RESEARCH ARTICLE

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Cognitive indicators of transition to preclinical and prodromal stages of Alzheimer's disease in Down syndrome

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Abstract

Introduction: There is a critical need to identify measures of cognitive functioning sensitive to early Alzheimer's disease (AD) pathophysiology in Down syndrome to advance clinical trial research in this at-risk population. The objective of the study was to longitudinally track performance on cognitive measures in relation to neocortical and striatal amyloid beta (Aβ) in non-demented Down syndrome.

Methods: The study included 118 non-demented adults with Down syndrome who participated in two to five points of data collection, spanning 1.5 to 8 years. Episodic memory, visual attention and executive functioning, and motor planning and coordination were assessed. Aβ was measured via [C-11] Pittsburgh Compound-B (PiB) PET.

Results: PiB was associated with level and rate of decline in cognitive performance in episodic memory, visual attention, executive functioning, and visuospatial ability in models controlling for chronological age.

Discussion: The Cued Recall Test emerged as a promising indicator of transition from preclinical to prodromal AD.

KEYWORDS
Alzheimer's disease, amyloid, Down syndrome, memory, preclinical

1 | INTRODUCTION

Adults with Down syndrome (DS) have an increased incidence and early onset of Alzheimer's disease (AD). More than half of adults with DS age 55 years[1] and two thirds in their 60s and 70s[2] receive an AD diagnosis. The increased AD risk is caused by the over-expression of the amyloid precursor protein gene, due to triplication of chromosome 21.[3] Deposition of amyloid beta (Aβ) is an early pathophysiological feature of AD in the general[4,5] and DS[6,7] populations. There is a critical need for clinical trials aimed at preventing or delaying AD in DS. These

clinical trials are likely to target the period prior to or early on in AD pathophysiology.[8] To advance these efforts, the DS field must identify cognitive measures sensitive to change during these early stages.

Hypothetical models of AD in the general[9] and DS[10] populations posit a temporal progression from cognitively stable (ie, normative aging) to preclinical (ie, early AD pathophysiology including Aβ plaques but no cognitive or functional decline), to prodromal mild cognitive impairment (ie, mild cognitive or functional declines) and then AD (ie, substantial cognitive and functional declines). In non-DS

populations, measures of episodic memory (eg, list learning tasks) have been found to indicate the transition to preclinical and prodromal stages.[11] Several studies have examined cognitive functioning in adults with DS in the years prior to clinical AD. In these studies, directly administered measures better captured early decline than caregiver-reported measures[12] and declines in episodic memory, attention, executive functioning, visuospatial ability, and motor planning and coordination were most consistently reported.[12-17] However, only a handful of studies have examined the preclinical and prodromal stages of AD in the DS population by assessing both cognitive functioning and biomarkers of early AD pathophysiology, such as Aβ. In cross-sectional analyses,[18] greater neocortical Aβ deposition using [C-11] Pittsburgh Compound-B (PiB) positron emission tomography (PET) imaging was associated with worse episodic memory and attention in non-demented adults with DS. In the only study to include two time points, our group[20] found that greater increase in PiB PET Aβ in the neocortical regions and/or striatum was associated with greater decline in episodic memory, visuospatial ability, and motor planning and coordination in 58 non-demented adults with DS. Moreover, the 13 adults with DS who were PiB+ (ie, elevated Aβ) had greater episodic memory decline than those who were PiB−.[21]

To inform AD clinical trials, it is also important to document DS population-level variability in transition to the preclinical and prodromal stages. Biological sex has been posited to influence age of clinical AD onset in DS, with estrogen the implicated mechanism.[21,22] However, findings are conflicting; some studies report an earlier age of clinical AD in females,[23] others report a later age in females,[24,25] and some report no male–female difference.[26] There is also evidence that clinical AD occurs earlier in adults with DS with lower lifetime cognitive ability (eg, premorbid intelligence quotient [IQ]);[13,27] however, other studies found no effect.[28]

