Patterns of glucose hypometabolism in Down syndrome resemble sporadic Alzheimer’s disease except for the putamen

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Abstract

Introduction: Adults with Down syndrome (DS) are predisposed to Alzheimer’s disease (AD) and the relationship between cognition and glucose metabolism in this population has yet to be evaluated.

Methods: Adults with DS (N = 90; mean age [standard deviation] = 38.0 [8.30] years) underwent [C-11]Pittsburgh compound B (PiB) and [F-18]fluorodeoxyglucose (FDG) positron emission tomography scans. Associations among amyloid beta (Aβ), FDG, and measures of cognition were explored. Interregional FDG metabolic connectivity was assessed to compare cognitively stable DS and mild cognitive impairment/AD (MCI-DS/AD).

Results: Negative associations between Aβ and FDG were evident in regions affected in sporadic AD. A positive association was observed in the putamen, which is the brain region showing the earliest increases in Aβ deposition. Both Aβ and FDG were associated with measures of cognition, and metabolic connectivity distinguished cases of MCI-DS/AD from cognitively stable DS.

Discussion: Associations among Aβ, FDG, and cognition reveal that neurodegeneration in DS resembles sporadic AD with the exception of the putamen, highlighting the usefulness of FDG in monitoring neurodegeneration in DS.

KEYWORDS
Alzheimer’s disease, amyloid positron emission tomography, cognitive decline, Down syndrome, fluorodeoxyglucose, individual metabolic brain network

1 INTRODUCTION

Adults with Down syndrome (DS) are predisposed to Alzheimer’s disease (AD), with a sharp increase in prevalence of dementia after age 50.1 The triplication of chromosome 21 results in overexpression of the gene encoding production of the amyloid precursor protein (APP), and an earlier presence of amyloid beta (Aβ) plaques in the brain.2,3 Histopathological studies have revealed that Aβ deposition in DS begins early in life, with severe cortical prominence evident by age 40,4,5 which is decades earlier than reported in cases of sporadic AD.6
In sporadic AD, the deposition of Aβ precedes symptoms of dementia by roughly two decades, and it is postulated that there is a temporal latency between Aβ presence and the progression of other AD biomarkers such as neurofibrillary tangles, glucose hypometabolism, gray matter atrophy, and cognitive decline.

The spatial extent of Aβ can be monitored in vivo with positron emission tomography (PET) throughout the time course of AD using Aβ-targeting radioligands, such as [C-11]Pittsburgh compound B (PiB). In non-demented DS, a pattern of striatum-first Aβ retention was identified using PiB PET with the youngest case of Aβ-positivity (Aβ+) in the striatum at age 38. This is reminiscent of the pattern seen in other early-onset forms of AD including autosomal dominant AD and APP duplication. With the exception of the striatum, PET studies in DS revealed that the spatial distribution of Aβ in the brain closely resembled the pattern observed in sporadic AD. Longitudinal PET imaging in DS identified Aβ increases of 3% to 4% per year with the striatum showing the earliest and most prominent change compared to other cortical regions, highlighting the striatum as a target region of interest to monitor early AD progression in DS.

Changes in cerebral glucose metabolism are well established in sporadic AD (non-DS) when measured with [F-18]fluorodeoxyglucose (FDG). The most prominent regions showing glucose hypometabolism early on during preclinical AD progression are the parietal cortex, precuneus, and posterior cingulate, followed by the medial temporal lobe. These regions also show the greatest increases of 3% to 4% per year with the striatum showing the earliest and most prominent change compared to other cortical regions, highlighting the striatum as a target region of interest to monitor early AD progression in DS.

To better characterize the transition from cognitively stable to MCI or mild cognitive impairment/AD (MCI-DS/AD) from cognitively stable and interregional metabolic connectivity distinguished mild cognitive impairment/AD (MCI-DS/AD) from cognitively stable DS. Future research should evaluate longitudinal FDG change in DS to characterize early regional metabolism change during the transition between cognitively stable and MCI-DS.

