and preprocessing

Florbetapir PET imaging was used to assess mean cortical-to-pontine florbetapir standard uptake value ratios (SUVRs) as the primary outcome measure of fibrillar Aβ burden. As in our previous florbetapir study [7], participants underwent a 10-minute emission scan 50 minutes after intravenous injection of 10 mCi (370 MBq) of [18F] florbetapir. Scans were performed on a Siemens Biograph XVI HiRez PET/CT scanner. The images were reconstructed using an iterative reconstruction algorithm (4 iterations, 16 subsets), with a 5-mm full-width at half-maximum Gaussian filter, and were corrected for radiation attenuation and scatter. If significant patient motion was observed, another 10-minute scan was acquired.

Table 1
Study subject demographic characteristics, clinical and functional ratings, and neuropsychological test scores

	NC	DS/AD−	DS/AD+	Total	*P*-value
N	9	10	5	24	–
Age	36 ± 10	36 ± 12	50 ± 6[‡,§]	39 ± 12	.036
Gender (M/F)	6/3	4/6	2/3	12/12	.37[*], .58[†]
MMSE	29 ± 2	15 ± 6[‡]	11 ± 5[‡]	20 ± 9	<.001
SIB	99 ± 1	87 ± 9[‡]	75 ± 26[‡]	90 ± 14	<.001
BPT	80 ± 0	70 ± 5[‡]	62 ± 17[‡]	73 ± 10	<.001
DLD cognitive	0 ± 0	2 ± 3[‡]	5 ± 1[‡]	2 ± 3	.004
DLD social	2 ± 2	2 ± 3	7 ± 5	4 ± 3	.06
Vineland—receptive	16 ± 0	9 ± 4[‡]	4 ± 4[‡]	11 ± 5	.001
Vineland—expressive	16 ± 0	9 ± 3[‡]	10 ± 6[‡]	11 ± 5	.001
Vineland—written	16 ± 0	6 ± 2[‡]	5 ± 5[‡]	10 ± 6	<.001
Vineland—personal	16 ± 0	8 ± 2[‡]	8 ± 6[‡]	11 ± 5	<.001
Vineland—domestic	16 ± 0	9 ± 3[‡]	8 ± 4[‡]	12 ± 4	<.001
vineland—community	17 ± 0	7 ± 3[‡]	4 ± 3[‡,§]	10 ± 6	<.001
Vineland—interpersonal relationships	16 ± 0	10 ± 2[‡]	10 ± 1[‡]	12 ± 3	<.001
Vineland—play and leisure time	16 ± 0	10 ± 1[‡]	8 ± 3[‡]	12 ± 4	<.001
Vineland—coping skills	16 ± 1	10 ± 5[‡]	10 ± 2[‡]	12 ± 4	<.001

Abbreviations: M/F, male/female; NC, normal control; DS/AD+ and DS/AD−, Down syndrome with and without Alzheimer's disease; MMSE, Mini-Mental State Examination; SIB, severe impairment battery; BPT, Brief Praxis Test; DLD, Dementia Questionnaire for People with Learning Disabilities.

Mean ± SD raw scores are reported for the MMSE, SIB, BPT, and DLD; scaled scores are reported for all Vineland subtests.

*Fisher exact test *P*-value for NC and DS/AD−.

†Fisher exact test *P*-value for NC and DS/AD+. Post hoc group-wise comparisons.

‡Significantly different from NC, $P < .05$.

§Significantly different from DS/AD−, $P < .05$.

SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used to linearly and nonlinearly deform each subject's florbetapir PET image into Montreal Neurological Institute (MNI) standard coordinate space with cubic voxel size of 2 × 2 × 2 mm and to smooth with 5-mm full-width-at-half-maximum Gaussian kernel.

Mean cortical-to-pontine SUVRs were computed using measurements from a pontine region of interest (ROI) using six automatically defined bilateral (frontal, temporal, parietal, anterior cingulate, posterior cingulate [PC], and precuneus) ROIs. Because of increased cerebellar uptake in the clinical stages of autosomal dominant AD [24], another form of AD that, like DS, is associated with genetically driven increases in Aβ production, pons was used as the reference region. SUVRs were typically less than 1.0 because of the relatively high nonspecific binding in pons. In post hoc analyses, SUVRs were characterized in each of the six cortical, thalamic, and striatum ROIs, and patterns of SUVR increases were characterized using the automated brain mapping routine in SPM8.