The current study examined level and rate of decline in cognitive measures in relation to PiB PET Aβ in 118 originally non-demented adults with DS across 2 to 8 years. Striatal Aβ was considered in addition to the neocortical regions given the striatal-first pattern of deposition in DS.[29-31] Analyses focused on cognitive domains most consistently reported to show early decline in AD in DS.[12-17] Analyses examined PET PiB as a continuous variable and change in PET PiB status as a categorical variable defined as presence (PiB+) versus absence (PiB−) of Aβ deposition, in line with previous studies.[19,20,30] Higher initial Aβ burden was hypothesized to be associated with lower initial performance and greater decline across cognitive measures. Given mixed evidence, hypotheses regarding biological sex and lifetime cognitive ability and decline rate were not made a priori. However, lower lifetime cognitive ability was expected to be associated with lower initial performance. Adults with DS consistently PiB− were hypothesized to evidence relatively high and stable performance. Those who converted PiB− to PiB+, and thus recently transitioned to the preclinical stage, were also hypothesized to evidence relatively high and stable cognitive performance. In contrast, participants who began and remained PiB+ were hypothesized to evidence low initial performance

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the state-of-science by searching for published articles (eg, PubMed) and conference abstracts. Despite adults with Down syndrome (DS) developing Alzheimer's disease (AD) pathophysiology in their 40s, clinical trials to prevent or delay AD in DS are lacking. To advance efforts, there is an urgent need to identify cognitive measures sensitive to early AD pathophysiology to inform participant selection and serve as outcome measures in clinical trials.

2. Interpretation: To our knowledge, this is the largest and longest evaluation of cognitive functioning in relation to positron emission tomography amyloid beta in DS. The Cued Recall Test, a measure of episodic memory, emerged an indicator of transition to the preclinical and prodromal stage of AD. Rate of cognitive decline did not differ by biological sex or baseline cognitive ability.

3. Future directions: Research should examine these cognitive measures in relation to other biomarkers of early AD pathophysiology.

and greater decline rate, as they are approaching or in the prodromal stage.

2 | METHODS

2.1 | Participants

Participants were part of the Alzheimer's Biomarker Consortium in DS (ABC-DS), an ongoing longitudinal multi-site study. A community sample of 118 adults with DS from the University of Wisconsin-Madison, University of Pittsburgh, and University of Cambridge sites who completed ≥ 2 data collection time points between 2010 and 2019, had interpretable imaging scans, and did not initially have clinical AD were included. Consecutive sampling was used based on the inclusion criteria: age ≥ 25 years, baseline mental age ≥ 30 months, genetic testing confirming DS (trisomy 21, mosaicism, or partial translocation), no conditions contraindicative for magnetic resonance imaging (MRI), and no medical/psychiatric conditions impairing cognition. Analyses of PiB status change included 70 of the 118 participants with ≥2 time points of imaging. The majority (N = 43, 90%) of other participants remained in the study, but were not within-window for additional scans. One participant passed away during study. There were no differences between participants with ≥2 time points of imaging (N = 70) versus those without (N = 48) in Time 1 biological sex, chronological age, or lifestyle cognitive ability. Participants with ≥2 points of imaging performed better at Time 1 on Purdue Pegboard

TABLE 1 Sample characteristics by time points of data collection

	Time 1	Time 2	Time 3	Time 4	Time 5
Sample N	118	118	65	48	17
% of Time 1 sample	–	100%	55%	41%	14%
Years since Time 1 M (SD)	–	2.36 (0.89)	5.01 (0.72)	6.67 (0.43)	8.76 (0.98)
Female	61 (52%)	61 (52%)	31 (48%)	23 (48%)	9 (53%)
Chronological age (in years)	37.24 (7.70)	39.89 (8.09)	42.18 (7.04)	44.11 (7.02)	45.77 (6.62)
Lifetime mental age (years)	7.89 (3.27)	7.66 (2.89)	7.92 (3.41)	7.90 (3.30)	8.86 (4.01)
Clinical status					
AD	0 (0%)	6 (5%)	3 (5%)	2 (4%)	1 (6%)
MCI-DS	9 (8%)	8 (7%)	7 (11%)	7 (15%)	4 (23%)
Unaffected	103 (87%)	101(86%)	53 (82%)	37 (77%)	12 (71%)
Unable to determine	6 (5%)	3 (3%)	2 (3%)	2 (4%)	0 (0%)
PET PIB scans					
Sample N	118	70	35	9	
Global SUVR M (SD)	1.21 (0.26)	1.27 (0.34)	1.31 (0.39)	1.26 (0.28)	–
Striatum SUVR M (SD)	1.41 (0.39)	1.54 (0.51)	1.62 (0.52)	1.51 (0.41)	–
Global PiB(+) N (%)	20 (17%)	26 (22%)	13 (37%)	2 (22%)	–
Striatum PiB(+) N (%)	29 (25%)	43 (36%)	19 (54%)	5 (56%)	–

Abbreviations: AD, Alzheimer's disease; MCI-DS, mild cognitive impairment-Down syndrome; PiB, Pittsburgh compound B; SD, standard deviation; SUVR, standard uptake value ratio.
Note: Lifetime mental age assessed with Peabody Picture Vocabulary Test-Fourth Edition.

than those who did not (t [117] = 2.15, P = .031). Informed consent was obtained prior to data collection. Participant characteristics are in Table 1.