**RESEARCH IN CONTEXT**

1. **Systematic review**: Previous [F-18]fluorodeoxyglucose (FDG) studies in Down syndrome (DS) have revealed glucose hypometabolism with increased amyloid beta (Aβ) in regions implicated in Alzheimer’s disease (AD). However, no association between Aβ and FDG has been observed in the striatum, a region subject to early and prominent Aβ retention in DS. Additionally, associations between FDG and cognitive performance have yet to be evaluated in this population.

2. **Interpretation**: Our findings in DS reveal the pattern of glucose hypometabolism resembles that of sporadic AD. A positive association between Aβ and FDG in the putamen was observed, suggesting this region is spared from neurodegeneration in DS. FDG hypometabolism was greatly associated with lower cognitive performance, and interregional metabolic connectivity distinguished mild cognitive impairment/AD (MCI-DS/AD) from cognitively stable DS.

3. **Future directions**: Future research should evaluate longitudinal FDG change in DS to characterize early regional metabolism change during the transition between cognitively stable and MCI-DS.
Due to the nature of early Aβ accumulation in the striatum, FDG uptake across the caudate and putamen was evaluated to identify any localized metabolic change. Finally, interregional FDG metabolic connectivity was assessed using an individual metabolic brain network and compared to a control group of age-matched siblings without DS to classify AD-related neurodegeneration in DS. In regard to cognition, we examined episodic memory, as this domain has been found to be especially sensitive to change in AD biomarkers early on in the transition to AD in DS, as well as a composite measure of the varied cognitive domains implicated in MCI in DS.

### 2 METHODS

#### 2.1 Participants

A total of N = 90 participants with DS (mean age [standard deviation (SD)] = 38.0 [8.3] years) and N = 14 age-matched siblings without DS (mean age [SD] = 46.6 [13.4] years) were recruited from the University of Wisconsin-Madison and University of Pittsburgh imaging sites of the ABC-DS. Age-matched sibling controls without DS and free of symptoms of dementia were enrolled in the study to act as a biomarker reference group. Institutional review board approval and informed consent were obtained during enrollment into the study by the participant or legally designated caregiver. Inclusion criteria included age ≥ 25 years and having receptive language ≥ 3 years. Genetic testing was performed to confirm cases of DS (trisomy 21, mosaicism, or partial translocation). Exclusion criteria included having a prior diagnosis of dementia or a psychiatric condition that impaired cognitive functioning. In the current study, 10 participants were classified having MCI-DS or AD, 77 were cognitively stable (CS-DS), and the remaining 3 showed cognitive decline but possibly due to non-AD reasons (eg, life stressors or medical conditions). These diagnostic classifications were performed independent of imaging findings and based on case consensus processing informed by directly administered and caregiver-reported measures as previously described. The three participants with cognitive decline possibly due to non-AD reasons evidenced low to moderate Aβ, but no FDG hypometabolism and were included in analyses associating Aβ and FDG with cognition. However, these three participants were excluded from analyses requiring a definitive cognitive consensus. DS participant demographics are outlined in Table 1.

### 2.2 Sociodemographics

Sex was reported by caregivers and coded as M/F. Chronological age was coded in years. The Peabody Picture Vocabulary Test–Fourth Edition (PPVT) administered at the first time point of the study was used to assess lifetime cognitive ability and has shown to be a valid measure of receptive language in adults with DS that strongly correlates with IQ. Highlights:

- Glucose hypometabolism in Down syndrome (DS) resembled that of sporadic Alzheimer’s disease (AD).
- A positive association was observed between amyloid beta and fluorodeoxyglucose (FDG) in the putamen.
- FDG hypometabolism strongly correlates with lower cognitive performance in DS.
- Metabolic connectivity distinguishes mild cognitive impairment-DS/AD from cognitively stable DS.