2.4. [18F]-Fluorodeoxyglucose PET acquisition and preprocessing

[18F]-Fluorodeoxyglucose (FDG)-PET was used to compare regional cerebral glucose metabolism across groups. Because reduced PC CMRgl is a relatively early indicator of AD in patients affected by and at risk for late-onset and autosomal dominant AD dementia [25], data from an automatically defined PC ROI were used as the primary rCMRgl outcome measure. Please note the CMRgl (or rCMRgl) we referred to in this study was a unitless semi-quantitative ratio of the PET counts from target region such as PC ROI over the counts from the whole brain. In this our rCMRgl is SUVR with whole brain as the reference region. Six 5-minute emission frames were acquired on the same PET/CT system 30 minutes after the intravenous administration of 5 mCi of [18F] FDG. FDG PET images were reconstructed, filtered, and corrected for radiation attenuation and scatter using the same procedures used for reconstruction of florbetapir PET images. The six emission frames were aligned and averaged. As with the florbetapir data, SPM8 was used to linearly and nonlinearly deform each subject's averaged FDG PET image into MNI standard coordinate space, to normalize individual images for the variation in whole-brain PET counts using proportionate scaling (i.e., our unitless CMRgl or SUVR) and to smooth with 5-mm full-width-at-half-maximum Gaussian kernel. In post hoc analyses, rCMRgl patterns were compared using the automated brain mapping routine in SPM8 [26].

2.5. MRI data acquisition and preprocessing

FreeSurfer estimated hippocampal volume (relative to intracranial volume, a unitless measure) was the primary MRI outcome measure. MRI was performed using a 1.5-T Signa system (General Electric) and a T1-weighted volumetric pulse sequence (inversion recovery-spoiled gradient recalled echo [IR-SPGR]; repetition time = 33 ms; echo time = 5 ms; $\alpha = 30°$; number of excitations = 1; field of view = 24 cm; 256 × 192 imaging matrix; slice thickness = 1.5 mm; 124 slices; scan time = 13:36 minutes).

A T2-weighted fluid attenuated inversion recovery (FLAIR) image was used to exclude the presence of strokes and edema and a long time echo gradient echo acquisition was used for the assessment of microhemorrhages.

Hippocampal-to-intracranial volume ratios were characterized from bilateral ROIs in each participant's T1-weighted MRI using the FreeSurfer 5.1 software package (http://surfer.nmr.mgh.harvard.edu) [27–29]. All images were visually inspected to verify ROI characterization.

Voxel-wise measurements of regional gray matter volume (rGMV, corrected for total intracranial volume) were determined using the voxel-based morphometry routine and Diffeomorphic Anatomical Registration using Exponential Lie Algebra protocol in SPM8 [30–32]. The gray matter partitions generated by this process in the MNI template space preserve the total amount of tissue from the native space images. This preservation is via voxel-by-voxel multiplication of the determinant of the Jacobian matrix for the nonlinear deformation only. The gray matter map for each subject was smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel. In post hoc analyses, rGMV patterns were compared using the automated brain mapping routine in SPM8.

2.6. Statistical analysis

To compare DS/AD+, DS/AD−, and NC groups, we assessed primary (florbetapir PET, FDG PET, and volumetric MRI) and secondary (clinical examination and functional and neuropsychological testing) outcomes using one-way analyses of variance (ANOVAs). Where dictated by a priori hypotheses, significant outcomes were additionally assessed by between-group t-tests. Each primary outcome measure also was evaluated for its association with age. Here, DS groups were pooled to provide a more complete span of ages, and a general linear model was used to determine whether the slope for a particular variable (plotted against age) deviated significantly from zero. Age-related differences between the DS group as a whole and the NC group were evaluated by comparing the age-associated slopes (age by group interaction) for each variable between groups, the same way as applied in a previous study [33]. Alpha ≤ 0.05 was used for all primary measures. For the post hoc brain mapping analyses, $P \leq .001$, uncorrected for multiple comparisons, was used to provide information about the pattern of between-group differences in each brain imaging measurement. Summary data are given throughout as mean ± standard deviation.

3. Results

Participants' demographic characteristics and clinical, functional, and neuropsychological test scores are shown in Table 1. The AD/DS+ group was significantly older than the DS/AD− and NC groups. As predicted, the DS groups performed significantly less well than the NC group, and the DS/AD+ group performed significantly less well than the DS/AD− group, on most of the clinical and neuropsychological tests.