2.2 | Measures

2.2.1 | Clinical AD status

AD status was based on a diagnostic case consensus that included at least three staff with clinical expertise in AD in DS. Information considered: (1) medical/psychiatric history and neurological exam; (2) caregiver report of participant's functioning and life events; (3) participant's adaptive skills on the Vineland Adaptive Behavior Scales;[32,33] (4) caregiver report of participant's dementia symptoms on Dementia Questionnaire for People with Learning Disabilities[34] or Dementia Scale for Down syndrome;[35] (5) participant's profile on the Down Syndrome Mental Status Examination,[36] Developmental Test of Visual-Motor Integration, 5th Edition,[37] Wechsler Intelligence Scale for Children[38] Block Design and Haxby extension,[39] and Developmental NEuroPSYchological Assessment[40] Word Generation Semantic Fluency. All time points of data were considered. Staff were blind to imaging.

Clinical status categories: (1) cognitively stable, indicating no cognitive decline beyond normative aging; (2) mild cognitive impairment-DS (MCI-DS), indicating mild cognitive and/or functional decline; (3) AD, indicating substantial cognitive and functional decline; (4) unable to

determine, indicating decline but might be caused by life circumstances or non-AD conditions.

2.2.2 | Biological sex and chronological age

Caregivers reported the participants' biological sex and his/her date of birth, which was used to calculate chronological age in years.

2.2.3 | Lifetime cognitive ability

The Peabody Picture Vocabulary Test-Fourth Edition[41] mental age administered at Time 1 assessed lifetime cognitive ability. This measure of receptive language is reliable and valid in adults with DS and highly correlated with IQ.[42]

2.2.4 | Episodic memory

The Cued Recall Test measures episodic verbal memory and has been shown to be reliable and valid in DS.[43] Participants attempt to learn 12 pictures that are linked to categories. The Free and Cued Recall score is the number of pictures recalled across three free and cued recall trials (ie, category given). Cued Recall Intrusions is the number of incorrectly recalled pictures in the cued recall trials.

2.2.5 | Attention

The Developmental NEuroPSYchological Assessment[40] Bunny Cancelation assesses visual attention and has adequate construct validity.[14] Individuals are shown pages with a series of small pictures and asked to strike out the bunnies. The total score is the sum of correct responses minus omission and commission errors.

2.2.6 | Executive functioning

The Cat and Dog Modified Stroop Task (44) assesses executive functioning. Individuals first name a series of pictures of cats and dogs and are then asked to reverse the names (switch trial). Cat-Dog Switch Errors is the number of incorrect responses in the switch trial and has been shown to be associated with other measures of executive functioning.[20]

2.2.7 | Visuospatial ability

The Wechsler Block Design[38] and Haxby extension[39] assess visuospatial ability. Raw scores were summed. These Block Design tasks have been found to be able to differentiate adults with DS with versus without dementia.[45]

2.2.8 | Motor planning and coordination

The Purdue Pegboard[46] assesses fine motor planning and coordination and has been found to be negatively associated with Aβ deposition in DS.[20] Individuals are asked to place pegs into holes on a pegboard. The Both Hands trial was used, in which participants use both hands simultaneously to put pegs into holes.

2.2.9 | MRI

Scans involved 3T MRI systems using T1-weighted pulse sequences on GE Discovery MR750 (Wisconsin), Siemens Trio or Prisma (Pittsburgh), and GE Signa PET/MR (Cambridge).

2.2.10 | PiB PET

[C-11]PiB (15 mCi, nominal) was injected intravenously, with scans 50 to70 minutes post-injection. Images were binned in 4- to 5-minute time frames. In Wisconsin, scanning was performed on Siemens HR+ with data reconstructed via direct Fourier transform (DIFT) for early scans and ordered subsets expectation maximization (OSEM) for later scans. In Pittsburgh, scans were initially acquired on Siemens HR+ and reconstructed via DIFT, and later on Siemens 4-ring Biograph mCT and reconstructed via OSEM.

In Cambridge, scans were performed on GE Signa PET/MR and reconstructed via VPHD, GE's fully 3D OSEM algorithm. Reconstruction corrected for attenuation, scatter, deadtime, and radioactive decay.