#### 2.3 Cognitive measures

Episodic memory was measured using the Cued Recall Test which has been shown to be reliable in DS. A composite for overall cognition was generated by summing Z-scores from a variety of cognitive tests that includes the Cued Recall Test (episodic memory), Down Syndrome Mental Status Examination (dementia symptoms/mental status), Developmental Test of Visual-Motor Integration–Fifth Edition (visual perception, fine motor skills, and hand–eye coordination), the Cat and Dog Modified Stroop Task (executive functioning), Purdue Pegboard (motor planning and coordination), and Developmental Neuropsychological Assessment Word Generation Semantic Fluency.
test (verbal fluency).61 These assessment tools have previously been shown to be promising outcome measures early on in the transition to AD in DS.41,50

2.4 | Magnetic resonance imaging

T1-weighted magnetic resonance imaging (MRI) scans were acquired on a 3T GE Discovery MR750 (Wisconsin) and a Siemens Trio or Prisma (Pittsburgh) scanner. MRI scans were acquired the same day as neuropsychological evaluation. MRI images were processed using FreeSurfer v5.3.0 for the purpose of extracting volumes from the lateral ventricles, and no DS template was used for the FreeSurfer spatial normalization. MRI from all 90 participants were used in the analysis.

2.5 | PET imaging

PET scans were performed on a Siemens ECAT HR+ scanner (Wisconsin). For the Pittsburgh site, both a Siemens ECAT HR+ and Siemens 4-ring Biograph mCT were used for PET imaging. All PET imaging was performed 1 day after the neuropsychological evaluation and MRI scan. A target dose of 15 mCi of [C-11] PiB was injected intravenously, and PET scans to measure brain Aβ plaques were acquired 50 to 70 minutes post-injection (four 5-minute frames). Sixteen months after PiB imaging, participants were imaged with FDG PET to assess brain glucose metabolism. A target dose of 5 mCi of FDG was injected intravenously, and scans were acquired 30 to 60 minutes post-injection (six 5-minute frames). PET images from all 90 participants were used in the analysis. PET frames were re-aligned to correct for motion, averaged, and spatially normalized to the Montreal Neurological Institute 152 space (MNI152) via DS-specific PET templates for PiB and FDG as previously described.20 Spatial normalization was required for all PET images for regional analysis using template space regions of interest (ROIs) that account for differences in DS brain morphology compared to conventional atlas-based ROIs, which have been previously validated for PET quantification in DS.20 For PiB images specifically, spatial normalization was required to calculate the amyloid load (AβL), a global measure of total Aβ computed by the linear least squares method between the PET image, and images of specific radioligand binding and nonspecific/off-target binding defined in a template space.62,63

Standardized uptake value ratio (SUVR) images were generated by voxel normalization to cerebellar gray matter (PiB) or a cerebral global mean (FDG). Global Aβ was calculated from the PiB SUVR images using the AβL index following methodology specific to DS brains.64 Regional values of SUVR were calculated for PiB and FDG in early-stage AD regions (parietal cortex, precuneus/posterior cingulate), late-stage regions (frontal cortex, temporal cortex, anterior cingulate), the caudate, and putamen. AβL+ derived from prior work in the DS population was defined in the striatum for SUVR ≥ 1.43, and globally for AβL ≥ 20.0.64

2.6 | Individual metabolic brain network

A novel method for generating a metabolic brain network from a single FDG image was recently developed65 and applied to the DS data. First, a correlation coefficient matrix was generated for FDG SUVR values across all ROIs in the sibling control group (MC). The mean (MC) and standard deviation (SC) SUVR for each individual ROI was then calculated across all sibling controls. For a single FDG image, an effect size difference (ESD) matrix between the individual DS participant and the control group was calculated:

\[ \text{ESD}(i,j) = \left( \frac{(x_i - MC) - (x_j - MC)}{sc(i,j)} \right) \]  

where \( x_i \) and \( x_j \) are the regional SUVR for regions \( i \) and \( j \) from an individual DS participant, \( MC \) and \( SC \) are the mean regional SUVR from the control group, and \( sc(i,j) \) is the pooled standard deviation between the regions in the control group. Using the Fisher transformation, ESD values were converted to correlation coefficient values (R) as follows:

\[ R(i,j) = \frac{(\exp(2 \times \text{ESD}(i,j)) - 1)}{(\exp(2 \times \text{ESD}(i,j)) + 1)}. \]