Fig. 1A shows comparisons on the three primary outcome measures. There were significant group differences in mean cortical-to-pontine SUVRs, with DS/AD+ (1.14 ± 0.13) followed by DS/AD− (0.94 ± 0.07) followed by NC (0.80 ± 0.03) (linear trend ANOVA, $P < 1.0e{-}6$). PC-to-whole-brain CMRgl also differed significantly between the

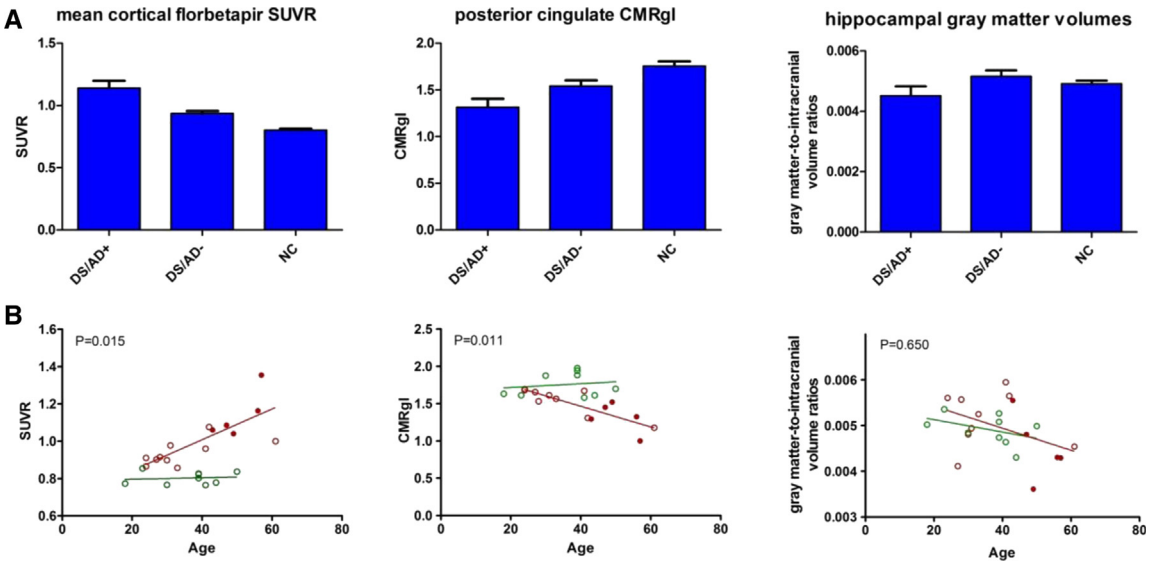

Fig. 1. Mean cortical florbetapir standard uptake value ratio (SUVR), posterior cingulate cerebral metabolic rate for glucose (CMRgl), and hippocampal gray matter volumes. (A) Greater florbetapir mean cortical-to-pons SUVR values for amyloid deposition (left); lower posterior cingulate CMRgl values (middle); and hippocampus gray matter volume (right) in Down syndrome patients with and without Alzheimer's disease (DS/AD+ and DS/AD−), and in normal control (NC). (B) Florbetapir mean cortical-to-pons SUVR values (left) and posterior cingulate CMRgl (middle), but not the hippocampus volume (right), had significantly greater association with age in DS participants (DS and DS/AD combined) than in NC.

groups, with DS/AD+ (1.32 ± 0.20), DS/AD− (1.54 ± 0.18), and NC (1.76 ± 0.16) demonstrating the lowest-to-highest readings, respectively (linear trend ANOVA, $P < .001$). Hippocampal GMVs, however, did not exhibit significant group differences, with similar mean values for DS/AD+ (0.005 ± 0.0007), DS/AD− (0.0052 ± 0.0006), and NC (0.0049 ± 0.00033) (linear trend ANOVA, $P = .12$). Associations between age and the increase in mean cortical SUVR and decline in PC CMRgl were significantly greater in the overall DS group than in the NC group ($P = .015$ and $P = .011$, respectively), whereas the associations between age and hippocampal GMV decline were not ($P = .85$) (Fig. 1B). In post hoc ROI analyses, there were significant between-group florbetapir SUVR differences in the frontal ($P = 1e{-}5$), temporal ($P = 1e{-}6$), parietal ($P = 8e{-}6$), anterior cingulate ($P = 1e{-}6$), PC ($P = 5e{-}6$), precuneus ($P = 2e{-}6$), and striatum ($P = 6e{-}6$) ROIs, and a nonsignificant trend in the thalamic ROI ($P = .054$).

The statistical brain maps in Figs. 2–4 show locations with significantly greater SUVRs, lower regional CMRgl, and lower regional GMV in (a) the DS/AD+ compared with NC group, (b) the DS/AD+ compared with DS/AD group, and (c) the DS/AD− compared with NC group, respectively ($P \leq .001$ in all comparisons).

The DS groups had significantly higher florbetapir SUVRs than the NC group bilaterally in the vicinity of posterior and anterior cingulate, precuneus, parietal, temporal, frontal, and striatal regions (Fig. 2A, row A and C), similar to patterns in the clinical and preclinical stages of late-onset AD in published reports [24,34]. These results were still apparent after controlling for age. The magnitude of increase was significantly greater in DS/AD+ (Fig. 2A, row B).