2.2.11 | Image processing

Reconstructed images were inspected for interframe motion and corrected using PMOD (PMOD Technologies, Zurich, Switzerland). Four time frames were averaged into a single frame 50- to 70-minute image. Freesurfer 5.3 was used to parcellate the image into regions of interest (ROIs) using established methods.[47] Forty-six of the FreeSurfer/CIC-based regional concentrations were combined into nine standard quantitation regions. Global regional activity was the volume weighted average of the nine regions. Cerebellar gray matter radioactivity concentrations were used to normalize regional values. Threshold for PiB+ was standard uptake value ratio (SUVR) above the following in at least one region[48]: anterior cingulate: 1.47; anterior ventral striatum: 1.37; orbito frontal: 1.39; insula: 1.30; lateral temporal: 1.28; parietal: 1.34; posterior cingulate: 1.49; precuneus: 1.51; and superior frontal: 1.33. Participants consistently PiB− were considered in normative aging. Converters from PiB− to PiB+ were considered to have recently transitioned to preclinical stage, and those consistently PiB+ were considered to be approaching or in prodromal stage.

2.3 | Procedure

Participants completed two to five time points between 2009 and 2019. Time points were spaced 16 to 36 months apart (mean [M] = 28.32, standard deviation [SD] = 14.23) based on study design. At each time point, a 2.5-hour cognitive battery was administered. Participants (N = 118) underwent MRI and PiB PET scans at one least once. A second (N = 70), third (N = 35), and fourth (N = 9) time point of PiB PET was collected for some participants at Time 2 and/or Time 3 and Time 5 (depending on when entered study). Clinical AD status was evaluated at each time point. Cross-site validation processes were used to standardize procedures.

2.4 | Statistical analysis

Distributions of variables and histograms of residuals were reviewed. Seven (6%) of the 118 participants were missing ≥ 1 cognitive score due to a lack of complying with instructions. Multilevel models using hierarchical linear modeling software[49] were conducted to examine the effect of initial PiB global SUVR (continuous variable) on within-person change in cognitive performance, while controlling for and examining between-person (level 2) differences in initial performance. Time was entered in level 1 and coded in months; Time 1 = 0 and each subsequent time point coded in months since 0. Initial PiB global SUVR was entered at level 2 and interacted with time. Biological sex and

lifetime cognitive ability were entered at level 2 and also interacted with time. To control for normative aging effects (outside of Aβ), Time 1 chronological age was entered at level 2 and interacted with time. Performance site dummy codes were entered to control for site differences.

Multilevel models were also used to examine the initial level and rate of decline in cognitive measures based on PiB status (ie, −/+) for the 70 participants who had two or more time points of PET data. Time was entered at level 1 and chronological age, biological sex, lifetime cognitive ability, and site were entered at level 2 and interacted with time. PiB status groups were: consistently PiB− across time points, consistently PiB+ across time points, and converted PiB− to PiB+. Groups were dummy coded and entered at level 2 to examine differences in initial performance and interacted with time to examine differences in decline rate.

3 | RESULTS

3.1 | Preliminary analyses

At Time 1, participants had an average age of 37.24 years (SD = 7.70) and lifetime mental age of 7.89 years (SD = 3.27; Table 1). Approximately one half were female (N = 61; 52%). Nine (8%) participants had a clinical status of MCI-DS, 6 (5%) unable to determine, and 103 (87%) cognitively stable. Across time points, 7 (6%) participants subsequently received a status of AD and 14 (12%) MCI-DS. At Time 1, 20 (17%) of the 118 participants were PiB+ and 98 were PiB−. Of the 70 participants with ≥ 2 time points of PET data, 48 (69%) participants were consistently PiB−, 11 (16%) consistently PiB+, and 11 (16%) converted PiB− to PiB+. At Time 1, floor level scores occurred on Free and Cued Recall (N = 1, 1%) Block Design (N = 2, 2%), and Cancellation (N = 1, 1%).

3.2 | Initial PiB SUVR and cognitive decline

Table 2 displays models examining the effect of initial global PiB SUVR on level and rate of performance decline. At the between-person level, when other variables were at their mean, chronological age had a significant negative effect on initial Free and Cued Recall and Cancelation scores and positive effect on Cued Recall Intrusion. Males initially performed better on Cancellation than females. Lower lifetime cognitive ability was related to worse initial performance on all measures. There was one significant effect of performance site (Block Design); thus, only this site contrast (Pittsburgh vs Cambridge) was included in final models. PiB global SUVR was significantly related to initial performance on all measures except Purdue Pegboard. In all cases, higher initial PiB SUVR was associated with worse performance.