A higher value of ESD corresponds to a stronger difference of SUVR variation between regions, resulting in a weaker regional correlation coefficient.65 A weighting factor was then applied across the regional correlation coefficients between the DS subject and the control group as \( W(i,j) = 1 - R(i,j) \), such that 0 < \( W(i,j) < 1 \). The final individual connectivity matrix \( M \) was calculated as

\[ M(i,j) = W(i,j) \odot MC(i,j). \]

where \( \odot \) represents element-by-element multiplication.

2.7 | Statistical analysis

To assess the association between global AβL and FDG SUVR in striatal, early, and late-stage AD regions in DS (described above), Pearson's correlation coefficients were calculated. Pearson's correlation coefficients were also used to evaluate the associations between striatal FDG SUVR and ventricular volume. To assess the association between AD biomarker progression and cognition, multiple linear regression models were performed. The models were performed as follows: each cognitive measure (episodic memory, overall cognition composite) was used as an outcome with AβL and regional FDG SUVR as independent variables. Regression models were repeated to adjust for chronological age and lifetime cognitive ability level (ie, PPVT). Associations were considered statistically significant for p-values ≤ 0.05 (adjusted for Holm-Bonferroni correction). Spearman’s correlations were then performed between regional PiB and FDG SUVR across groups of Aβ- and Aβ+ individuals to assess the influence of localized Aβ on glucose metabolism. Spearman’s correlations were repeated to assess the influence of global AβL on regional FDG SUVR. For the individual
metabolic brain network analysis, a threshold value for connectivity was selected as the minimum from the CS-DS group as described previously, which was calculated as $M = 0.10$. For the subsequent analyses, only connectivity values exceeding this threshold were analyzed. Interregional connectivity from ROI data was compared across the sibling control, DS-$A_\beta^-$ and DS-$A_\beta^+$ groups using analysis of covariance (ANCOVA) adjusting for age and sex. Post hoc Student’s t-tests were then performed across the individual groups while adjusting for Bonferroni correction. The analyses were repeated comparing the sibling control, CS-DS, and MCI-DS/AD groups. Because different scanners were used for image collection, all models were corrected for imaging site. Statistical analyses were performed using SAS v9.4.

3 | RESULTS

3.1 | $A_\beta$ and FDG correlations

Negative associations between global $A_\beta_L$ and regional FDG SUVR were observed in early-stage (Pearson’s $r$ [95% confidence interval (CI)] = $-0.70[-0.79, -0.58]$; $P$-value: .00001) and late-stage AD regions (Pearson’s $r = -0.33[-0.50, -0.13]$; $P$-value: .0015; Figure 1). For the striatum, a negative association with a large magnitude effect size (Cohen’s $d$) was observed in the caudate (Pearson’s $r = -0.63[-0.74, -0.49]$; $P$-value: .00001), while a positive association with a lower magnitude effect size was observed in the putamen (Pearson’s $r = 0.24[0.04, 0.43]$; $P$-value: .022). FDG in the caudate was associated with increased ventricle volume (Pearson’s $r = -0.73[-0.81, -0.62]$; $P$-value: .00001), with a large magnitude effect association, and a low effect magnitude association was observed between ventricle volume and FDG in the putamen (Pearson’s $r = 0.19[-0.02, 0.38]$; $P$-value: .068; Figure 2). This suggests that the positive association observed between $A_\beta$ and FDG in the putamen is independent of ventricular enlargement. Additionally, the association observed between FDG SUVR in the caudate and in the putamen was very small (Pearson’s $r = -0.073[-0.28, 0.14]$; $P$-value: .49), suggesting that putamen FDG was not associated with the observed caudate hypometabolism. To account for the partial volume effect, the striatal analysis was repeated using the Rousset geometric transfer matrix (GTM) method. After GTM correction, the association observed between $A_\beta_L$ and FDG in the caudate (Pearson’s $r = 0.08[-0.13, 0.28]$; $P$-value: .45) was also extremely small while the putamen showed a positive association (Pearson’s $r = 0.74[0.63, 0.82]$; $P$-value: .00001) with a large effect size (Figure 2). For all associations, imaging site did not influence the model outcomes.

