Cognitive Decline and Brain Amyloid-β Accumulation across 3-years in Adults with Down Syndrome

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Abstract

Adults with Down syndrome (DS) have a high incidence of Alzheimer's disease (AD), providing a unique opportunity to explore the early, preclinical stages of AD neuropathology. We examined change in brain amyloid-β accumulation via the PET tracer [11C] Pittsburgh compound B (PiB) across two data collection cycles, spaced 3 years apart, and decline in cognitive functioning in 58 adults with DS without clinical AD. PiB retention increased in the anterior cingulate gyrus, precuneus cortex, parietal cortex and anterior ventral striatum. Across the two cycles, 14 (27.5%) participants were consistently PiB+, 31 (60.8%) were consistently PiB−, and 6 (11.7%) converted from PiB− at Cycle 1 to PiB+ at Cycle 2. Increased global amyloid-β was related to decline in verbal episodic memory, visual episodic memory, executive functioning, and fine motor processing speed. Participants who were consistently PiB+ demonstrated worsening of episodic memory, whereas participants who were consistently PiB− evidenced stable or improved performance.

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Amyloid-β accumulation may be a contributor to or biomarker of declining cognitive functioning in preclinical AD in DS.

Keywords

Down syndrome; Alzheimer's disease; PiB; amyloid-β; mild cognitive impairment; dementia; amyloid

Down syndrome (DS), estimated to occur in 1 in 691 live births (Parket et al., 2006), is a developmental disability most commonly due to a third copy of chromosome 21. Adults with DS evidence 'accelerated aging' (Horvath et al., 2015; Patterson & Cabelof, 2012), including earlier onset and increased incidence of Alzheimer's disease (AD). Indeed, nearly all adults with DS evidence neuropathology of AD by their fourth decade of life (Mann & Esiri, 1989; Wisniewski, Wisniewski, & Wen, 1985) and more than half of adults with DS in their 60s exhibit clinical symptoms of AD (Coppus et al., 2006; McCarron et al., 2014). The early onset and increased incidence of AD in adults with DS is attributed to the overproduction of amyloid-β due to the triplication of chromosome 21, which contains the gene for the amyloid precursor protein (APP) (Wiseman et al., 2015). The accumulation of amyloid-β plaques, followed by neurofibrillary tangles of the protein tau, is an early event in the pathogenesis leading to clinical AD years to decades later (Hardy & Higgins, 1992). However, whether amyloid-β accumulation is a contributor to or a relevant biomarker of subtle declines in cognitive functioning during the transitionary stage (mild cognitive impairment [MCI]), prior to the clinical onset of AD, is unclear. The current study examined the impact of amyloid-β accumulation across two data collection cycles (3 years apart) on declines in cognitive functioning in 58 adults with DS without clinical AD at Cycle 1.

Longitudinal studies on the general population have examined amyloid-β accumulation, via the positron emission tomography (PET) tracer [^{11}C] Pittsburgh compound B (PiB), during the later-stages of AD and found a consistent worsening of cognitive functioning based on initial PiB retention (indicating higher amyloid-β accumulation) (Kadir et al., 2012; Villemagne et al., 2011; Yau et al., 2015). However, findings regarding PiB retention and cognitive functioning during the earlier-stages of AD (MCI) are varied. Some studies report that higher PiB retention was associated with poorer memory and executive functioning performance (Mormino et al., 2009; Rowe et al., 2010; Wolk et al., 2009) while other studies found no association (Aizenstein et al., 2008; Forsberb et al., 2010; Jack et al., 2008; Sperling et al., 2009; Storandt et al., 2009).

In the DS population, there is some evidence that neocortical amyloid-β accumulation, as assessed via the PET tracer PiB is associated with lower cognitive performance. However, conclusions are limited due to cross-sectional designs (Annus et al., 2016; Handen et al., 2012; Hartley et al., 2014; Nelson et al., 2011), small sample sizes (Handen et al., 2012), and restricted neuropsychological batteries of cognitive functioning (Nelson et al., 2011). In the largest cross-sectional study, and the one with the most extensive battery of directly-administered neuropsychological measures, Hartley et al. (2014) found a negative association between neocortical PiB retention and verbal and visual episodic memory, executive functioning, and expressive language in 63 adults with DS (aged 30–50 years)