At the within-person level, time had a significant effect on Free and Cued Recall, Cued Recall Intrusion, and Purdue Pegboard with performance worsening across time. However, there was also a significant interaction of time x initial PiB global SUVR on Free and Cued Recall, Cancellation, and Block Design. On these measures, higher initial PiB global SUVR was associated with greater rate of decline. There was also a significant interaction of time x chronological age on Free and Cued Recall, Cued Recall Intrusions, Cancellation, and Purdue Pegboard, with older participants evidencing greater decline rate than younger.

There was not a significant interaction of time x biological sex nor interaction of time x lifetime cognitive ability on measures. Three-way interactions of time x PiB global SUVR x biological age or time x PiB global SUVR x lifetime cognitive ability were tested but not significant. Insignificant interactions were removed to aid in the interpretation of significant coefficients.

3.3 | PET PiB status change and cognitive decline

Table 3 displays results assessing level and decline based on PiB status groups. At the between-person level (level 2), chronological age and lifetime cognitive ability had significant effects on initial performance in line with the previous models. In addition, females initially performed worse than males on Cued Recall Intrusions. PiB group status was significantly associated with initial Free and Cued Recall, Cued Recall Intrusions, Cancellation, and Block Design. For Free and Cued Recall and Cued Recall Intrusions, the consistently PiB+ group initially performed worse than the consistently PiB− group, and worse than the converter PiB− to PiB+ group. There was not a significant difference in initial Free and Cued Recall or Cued Recall Intrusions between the consistently PiB− and converter PiB− to PiB+ groups. For Cancellation, Cat and Dog Errors, Block Design, there was only a significant difference between the consistently PiB+ and converter PiB− to PiB+ groups.

At the within-person level (level 1), time had a significant effect on decline rate in Free and Cued Recall, Cued Recall Intrusions, Block Design, and Purdue Pegboard. Across time, participants evidenced performance worsening. There was a significant interaction of time x chronological age for Free and Cued Recall and Cancellation—older participants evidenced greater decline than younger. There was a significant interaction of time x PiB status groups for Free and Cued Recall, Cued Recall Intrusions, Cancellation, and Block Design. For Free and Cued Recall and Cued Recall Intrusions, the consistently PiB+ group declined at a greater rate than the consistently PiB− and converters PiB− to PiB+ groups. Figures 1 and 2 display individual spaghetti plots for the Cued Recall scores by PiB status groups.

On Cancelation and Block Design, the consistently PiB+ group evidenced greater rate of decline than the consistently PiB− group. There was not a significant difference in rate of decline between the consistently PiB+ group and converters PiB− to PiB+ for these measures. There was not a significant interaction of time x PiB status groups for remaining measures.

TABLE 2 Multilevel model of within-person change in cognitive performance based on time 1 global PIB SUVR (N = 118)

	Verbal episodic memory		Visual attention	Executive functioning	Visuospatial ability	Motor planning and coordination
	Free and Cued	Cued Recall intrusions	Cancellation	Cat & Dog errors	Block Design	Purdue Pegboard
	Coefficients (standard error), t values					
Level 1 (within-subject)						
Intercept	32.66 (1.11), 29.53**	2 (0.67), 2.99**	16.73 (0.62), 26.53**	0.80 (0.93), 0.86	25.07 (2.30), 10.22**	7.76 (0.45), 17.38**
Time	−0.94 (0.25), −3.72**	0.90 (0.18), 4.87**	0.09 (0.14), −1.09	−0.17 (0.18), 0.93	0.04 (0.26), −1.43	−0.31 (0.08), −4.17**
Level 2 (between-subject)						
Site	−0.58 (0.51), −1.14	0.54 (0.39), 1.42	0.47 (0.25), −1.98	0.49 (0.46), 1.06	−2.01 (0.84), −2.12*	−0.08 (0.21), −0.39
Chronological age	−0.17 (0.06), −2.61*	0.14 (0.05), 2.98**	−0.07 (0.02), −2.70**	0.04 (0.04), 1.11	−0.03 (0.12), −0.21	−0.03 (0.02), −1.19
Biological sex	−0.20 (0.73), −0.27	0.50 (0.48), 1.06	0.92 (0.36), 2.59*	0.57 (0.59), 0.97	1.98 (1.43), 1.41	−0.51 (0.28), −1.83
Lifetime cognitive ability	0.62 (0.17), 3.73**	−0.31 (0.10), −3.12**	0.30 (0.07), 4.42**	−0.54 (0.13), −4.12**	1.85 (0.24), 7.52**	0.26 (0.04), 6.93**
T1 PiB SUVR	−8.67 (1.72), −5.04**	4.73 (1.21), 3.89**	−2.23 (0.79), −2.81**	3.70 (1.24), 2.99**	−6.74 (2.32), −282**	−0.83 (0.45), −1.84
Level 1 x Level 2						
Time X T1 PiB SUVR	4.60 (0.81), −5.70**	1.36 (0.73), 1.98	−2.79 (0.98), −2.41*	0.95 (0.59), 1.62	−1.18 (0.52), −2.71*	−0.29 (0.25), −1.17
Time x chronological age	−0.09 (0.04), −2.16*	0.09 (0.03), 2.79**	−0.10 (0.04), −0.30*	0.01 (0.04), 0.42	−0.01 (0.02), −1.86	−0.03 (0.01), −2.91**