Putamen FDG was then compared across the $A_\beta^-$, $A_\beta^+$, and sibling control groups using analysis of variance (ANOVA) with post hoc Student’s t-tests while adjusting for Bonferroni correction. The $A_\beta^-$ and $A_\beta^+$ groups showed elevated putaminal FDG compared to the sibling controls (ANOVA; $P = .0003$). From the post hoc tests, no significant difference was observed between putamen FDG in the $A_\beta^-$ and $A_\beta^+$ groups ($P > .05$ adjusted for Bonferroni correction).

Due to the large magnitude effect association between FDG in the caudate and ventricle volume, multiple linear regressions were performed between these measures considering linear, quadratic, and cubic polynomials. The association between caudate FDG and ventricle volume was best represented by the model that included both the quadratic and cubic terms ($R^2 = 0.57$) compared to model considering only the linear term (one-way ANOVA $F = 9.04; P = .0003$) and the model considering the linear and quadratic terms (one-way ANOVA $F = 18.1; P = .00005$).

3.2 | Impact of $A_\beta$ and FDG on cognition

First-level analysis with Pearson’s correlations revealed significant associations between $A_\beta_L$ and between regional FDG SUVR with cognition in both early and late-stage AD regions (all $P < .05$). No associations were observed between FDG SUVR and cognition in the caudate or putamen, and these regions were excluded from the regression analysis. From the regression models (Table 2), each variable, $A_\beta_L$ and then FDG SUVR in both early- and late-stage regions, showed significant associations (presented as slope estimates [regression coefficients] with 95% CIs) with episodic memory and overall cognition (all $P < .05$ adjusted for Holm-Bonferroni correction). Associations with episodic memory and overall cognition remained significant for the $A_\beta_L$ regressions and early-stage FDG SUVR regressions after adjusting for chronological age and lifetime ability (ie, PPVT; Table 2). For late-stage FDG regions, significant associations with overall
FIGURE 2  Pearson’s correlations (with corresponding p-values) for fluorodeoxyglucose standardized uptake value ratio (FDG SUVR) and ventricle volume, FDG SUVR and global amyloid load (AβL), and geometric transfer matrix-corrected (GTM) FDG SUVR and global AβL in the caudate (top row) and putamen (bottom row).

TABLE 2  Linear regression coefficient estimates (with 95% CIs) for models using cognitive measures as the outcome variable and AβL and FDG SUVR as independent variables. Regressions were repeated for each outcome variable while adjusting for chronological age and lifetime cognitive ability (PPVT). P-values were adjusted for multiple comparisons using the Holm-Bonferroni method.

| Outcome       | AβL          | Early-stage FDG | Late-stage FDG |
|---------------|--------------|-----------------|----------------|
| Episodic memory | -4.2[-5.3, -3.0]** | 0.016[0.0096, 0.022]** | 0.009[0.0033, 0.015]* |
| Age adjusted  | -2.4[-3.5, -1.3]** | 0.013[0.0055, 0.020]** | 0.008[0.0015, 0.015] |
| Age and PPVT adjusted | -2.6[-3.9, -1.2]** | 0.013[0.0042, 0.022]* | 0.004[0.0035, 0.013] |
| Overall cognition | -1.5[-1.9, -1.0]** | 0.0061[0.0038, 0.0083]** | 0.003[0.0018, 0.0058]** |
| Age adjusted  | -0.89[-1.3, -0.53]** | 0.0049[0.0025, 0.0072]** | 0.0035[0.0013, 0.0057]* |
| Age and PPVT adjusted | -1.4[-2.0, -0.82]** | 0.0077[0.0039, 0.012]** | 0.0035[-0.0013, 0.0070] |

Significance: *P < .05; **P < .01.
Abbreviations: AβL, amyloid beta load; CI, confidence interval; FDG, fluorodeoxyglucose; PPVT, Peabody Picture Vocabulary Test–Fourth Edition; SUVR, standardized uptake value ratio.