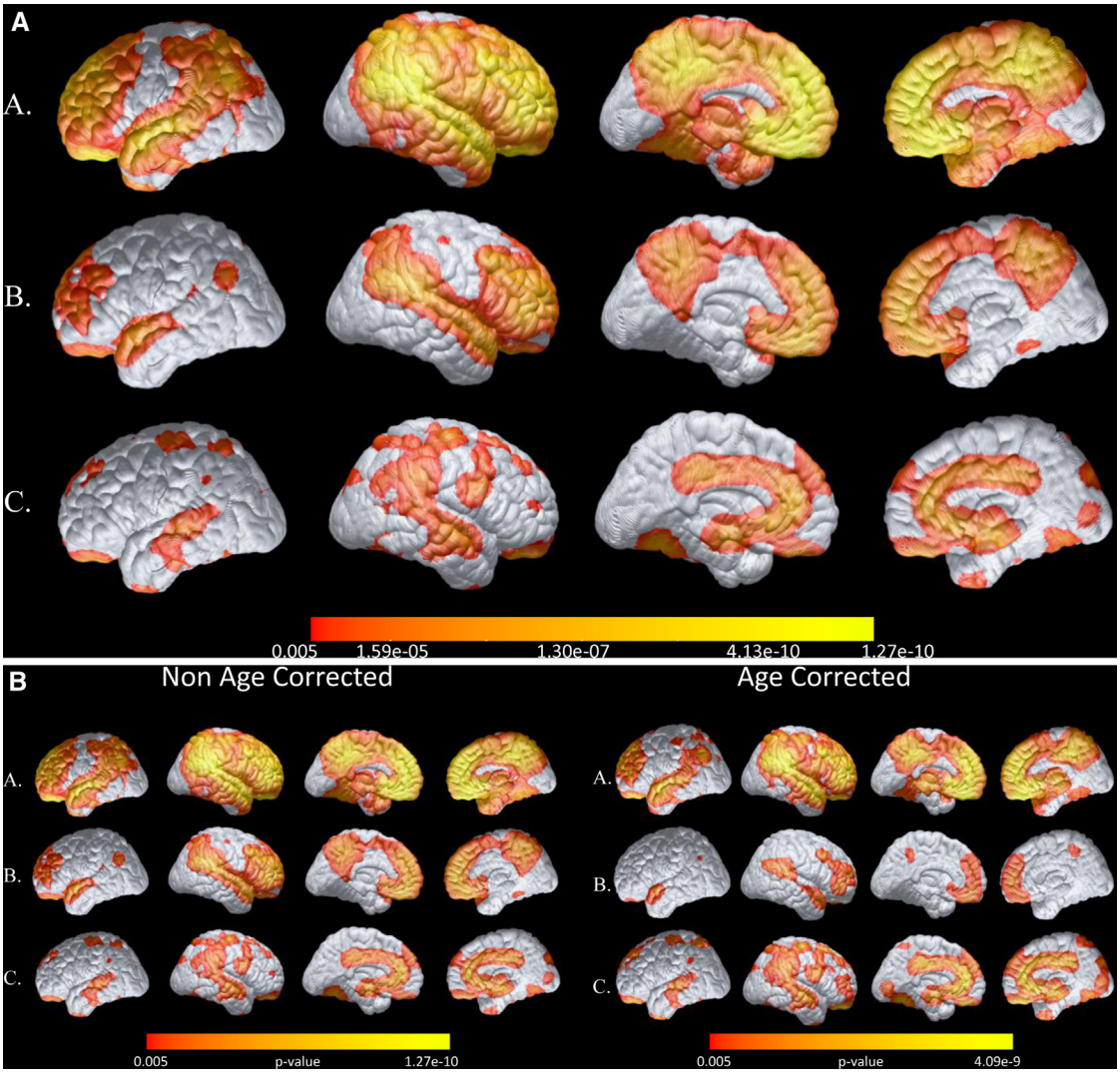

Fig. 2. Statistical brain maps showing significantly greater cerebral-to-pontine florbetapir standard uptake value ratios (SUVRs) in (A) the Down syndrome with Alzheimer's disease (DS/AD+) versus normal control (NC) group, (B) the DS/AD+ versus Down syndrome without AD (DS/AD−) group, and (C) the DS/AD− versus NC group. Significant central metabolic rate for glucose (CMRgl) reductions ($P \leq .001$, uncorrected for multiple comparisons) are projected onto the lateral and medial surfaces of the brain.