Note: **$P \leq .01$; *$P < .05$. T1 = Time 1. Site = Pittsburgh versus Cambridge (0); Sex: 1 = female, 2 = male.

Abbreviations: PiB, Pittsburgh compound B; SUVR = standard uptake value ratio.

TABLE 3 Multilevel model of within-person change in cognitive performance based on PiB status groups (consistently PiB− vs converters PiB−/+ vs consistently PiB+; N = 70)

	Verbal episodic memory		Attention	Executive functioning	Visuospatial ability	Motor planning and coordination
	Free and Cued	Cued Recall intrusions	Cancellation	Cat & Dog errors	Block Design	Purdue Pegboard
	Coefficients (standard error), t values					
Level 1 (within-subject)						
Intercept	31.58 (1.31), 24.04**	3.24 (0.89), 3.65**	16.48 (0.82), 20.02**	1.53 (1.21), 1.26	24.16 (3.10),7.81**	7.10 (0.81), 8.72**
Time	−0.06 (0.01), −6.58**	0.04 (0.007), 5.81**	−0.007 (0.005), −1.36	0.001 (0.007), 0.22	−0.02 (0.01), −2.12*	−0.04 (0.01), 7.35**
Level 2 (between-subject)						
Site	−0.69 (1.09), −0.61	0.01 (0.80), 0.01	−0.37 (0.54), −0.68	0.38 (0.88), 0.43	−3.15 (2.09), −1.50	−0.30 (0.54), 0.56
Chronological age	−0.08 (0.09), −0.92	0.08 (0.06), 1.24	−0.09 (0.05), −2.08*	0.08 (0.08), −3.05**	0.05 (0.20), −0.23	0-0.08 (0.05), −1.77
Biological sex	−0.30 (0.94), −0.32	−0.28 (0.12), −2.35*	0.79 (0.52), 1.52	0.67 (0.82), 0.82	1.71 (1.91), 0.89	−0.25 (0.49), −0.52
Lifetime cognitive ability	0.46 (0.16), −3.94**	−0.31 (0.10), −3.12**	0.27 (0.09), 3.08**	−0.50 (0.17), −3.06**	1.79 (0.33), 5.14**	−0.29 (0.07), 4.35**
PiB status across time						
PiB− vs PiB+	−7.07 (2.24), −3.15**	4.07 (1.66), 2.46*	−1.92 (1.03), −1.86	3.09 (1.93), 1.60	−6.31 (4.24), −1.49	−1.14 (0.96), −1.20
PiB− vs PiB− to PiB+	0.46 (1.50), 0.31	−0.44 (0.84), −0.53	0.16 (0.43), 0.36	−0.11 (1.50), −0.08	−0.77 (3.82), −0.20	0.43 (0.98), 0.45
PiB+ vs PiB− to PiB+	10.05 (1.97), 5.10**	−6.41 (1.50), −4.28**	2.31 (0.79), 2.95**	−5.08 (1.77), −2.86**	4.77 (2.01), 2.32*	1.19 (0.87), 1.38
Level 1 x Level 2						
Time X age	−4.60 (0.81), −5.70**	1.36 (0.73), 1.98	0.01 (0.01), 0.69**	0.002 (0.001), 1.35	−0.002 (0.002), -0.90	−0.002 (0.0009), −1.89
Time X PiB− vs PiB+	−0.19 (0.04), −4.77*	0.09 (0.03), 2.87**	−0.06 (0.02), −2.83**	0.02 (0.02), 1.04	−0.14 (0.04), −3.22**	−0.04 (0.02), −1.70
Time X PiB− vs PiB− to PiB+	−0.03 (0.03), −1.12	0.04 (0.02) 1.81	−0.01 (0.02), −0.47	−0.04 (0.03), −1.75	−0.05(.04), −1.28	0.003 (0.02), 0.19
Time x PiB+ vs PiB− to PiB+	0.17 (0.04), 4.70**	−0.10 (0.02), −4.43**	0.04 (0.02) 1.82	−0.05 (0.04), −1.45	0.10 (0.05), 2.05	0.03 (0.02), 1.57