3.3  FDG in relation to Aβ status

Regional PiB SUVR and global AβL were compared against regional FDG SUVR across groups of Aβ− and Aβ+ individuals (considering both striatal and global Aβ+ cutoffs) using Spearman correlations (Table 3). For both the striatal Aβ+ and global Aβ+ groups, large effect sizes were observed between regional PiB and FDG SUVR in early-stage AD regions (striatal Aβ+: r = -.60; global Aβ+: r = -.50), and late-stage AD regions (striatal Aβ+: r = -.62; global Aβ+: r = -.67). Large effect sizes were also displayed between global AβL with early-stage AD regions (striatal Aβ+: r = -.73; global Aβ+: r = -.68) and late-stage AD regions (striatal Aβ+: r = -.68; global Aβ+: r = -.68). A medium effect size was observed between global AβL and putaminal FDG SUVR in only
TABLE 3  Spearman correlation coefficients (with 95% CIs) comparing regional PiB and FDG SUVR, as well as global AβL and regional FDG SUVR across different Aβ− and Aβ+ groups

|                      | Striatum Aβ− | Striatum Aβ+ | Global Aβ− | Global Aβ+ |
|----------------------|--------------|--------------|-------------|-------------|
|                      | N = 65       | N = 25       | N = 74      | N = 16      |
| Early-stage PiB vs Early-stage FDG | -0.082 [-0.32, 0.17] | -0.60 [-0.80, -0.27]** | -0.061 [-0.29, 0.17] | -0.50 [-0.80, -0.0057]* |
| Late-stage PiB vs Late-stage FDG | -0.26 [-0.47, -0.019]* | -0.62 [-0.82, -0.30]*** | -0.20 [-0.41, 0.031] | -0.67 [-0.88, -0.27]** |
| Putamen PiB vs Putamen FDG | -0.12 [-0.35, 0.13] | 0.38 [0.014, 0.68] | -0.18 [-0.39, 0.052] | 0.012 [-0.49, 0.50] |
| Caudate PiB vs Caudate FDG | -0.21 [-0.44, 0.031] | 0.11 [-0.30, 0.48] | -0.18 [-0.40, 0.047] | 0.39 [-0.13, 0.74] |
| Global AβL vs Early-stage FDG | -0.23 [-0.45, 0.014] | -0.73 [-0.87, -0.47]*** | -0.16 [-0.38, 0.070] | -0.68 [-0.88, -0.28]** |
| Global AβL vs Late-stage FDG | -0.24 [-0.46, -0.0011]* | -0.68 [-0.85, -0.39]*** | -0.15 [-0.37, 0.080] | -0.68 [-0.88, -0.28]** |
| Global AβL vs Putamen FDG | -0.095 [-0.33, 0.15] | 0.45 [0.070, 0.72]*** | -0.15 [-0.37, 0.078] | 0.079 [-0.43, 0.55] |
| Global AβL vs Caudate FDG | -0.17 [-0.40, 0.073] | 0.058 [-0.35, 0.44] | -0.13 [-0.35, 0.10] | -0.056 [-0.54, 0.45] |

Significance: *P < .05; **P < .01; ***P < .001.
Abbreviations: AβL, amyloid beta load; CI, confidence interval; FDG, fluorodeoxyglucose; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio.