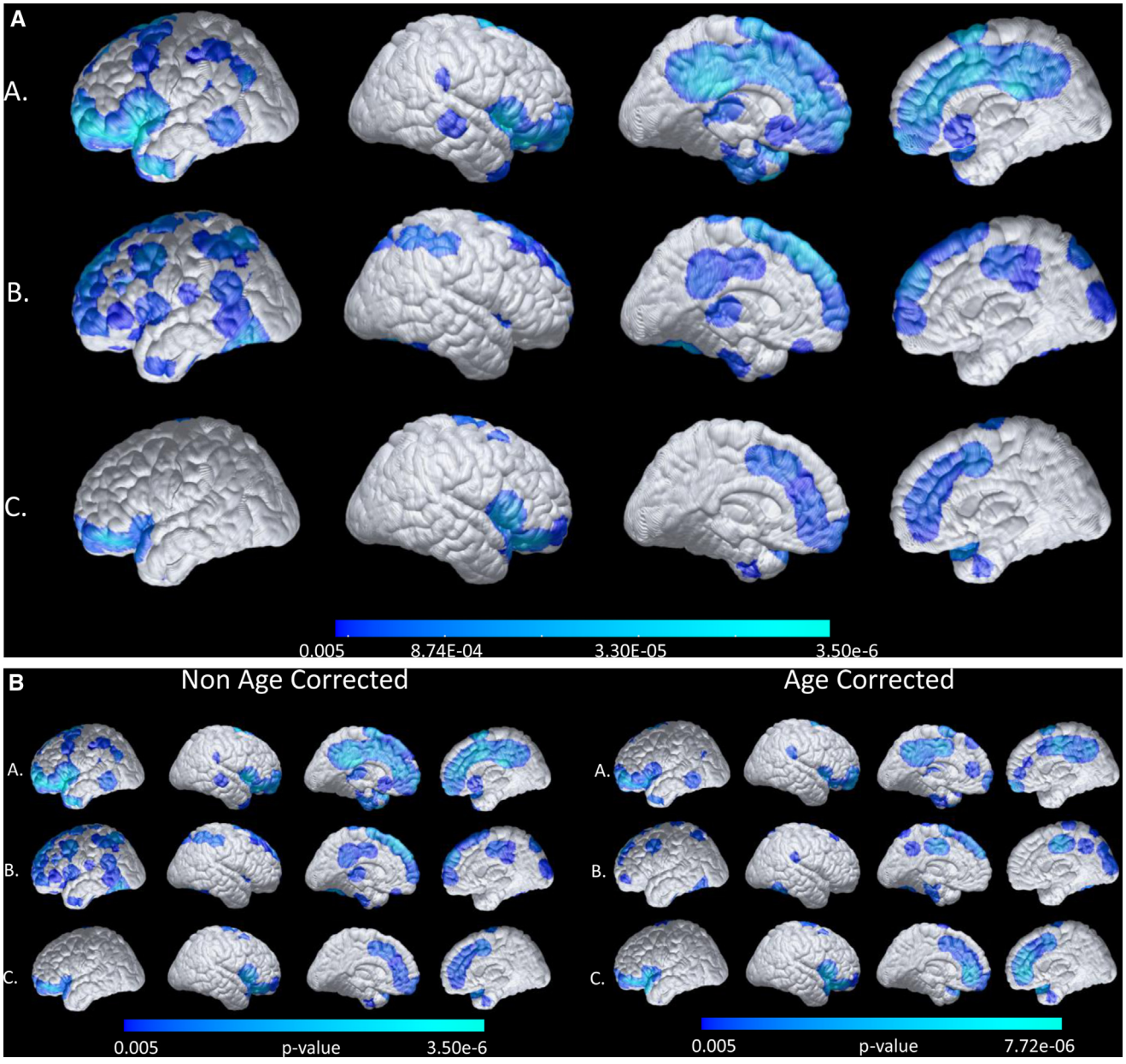

Fig. 3. Statistical brain maps showing significantly lower central metabolic rate for glucose (CMRgl) in (A) the Down syndrome with (DS/AD+) versus normal control (NC) group, (B) the DS/AD+ versus Down syndrome without (DS/AD−) group, and (C) the DS/AD− versus NC group. Significant SUVR increases ($P \leq .001$, uncorrected for multiple comparisons) are projected onto the lateral and medial surfaces of the brain.

The DS/AD+ group was distinguished from the DS/AD− and NC groups by significantly lower CMRgl bilaterally in the vicinity of PC, lateral parietal, and temporal and frontal regions, which have been previously shown to be preferentially affected in the clinical and preclinical stages of late-onset AD (Fig. 3A, Row A and C) [35,36]. The DS/AD+ and DS/AD− groups were also distinguished from the NC group by significantly lower CMRgl in the vicinity of additional medial frontal regions.