Notes: ** $P < .01$; * $P < .05$. T1 = Time 1. Site = Wisconsin (1) versus Pittsburgh and Cambridge (2); Sex: 1 = female, 2 = male. PiB status group comparisons used dummy coding with the first group coded as 0 and the second group coded as 1 in each comparison. Consistently PiB (1) = 48; Consistently PiB+ = 11, converters PiB− to PiB+ = 11.

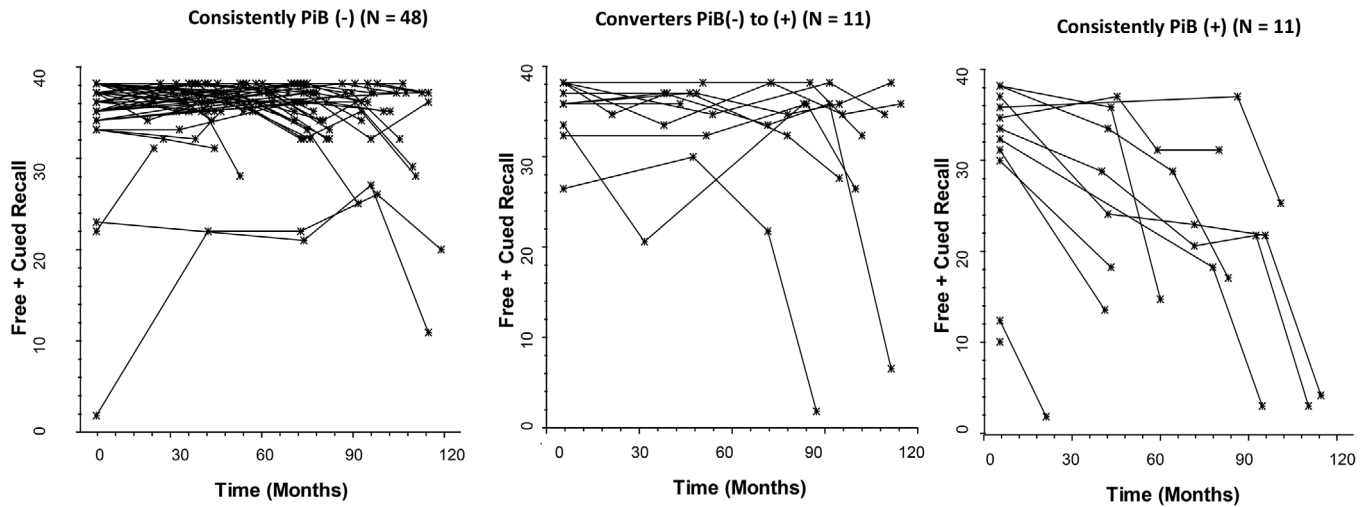Abbreviations: PiB, Pittsburh compound B; SUVR = standard uptake value ratio.