who did not exhibit clinical signs of AD. A handful of studies have also examined neocortical amyloid-β accumulation in the preclinical stages of AD in DS using the PET tracer Florbetapir (Rafii et al., 2015; Sabbagh et al., 2015). In a sample of 12 adults with DS without clinical AD, Florbetapir-PET was not significantly associated with cognitive functioning (Rafii et al., 2015). Chronological age was strongly associated with PiB - or Florbetapir-PET retention in several previous cross-sectional studies (Annus et al., 2016; Hartley et al., 2014; Nelson et al., 2011; Sabbagh et al., 2015), such that the effect of normative age-related decline may have been indistinguishable from the effect of amyloid-β accumulation.

The current study builds on the Hartley et al. (2014) study by examining change in global PiB retention using PET-PIB in relation to subtle declines in cognitive functioning across two time points (3 years apart) in the same sample. In addition to assessing neocortical PiB retention, we examined PiB retention in the striatum, as it is the brain region with the earliest amyloid-β accumulation in the DS population (Annus et al., 2016; Lao et al., 2016). PiB retention was evaluated as both a continuous variable and dichotomous variable by categorizing adults with DS as PiB + versus PiB−, in line with previous studies (Annus et al., 2016; Hartley et al., 2014; Nelson et al., 2011; Lao et al., 2016). Analyses were conducted with and without controlling for chronological age to separate out the effects of normative aging from those of amyloid-β accumulation. An increase in global PiB retention from Cycle 1 to Cycle 2 was hypothesized to be associated with a decline in cognitive functioning, particularly verbal and visual episodic memory, executive functioning and expressive language, in adults with DS. Moreover, adults with DS who converted from PiB− to PiB+ or who were consistently PiB+ across the study cycles were predicted to experience greater declines in cognitive functioning relative to adults with DS who were consistently PiB− across study cycles.

Methods

Participants

Participants were part of a longitudinal study consisting of 81 adults with DS at Cycle 1. There were two study sites: [removed for review] and [removed for review]. The Internal Review Board at both study sites reviewed and approved the study. Consent or assent for study participation was obtained from all adults with DS. Proxy consent was obtained from caregivers who served as legal guardians. Inclusion criteria included being   30 years, genetic testing indicating trisomy 21, mental age   2.5 years, at least minimal verbal communication (3 word utterances), no medical condition that contraindicated brain imaging, no medical/psychiatric condition impairing cognition, and not having received a diagnosis of AD or other dementia. The Dementia Scale for Down syndrome (DSDS; Geyde, 1995) was conducted with caregivers to verify that participants did not exhibit dementia. All but two participants scored in the asymptomatic range (< 3 Cognitive Cutoff Score) on the DSDS at Cycle 1. The two participants above this cutoff (both score of 3) were judged to not have AD (based on clinical case consensus review using information from a directly-administered dementia screen and caregiver interview), but thought to have MCI. None of the participants took memory enhancement/AD medications at Cycle 1. Of the 81

adults with DS at Cycle 1, 58 had neuropsychological data at Cycle 2 (2 medical condition precluded imaging, 5 declined, 5 could not be reached, and 11 did not reach Cycle 2 window but will be followed in later study) and are included in current analyses. Independent sample t-tests and chi-square statistics indicated no significant differences in race/ethnicity, sex, mental age, or Cycle 1 PiB retention between these 58 participants and the participants without Cycle 2 data. Table 1 presents the socio-demographics of the 58 participants in current analyses. Five participants did not have useable brain imaging scans at both cycles (1 did not complete and 4 had excessive motion); thus 53 participants are in analyses involving change in PiB retention.

Procedure

Participants completed two cycles of data collection between 2010 and 2015, spaced 3 years apart (range: 2.1 to 4.3 years). Each cycle consisted of Day 1 neuropsychological evaluation (3–4 hours) and Day 2 brain imaging scans (3 hours). Day 2 was performed within 5 months of Day 1 ($M = 20.8$ days, $SD = 57.3$ days). Participants were evaluated at two sites; examiners underwent training and cross-site validation. Examiners were blind to imaging results, caregiver interview data, and Cycle 1 neuropsychological scores.