FIGURE 3  Interregional fluorodeoxyglucose connectivity matrices across the sibling control and Down syndrome groups. The plots display the number of interregional connections across all individuals in each group

3.4 Individual metabolic brain network

Relative to the sibling control group, reductions in the number of interregional FDG connections were evident in the DS-Aβ−-, DS-Aβ+, CS-DS, and MCI-DS/AD groups (Figure 3). From ANCOVA, significant differences between all groups were observed (all P < .05 surviving adjustment for age, but not sex. Inclusion of imaging site did not influence the model outcomes. From the post hoc analysis, the frequency of significant connections (presented as mean [SD]) for the sibling controls (0.60 [0.23]), DS-Aβ− (0.44 [0.23]) and DS-Aβ+ (0.28 [0.21]) were significantly different across all group pairings (P < .05 adjusted for Bonferroni correction). Significant differences were also observed between the sibling controls and the CS-DS (0.43 [0.23]) and MCI-DS/AD (0.29 [0.20]) groups (P < .05 adjusted for Bonferroni correction). Within the Aβ+ and MCI-DS/AD groups, the weakest interregional connectivity values were evident in the early-stage AD regions (parietal cortex, precuneus/posterior cingulate).
4 | DISCUSSION

In the DS population, we report FDG hypometabolism with elevated Aβ in typical AD regions (parietal cortex, precuneus/posterior cingulate, frontal cortex, temporal cortex) similar to the patterns observed in sporadic AD. However, a positive association between global AβL and putamen FDG SUVR emerged. Previous imaging studies in DS have attempted to relate Aβ with striatal FDG and found no association; however, this is possibly a consequence of examining the striatum as a whole rather than across individual striatal subunits. Our data revealed a significant relation between lower glucose metabolism in the caudate and higher volume of the lateral ventricles. Thus, with striatal regions grouped, it is conceivable that this positive association between AβL and FDG in the putamen could be offset by caudate hypometabolism related to ventricular enlargement. After partial volume correction, the positive association between global AβL and FDG in the putamen remained significant, while the signal in the caudate showed no association with AβL. This effect may result from correction of signal spill-in from white matter, which shows a greater effect in the putamen because it is bounded by large white matter tracts and reveals little atrophy. The analysis was then repeated using the cerebellum as the reference region for FDG SUVr calculation to ensure that the finding was not an artifact of region for normalization. The FDG and AβL associations in the caudate and putamen were similar to those observed with the global normalization, suggesting that these regions are spared from hypometabolism during the progression of AD.

Histopathological studies in DS have revealed the presence of diffuse and cored Aβ plaques in the striatum, which accumulates larger amounts of diffuse plaques compared to the surrounding neocortical areas. The abundance of diffuse plaques compared to the more neurotoxic cored plaques may spare the striatum from AD-related neurodegeneration, as observed by the lack of FDG hypometabolism. Compared to sibling controls, the putamen showed elevated baseline FDG in DS; however, no significant difference in FDG was observed between Aβ− and Aβ+ groups. This may indicate higher basal metabolism in DS sparing the putamen from neurodegeneration. Because no measurable increase in FDG is observed in DS, the positive association between Aβ and FDG cannot be used as a direct confirmation of hypermetabolism in the putamen. However, the positive association between Aβ and FDG in the putamen may reflect an inflammatory response to Aβ, although a similar response would be expected in the caudate. These possibilities should be examined in future research that uses PET imaging of neuroinflammation (e.g., translocator protein ligand) in the DS population. While striatal Aβ is indicative of preclinical AD progression in DS, the lack of FDG hypometabolism suggests this region would not be a useful marker to monitor early AD neurodegeneration.

The regression analysis revealed significant associations between Aβ and FDG and AD-related domains of cognitive functioning in DS. A negative association was observed between Aβ and episodic memory and the overall composite of cognitive functioning. FDG hypometabolism in both early-stage (parietal cortex, precuneus/posterior cingulate) and late-stage (frontal cortex, temporal cortex, anterior cingulate) AD regions was associated with lower cognitive performance, and these associations were independent of chronological age. Due to the modest size of the slope estimates between FDG and our measures of cognition, a correlation analysis was performed across groups based on AβL status and AD clinical status (cognitively stable, MCI-DS, or AD). The associations between measures were found to be primarily influenced by individuals that were globally Aβ+, which includes those classified as having MCI-DS or AD, suggesting that FDG is useful to monitor subtle changes in AD progression. Measures of episodic memory in particular have shown to be sensitive indicators of the transition between preclinical and prodromal AD in non-DS populations, and the relations of these measures in DS with FDG highlight their utility in monitoring AD progression.