FIGURE 1   Free and Cued Recall Total score across time for adults with Down syndrome who were consistently Pittsburgh compound B negative (PiB−) versus those who converted PiB− to positive (+) or were consistently PiB+
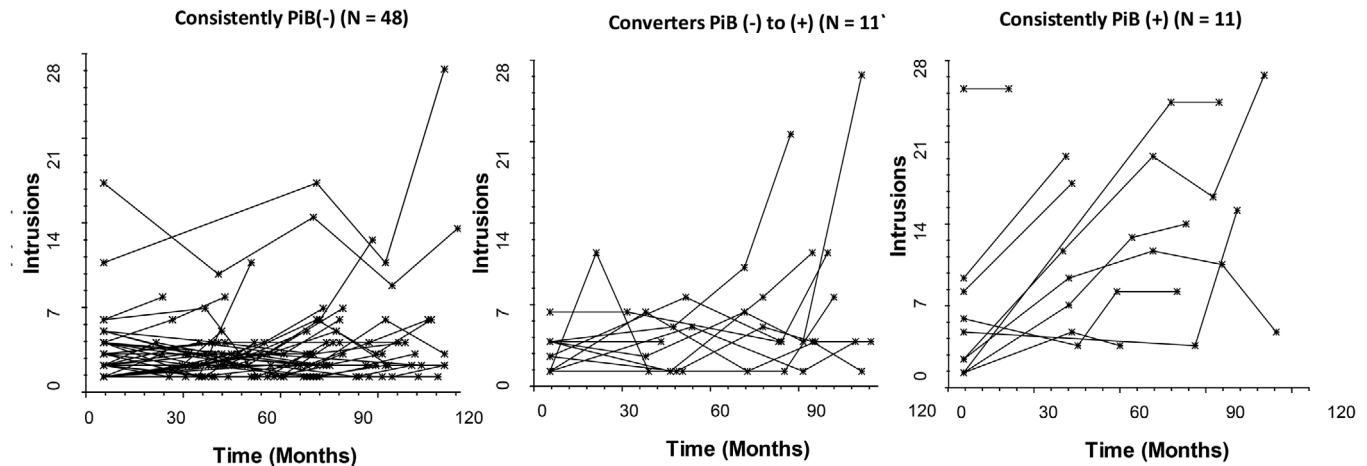

FIGURE 2   Intrusions to Cued Recall across time for adults with Down syndrome who were consistently Pittsburgh compound B negative (PiB−) versus those who converted PiB−to positive (+) or were consistently PiB+

4 | DISCUSSION

To our knowledge, this is the largest and longest evaluation of cognitive performance and imaging biomarkers in adults with DS that captures the transition to preclinical and prodromal AD. Across episodic memory, visual attention and executive function, adults with DS with higher Aβ burden evidenced lower initial level and greater decline rate in performance than those with lower Aβ burden. This was true after controlling for chronological age, and thus accounting for normative aging.

Mixed evidence has been previously reported regarding biological sex[22-24] and lifetime cognitive ability[27,28] and age of clinical AD onset in DS. In the current study, there were only modest biological sex differences in initial level of visual attention and episodic memory, with females performing worse than males. However, males and females had a similar normative aging rate of decline, and Aβ burden had a

similar effect on rate of decline. Adults with DS with lower lifetime cognitive ability performed worse, but declined at the same rate and were similarly impacted by Aβ burden, as those with higher lifetime cognitive ability. Previous studies reporting biological sex or lifetime cognitive ability effects focused on transition to clinical AD.[22-24,27,28] Thus, it is possible that biological sex and lifetime cognitive ability alter later but not earlier AD stages in DS.

When examining PiB status, adults with DS who were consistently PiB+ initially performed worse on the episodic memory measure than those consistently PiB− or who converted PiB− to PiB+. Moreover, adults with DS consistently PiB+ initially performed worse on visual attention, executive functioning, and visuospatial tasks than those who converted PiB− to PiB+. With regard to rate of decline, measures of episodic memory, visual attention, and visuospatial ability differentiated adults with DS consistently PiB+ from those who were

consistently PiB−. However, only the Cued Recall Test also differentiated the consistently PiB+ group from converters PiB− to PiB+. Rate of decline in executive functioning and motor planning and coordination did not differ by PiB status groups, and thus these measures may not be sensitive to early AD. The absence of differences between the consistently PiB− group and converters PiB− to PiB+ underscores that cognition remains intact for a period after elevated Aβ.

Overall, the Cued Recall Test emerged as a promising indicator of transition to MCI-DS, in models controlling for chronological age. Adults with DS without elevated Aβ burden had relatively high and stable performance on this measure. Similarly, those who recently transitioned to the preclinical stage by developing Aβ burden (converted PiB− to PiB+) did not differ from this cognitively stable group. In contrast, adults with DS who began and remained PiB+, and thus had elevated Aβ for longer, differed from these former groups and evidenced a lower level and greater decline across time. The Cued Recall Test may be a valuable tool as an outcome in AD clinical trials by identifying MCI-DS.

There are strengths to the study. The study drew on a large study, leveraged all available time points, and employed directly administered cognitive measures. The study also had limitations. Inclusion criteria included baseline mental age of ≥30 months. Only 11 adults with DS converted PiB− to PiB+, and it is not known how long adults with DS who began PiB+ had elevated Aβ burden. Determining diagnostic status is also inherently difficult. In line with theoretical models,[10] future studies should combine biomarkers of Aβ with other pathophysiology to further identify cognitive indicators of preclinical and prodromal AD in DS.

FUNDING

CONFLICTS OF INTEREST

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