The DS/AD+ group had significant regional gray matter reduction compared with NC (Fig. 4A, Row A) and to DS/AD− groups (Fig. 4A, Row B). The most prominent reductions were in bilateral basal, medial, and prefrontal lobes, bilateral temporal lobes, lateral parietal cortex, and precuneus. However, lateral parietal cortex and precuneus changes in the DS/AD+ versus NC comparison became nonsignificant after accounting for age effects. DS/AD− subjects also had lower volumetric MRI measures than NC subjects in the medial, prefrontal, and occipital lobes (Fig. 4A, Row C).

The DS/AD+ group was distinguished from the DS/AD− and NC groups by significantly lower GMV bilaterally in the vicinity of PC, parietal, temporal, and frontal regions, which are preferentially affected by AD [37]. The DS/AD+

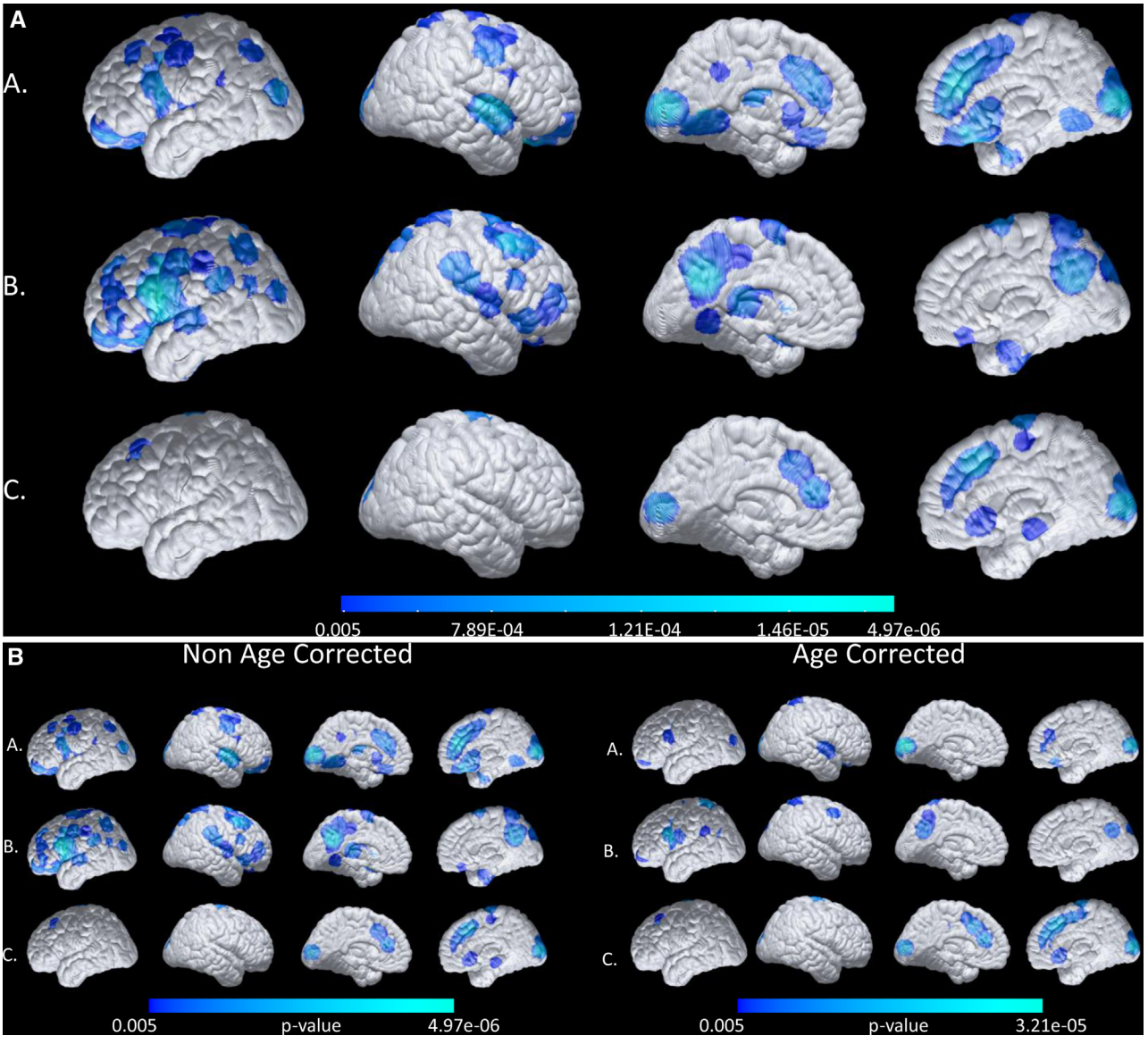

Fig. 4. Statistical brain maps showing significantly lower gray matter volume (GMV) in (A) the Down syndrome with (DS/AD+) versus normal control (NC) group, (B) the DS/AD+ versus Down syndrome without (DS/AD−) group, and (C) the DS/AD− versus NC group. Significant GMV reductions ($P \leq .001$, uncorrected for multiple comparisons) are projected onto the lateral and medial surfaces of the brain.

and DS/AD− groups were also distinguished from the NC group by significantly lower GMV in the vicinity of additional medial frontal regions, which we again postulate to reflect differences in brain development. In addition to the voxel-wise correlation with cog scores, we also examined such correlations for the primary image outcomes (florbetapir, mean cortical SUVR; FDG, posterior cingulate; MRI, hippocampus volume): The correlation is significant for florbetapir SUVR, for FDG-PET CMRgl, but not for hippocampus volume.