Neuropsychological Evaluation

Adaptive behavior—The Vineland Adaptive Behavior Scales, 2nd Edition (Sparrow et al., 2005), was completed by caregivers. The General Adaptive Composite score assessed adaptive functioning and has strong psychometric properties (Sparrow et al., 2005).

Dementia screens—The DSDS is a caregiver-interview screen for dementia in adults with DS that has a specificity rate of 0.90 and a sensitivity rate of 0.85 (Gedye, 1995). The Severe Impairment Battery Short Form (SIB; Saxton et al., 2005) is a 26-item direct assessment of cognitive impairments indicative of dementia.

Verbal learning and memory—The Cued Recall Test (Zimmerli & Devenny, 1995) assesses verbal learning and episodic memory. The Free Recall (number of objects correctly recalled during the free recall trials), Free and Cued Recall (number of objects correctly recalled in free recall and cued recall trials), and Cued Recall Intrusion (number of incorrect responses in the cued recall trials) scores are sensitive to dementia in DS (Zimmerli & Devenny, 1995). The Wechsler Memory Scale, 4th Edition (WISC-IV; Wechsler, 2004) Story Recall Logical Memory I and Logical Memory II assess immediate and delayed recall of verbal information and are sensitive to memory decline in DS (Brugge et al., 1994).

Visual memory—The Visual Memory subtests of the Rivermead Behavioral Memory Test for Children (RBMT; Wilson et al., 1991) assesses visual episodic memory and have been used in DS (Hartley et al., 2014).

Attention and processing speed—The Wechsler Intelligence Scales for Children-Revised (WISC-R; Wechsler, 1974) Digits Forward (sum of the number of digits in trials remembered correctly) has been used with adults with DS (Devenny et al., 2005). The Corsi Block Tapping Forward (sum of the number of digits in trials remembered correctly)

measures visuospatial memory (Shapiro et al., 1992). The NEPSY Visual Attention subtest assesses visual attention (Visual Attention Accuracy) and processing speed (Visual Attention Time) and is appropriate in DS (Heller et al., 2006).

Executive and working memory—The Stroop Dog and Cat Task (Ball et al., 2008), is a modified Stroop task of executive functioning shown to identify memory changes in adults with DS (Nash & Snowling, 2008). The Cat Dog Switch Error score is the number of errors made in the switch trial. The Cat Dog Switch Time score is the switch trial time minus the initial trial time. The WISC-IV (Wechsler, 2004) Digit Span Backwards (sum of the number of digits in trials remembered correctly) and Corsi Span Backward (sum of the number of digits in trials remembered correctly) assess short-term working memory and are valid in DS (Devenny et al., 2005).

Visuospatial construction—The Developmental Test of Visual-Motor Integration, 5th Edition (VMI; Berry et al., 2004) assesses visual-motor integration skills. The Purdue Pegboard (Bega, 1969) assesses fine motor functioning speed (Purdue Single and Both Time) and executive functioning (Both Hands score). The WISC-IV (Wechsler, 2004) Block Design and Haxby extension (Haxby, 1989) assesses visuospatial construction and are sensitive to dementia in DS (Shapiro et al., 1992).

Language—The NEPSY-2nd Edition (Korkman et al., 2007) Word Generation Semantic Fluency subtest is a valid measure of verbal fluency in DS (Devenny et al., 2005). The Expressive-One Word Picture Vocabulary Test (Brownell, 2000) assesses expressive language. The Peabody Picture Vocabulary Test-4 (PPVT; Dunn & Dunn, 2007) assesses receptive language. Both of these measures have been found to be sensitive to language impairments in individuals with intellectual disability (Ypsilanti, et al., 2005).

Neuroimaging

Magnetic resonance imaging—Structural T_1-weighted 3 T MRI scans using GE Medical Systems (site name) or Siemens Magnetom Trio (site name) scanners were used to acquire high resolution volumetric spoiled gradient or MPRAGE sequence. MRI data was used for PET-MRI registration, region definition, and magnetic resonance-guided correction of PET data for atrophy-related CSF dilution.