For the group analysis, DS participants were classified as Aβ− or Aβ+ using either striatal or global thresholds. Large effect sizes were observed between Aβ and FDG across both striatal and global AβL groups, suggesting that both classifications of Aβ+ are useful in monitoring AD progression. In the putamen, a greater association between Aβ and FDG was evident in the striatal Aβ+ group, indicating that metabolic change occurs in this region early in the course of Aβ deposition. While Aβ deposition in the striatum is detectable with PET prior to that in the neocortex, the occurrence of histologically detectable diffuse and cored plaques in the neocortex precedes that in the striatum based on post-mortem studies. Thus, use of a striatal classification for Aβ+ may provide more information on early metabolic change in neocortical regions. In general, FDG hypometabolism was not evident prior to the onset of Aβ+, suggesting Aβ may be a precursor to AD-related metabolic change in DS and that the trajectories of these biomarkers are in accordance with the disease staging in sporadic AD.

Regional PiB SUVr and global AβL were compared against regional FDG across the different Aβ+ groups to evaluate whether any local associations are lost when using a global measure. While regional PiB SUVr was able to distinguish FDG change across Aβ+ and Aβ− groups, the global AβL measure displayed larger effect sizes and may be a more sensitive metric to predict FDG change. Previous studies have shown that the AβL metric improves quantification due to its suppression of nonspecific radioligand binding signal, resulting in greater sensitivity to detect small increases in Aβ. This improved sensitivity to measure Aβ with AβL may translate to a more sensitive prediction of FDG change during the early stages of AD progression.

For sporadic AD, FDG PET has been used as a proxy for neurodegeneration as described by the AT(N) (Aβ/neurofibrillary tau/neurodegeneration) classification scheme for AD. To assess the potential of FDG PET for classifying neurodegeneration in DS, an individual metabolic brain network was used to compare interregional metabolic connectivity from the FDG scan of a single participant to a group of healthy sibling controls. The metabolic brain network revealed that the number and strength of interregional connections were lower in both cognitively stable DS and MCI-DS or AD compared to the sibling controls. Also evident was a significant difference in connectivity between the cognitively stable DS and MCI-DS or AD that was independent of normal aging effects. One limitation to the current study was the limited sample size of participants classified as having MCI-DS or AD (n = 10). Given the small number of adults with
DS with MCI and AD, these classification groups were combined in the analysis to improve statistical power. However, in future studies it will be important to determine whether FDG PET differences are observed in the MCI group prior to conversion to AD. Additionally, n = 2 participants classified as having MCI-DS/AD were considered Aβ⁻ (Table 1); however, both participants had global Aβ⁺ values >19 at the baseline visit and likely surpassed the Aβ⁺ threshold by the time of FDG imaging, which occurred 16 months after baseline. This may also suggest that our global cutoff for Aβ⁺ in DS may be too conservative, which is evidenced by the FDG hypometabolism observed in participants that are Aβ⁺ in the striatum but not globally. After consideration of a lower baseline metabolic connectivity, the individual metabolic brain network was capable of distinguishing cases of MCI and AD from cognitively stable DS, suggesting FDG PET is a useful marker for neurodegeneration in DS within the AT(N) framework.

5 | CONCLUSION

Evaluating FDG PET in a large DS population revealed that the regional patterns of glucose hypometabolism throughout AD progression are largely similar to the observations in sporadic AD. Compared to Aβ⁺ PET, regional hypometabolism was not evident prior to the onset of Aβ⁺ status. However, a positive association between Aβ and FDG emerged in the putamen, a region subject to early and rapid accumulation of diffuse Aβ plaques in DS. FDG PET showed significant associations with measures of episodic memory and overall cognition, suggesting the utility of FDG for monitoring declines in cognition. Finally, FDG was capable of distinguishing individuals with DS with a prior diagnosis of MCI and AD from those who were cognitively stable, highlighting the utility of FDG as a marker for AD progression.

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CONFLICTS OF INTEREST

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