Cognitive measures did not differ significantly between DSAD+ and DSAD−. Table 2 summarizes the correlations between cognitive measures and imaging parameters. The SIB appears to correlate better with imaging modalities than other cognitive measures.

4. Discussion

This brain imaging study provides new information about the fibrillar Aβ, CMRgl, and GMV alterations associated with the clinical and preclinical stages of AD in participants with DS. DS subjects had florbetapir PET evidence of fibrillar Aβ burden in the symptomatic dementia stage. Furthermore, fibrillar Aβ was detected in DS subjects without evidence of cognitive decline (DS/AD−) as early as 35 years of age (see Fig. 1). Increases in florbetapir uptake were associated with dementia status and older age. More specifically, florbetapir uptake strongly increases with and correlates with age. DS participants with AD dementia also had lower CMRgl and GMV in brain regions known to be preferentially affected by late-onset AD. Finally, DS

Table 2
Cognitive measures correlating with imaging parameters

		dmr_soc_sum	dmr_cog_sum	sib_tot	vin_comm_dom_ss	vin_gross
Flobetapir MC/pons SUVR	P	.005	.002	1.2e−4	.003	.001
	R	.556	.604	−.706	−.586	−.616
Precuneus/pons CMRgl	P	.021	.058	1.3e−4	.010	.002
	R	−.477	−.402	.714	.537	.605
Precuneus/global MRgl	P	.010	.045	4e−4	.110	.006
	R	−.528	−.422	.676	.351	.554
MRI hippocampus volume	P	.330	.841	.438	.898	.275
	R	−.213	.044	.170	.029	.238

Abbreviations: MC, mean cortical; SUVR, standard uptake value ratios; CMRgl, cerebral metabolic rate for glucose; MRI, magnetic resonance imaging.

participants with and without dementia had lower CMRgl and GMV than NC subjects in additional frontal regions. We believe these latter alterations may reflect differences in brain development.

In this study, we used pons as the reference region for the examination of amyloid deposits measured by florbetapir. Such practice was based on its previous use in the autosomal dominant AD subjects [24]. We felt that given the similarity between PS1 and DS as amyloid overproducing conditions, this methodology was appropriate to use. In addition, neuropathologic studies have suggested the presence of cerebellar amyloid deposition in the clinical stages of early onset amyloid β (Aβ) overproducing syndromes, including autosomal dominant AD mutation carriers and patients with DS. Interestingly, our results showed the greater cerebellar SUVR in DS/AD+ than in DS/AD− or in NC group, and in DS/AD− than in NC. Rather than that, the overall amyloid pattern findings are similar using either Pons or cerebellum as the reference region.

Cognitive measures did not differ significantly between DSAD+ and DSAD−. This is likely because of smaller sample size and the possibility that the tests were not as sensitive as the neuroimaging based biomarkers. Our study was not designed to examine the difference between DSAD+/− subjects. Rather one of our focuses was to examine the earliest changes we can detect in DS subjects compared with the NC (the age trajectory of various biomarkers).