Positron emission tomography—[11]C-PiB was synthesized at high specific activity (>2000 mCi/μmol). A nominal dose of 15 mCi of radiotracer was injected by bolus (20–30 s) through an intravenous catheter. Following a 40-min uptake, a 30-min PET acquisition (5 minute frames) was conducted, followed by a 6–10 minute transmission scan to correct for attenuation of annihilation radiation. Siemens ECAT EXACT HR + PET scanners were operated in 3D mode. The data were reconstructed using filtered back-projection and corrected for deadtime, normalization, scatter, and radioactive decay.

Image processing—PET-MRI registration followed automatic methods (Minoshima et al., 1993). Images were re-oriented along the anterior–posterior commissure (AC-PC line). Between-frame motion of PET data was corrected on frame-by-frame basis. PiB retention

was expressed as standardized uptake value ratio (SURV) during 50–70 minute post-injection, using the cerebellar grey matter as the reference region. Regions of interest (ROI) were defined using T1W MRI and transferred to PET data for sampling over single and multiple transverse planes (Rosario et al., 2011) for the six brain regions: frontal cortex, anterior cingulate gyrus, parietal cortex, lateral temporal cortex, and precuneus cortex, and also the striatum (anterior ventral region [AVS]). A composite index of Global PiB representing an average of the six brain regions was also calculated for measuring changes in amyloid burden between imaging cycles. Two-component magnetic resonance-based CSF correction corrected for the partial volume effect of expanded CSF spaces accompanying normal aging and disease-related cerebral atrophy on PiB retention (Meltzer et al., 1999).

PiB+ versus PiB−—Using sparse k-means clustering with resampling (Cohen et al., 2013), PiB+ was defined as exceeding the cut-off in one (or more) of the six regions in the global PiB. Cut-off points (SUVR): frontal cortex = 1.71, anterior cingulate gyrus = 1.78, parietal cortex = 1.63, lateral temporal cortex = 1.50, precuneus cortex = 1.73, and AVS = 1.48 [46].

Data Analysis Plan

Distributions of variables and histograms of residuals were reviewed to assess normalcy of data; there was a normal distribution of data without skew. Although multiple analyses were conducted, an alpha of p 0.05 was used for statistical significance given that small declines in cognitive functioning are anticipated during the transitionary stage of AD. Across cycles, four participants had some missing neuropsychological data due to lack of understanding and/or complying with instructions. At Cycle 1, floor effects (i.e., lowest possible score) occurred in Story Recall Logical Memory (n = 10, 17.9%), Digit Span Backwards (n = 10, 17.9%), Corsi Span Backward (n = 9, 16.4%), and Rivermead Picture Recognition (n = 4, 7.1%). Information on PiB retention change across cycles is provided elsewhere (Lao et al., under review).

Analyses first examined within-person differences on neuropsychological measures from Cycle 1 to Cycle 2 without controlling for chronological age (paired sample t-tests), and then controlling for chronological age (paired sample t-test with covariate). Analyses then examined the association between change in neuropsychological measures (from Cycle 1 to Cycle 2) and change in both global and AVS-only PiB retention (from Cycle 1 to Cycle 2) as a continuous variable, without controlling for chronological age (Pearson correlations) and then controlling for chronological age (multiple linear regressions). The AVS was analyzed individually because this region reveals the earliest presence of elevated PiB binding in the DS population (Annus et al., 2016; Hartley et al., 2014; Nelson et al., 2011; Lao et al., 2016). Finally, one-way analyses of variance (ANOVAs) and Bonferroni-corrected post-hoc comparisons examined differences in neuropsychological measures by PiB categorization status (consistently PiB−, consistently PiB+, and converted from PiB− to PiB+). These analyses were re-run controlling for chronological age using analyses of covariance (ANCOVAs).

Results

Across Cycle 1 to Cycle 2, participants evidenced significant increases in PiB retention in four of the six brain regions: anterior cingulate gyrus, precuneus cortex, parietal cortex and AVS (Table 2). Across cycles, 14 (27.5%) participants were consistently PiB+, 31 (60.8%) participants were consistently PiB−, and 6 (11.7%) participants converted from PiB− at Cycle 1 to PiB+ at Cycle 2. No participant reverted from PiB+ at Cycle 1 to PiB− at Cycle 2.