A small number of published studies have used PET to characterize fibrillar Aβ burden in persons with DS [6–9]. For instance, Handen et al. used Pittsburgh Compound B (PiB) PET to study seven 20- to 44-year-old DS/AD− participants and found evidence of fibrillar Aβ burden in the two individuals who were at least 38 years of age [9]. Landt et al. used PiB PET to study 5 DS/AD+ participants, 4 DS/AD− participants, and 14 NCs and found evidence of fibrillar Aβ burden after the age of 45 years [6]. Both PiB PET studies found preferential evidence of fibrillar Aβ deposition in the striatum, similar to that found in some PiB studies of autosomal dominant AD mutation carriers. Nelson et al. used fluoroethyl-methylamino-naphthyl-ethylidene malononitrile PET to investigate fibrillar and tau burden in 19 (mean age 36.7 years old) DS/AD− participants and reported increased SUVRs in brain regions similar to that observed in late onset AD [8]. We previously used florbetapir PET to characterize fibrillar Aβ burden in an end-of-life DS/AD+ participant [7]. Here, we found a regional pattern of fibrillar Aβ deposition similar to that observed in late-onset AD[7]. In our florbetapir PET study of PSEN1 E280 A mutation carriers, we also found a regional pattern of fibrillar Aβ deposition similar to that observed in late-onset AD [24,38]. We subsequently confirmed the magnitude and pattern of fibrillar Aβ deposition at autopsy [7]. We interpret our florbetapir PET data to preferentially affect the same brain regions that might be affected in late-onset AD. Although there was a close correlation between antemortem PET and postmortem histopathologic measurements of Aβ plaques in this DS participant with AD dementia, florbetapir PET measurements may be less sensitive to the detection of the primarily diffuse Aβ plaques that have been reported in virtually all DS/AD− individuals who expired by the age of 35 years [39]. Previously published FDG PET studies have reported a pattern of CMRgl reductions in DS adults with and without AD dementia similar to that observed in late-onset AD [40], consistent with the findings reported in our study. In addition, Haier et al. reported increased inferior and medial temporal CMRgl [11,12] in middle-aged DS/AD− participants, raising the possibility of compensatory increases in local neuronal activity in preclinical stages of AD.

Although we are not aware of previously published volumetric MRI studies in DS/AD+ individuals, previously published volumetric MRI studies have reported alterations in GMV and white matter volume alterations in DS/AD− individuals and their associations with older age [14–17]. For example, Teipel et al. [15] found significant age-related CMV reductions in precuneus, lateral parietal, and temporal, frontal, occipital, and parahippocampal regions in these individuals. Our findings are generally consistent with the GMV findings in those reports and extend them to individuals with DS/AD+.

In addition to progressive CMRgl and GMV reductions in brain regions known to be preferentially affected by AD, the DS/AD+ and DS/AD− groups had lower CMRgl and GMV than NCs in additional medial and basal frontal regions.

Others have identified a greater occipital atrophy and relative sparing of both medial and lateral temporal regions on MRI and FDG. Although we cannot exclude the possibility that these changes are related to preclinical AD processes that do not continue to progress with age or to clinical severity after middle age, we postulate that these changes might reflect DS-related alterations in brain development.

Additional studies are needed to (a) further characterize and confirm our fibrillar Aβ, CMRgl, and brain tissue volume findings in a larger number of participants; (b) control for the effects of APOE genotypes and premormid IQs; and (c) clarify the extent to which the brain imaging alterations predict subsequent clinical decline. Additional studies also are needed to track these changes over time and provide sample size estimates for the evaluation of preclinical and clinical AD treatments using these brain imaging endpoints in proof-of-concept trials. Additional studies in DS individuals also are needed to characterize the most sensitive indicators of cognitive and functional decline in the preclinical and clinical stages of AD and provide sample size estimates for the evaluation of treatments using these endpoints in license-enabling trials.

DS represents the largest population of individuals at risk for early onset Aβ pathology, far exceeding the number of patients who carry autosomal dominant AD mutations. With the growing number of DS individuals living to older ages, there is an urgent need to find effective clinical and preclinical AD treatments in this vulnerable population [41–44].

5. Conclusions

DS is associated with characteristic fibrillar Aβ, regional CMRgl, and regional GMV alterations in the symptomatic dementia stage and before the onset of cognitive decline. Amyloid signal strongly increases with age in DS. This brain imaging study provides a foundation for the longitudinal studies needed to inform AD treatment and prevention trials in this vulnerable population.

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RESEARCH IN CONTEXT

1. Systematic review: AD dementia occurs in up to 60-75% of those over the age of 60 in Down Syndrome (DS). A small number of published studies have used PET to characterize fibrillar A burden in persons with DS.
2. Interpretation: DS subjects had florbetapir PET evidence of fibrillar A burden in the symptomatic dementia stage. Further, fibrillar A was detected in DS subjects without evidence of cognitive decline (DS/AD-) as early as 35 years of age (see Fig. 1). Increases in florbetapir uptake were associated with dementia status and older age. More specifically, florbetapir uptake strongly increases with and correlates with age. DS participants with AD dementia also had lower CMRgl and GMV in brain regions known to be preferentially affected by late-onset AD Finally, DS participants with and without dementia had lower CMRgl and GMV than NC subjects in additional frontal regions.
3. Future directions: The goal is to assess imaging characteristics in DS with and without dementia to determine whether they proceed or coincide with cognitive decline? DS is associated with characteristic fibrillar A, regional CMRgl, and regional GMV alterations in the symptomatic dementia stage and prior to onset of cognitive decline. Amyloid signal strongly increases with age in DS. Our brain imaging study provides a foundation for the longitudinal studies needed to inform AD treatment and prevention trials in this vulnerable population.

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