At Cycle 2, five participants received a DSDS score above the Cognitive Cutoff Score (scores of 3, 3, 4, 4, and 5) indicative of possible dementia. Based on clinical case consensus review using information from dementia screens (SIB and DSDS) and caregivers (Vineland and behavioral/medical history), but without knowledge of PiB retention, three of these participants were deemed to have clinical AD. One converted from PiB− to PiB+ and two were consistently PiB+ across the cycles.

Table 3 displays the means and standard deviations for neuropsychological measures at Cycle 1 and Cycle 2 and the results of the paired sample t-tests examining within-person change across the cycles. Across the sample, there were significant within-person declines on Vineland, Verbal Fluency Number, and Purdue Pegboard Single Hand, and Purdue Pegboard Both Hands, and an increase in Cued Recall Intrusions. Estimated change in neuropsychological measures from Cycle 1 to Cycle 2 when controlling for chronological age is also displayed in Table 3. When chronological age was a co-variate, the same pattern emerged with the addition of significant within-person declines in Free and Cued Recall, Expressive One Word, and VMI (Table 3).

Correlations between change in neuropsychological measures (from Cycle 1 to Cycle 2) and change in PiB retention as a continuous variable (from Cycle 1 to Cycle 2) are presented in Table 4. Correlations were conducted for global PiB retention and then AVS PiB retention alone. Across the two cycles, worsening of performance in Free and Cued Recall Total, Cued Recall Intrusions, Block Design Total, Purdue Pegboard Single Hands, and Rivermead Picture Recognition was significantly associated with an increase in global PiB retention. Table 4 also presents estimates for the association between change in neuropsychological measures (from Cycle 1 to Cycle 2) and change in PiB retention controlling for chronological age. Findings for global PiB retention were the same with and without controlling for chronological age (Table 4). In regard to AVS, worsening of performance in Purdue Pegboard Single Hands was significantly associated with an increase in AVS PiB retention when not controlling for chronological age. However, when controlling for chronological age, a worsening of performance in the VMI and Cat Dog Switch Time were significantly associated with an increase in AVS PiB retention (Table 4).

Table 5 displays the means and standard deviations for neuropsychological measures in Cycle 1 and Cycle 2 by PiB categorization status (consistently PiB−, consistently PiB+, and converted from PiB− to PiB+). One-way ANOVAs indicated a significant difference among PiB categorization status groups in amount of change in Free Recall Total, Free and Cued Recall Total, Cued Recall Intrusions, Block Design, Purdue Pegboard Single Hand, and Corsi Forward (Table 5). Bonferroni post-hoc comparisons (interpreted at $p < .05$) indicated

that the consistently PiB– group exhibited either no change or improvement from Cycle 1 to Cycle 2, whereas the consistently PiB+ group exhibited worsening of performance. The group that converted from PiB– to PiB+ did not significantly differ from the other groups. Based on descriptive statistics, the group that converted from PiB– to PiB+ had a pattern in-between the other groups; on average, they exhibited improvement on Free Recall Total, Block Design, and Corsi Forward from Cycle 1 to Cycle 2 but a worsening of performance on Free and Cued Recall Total, Cued Recall Intrusions, and Purdue Pegboard Single Hands. Table 5 also displays results of the one-way ANCOVAs controlling for chronological age in examining change in neuropsychological measures by PiB categorization status group. There was a significant group difference in Free and Cued Recall Total and Cued Recall Intrusions. Figures 1 and 2 display change from Cycle 1 to Cycle 2 in these two measures by PiB categorization status group. There was also trend-level group difference in Block Design. Bonferroni post-hoc comparisons (interpreted at $p < .05$) indicated that the consistently PiB– group exhibited no change or improvement from Cycle 1 to Cycle 2, whereas the consistently PiB+ group exhibited worsening of performance. There was not a significant group difference in Free Recall, Purdue Pegboard Single Hands, or Corsi Forward when controlling for chronological age.

Discussion

The current study provides the first longitudinal examination of the association between amyloid-β accumulation and declines in cognitive functioning prior to the clinical onset of AD in adults with DS. The study also builds on previous cross-sectional studies in DS (e.g., Annus et al., 2016; Nelson et al., 2011) by including an extensive neuropsychological battery. Across the 3 years, adults with DS evidenced increased amyloid-β accumulation in the AVS and across the neocortex (details see Lao et al., under review).

Overall, an increase in global amyloid-β across the 3-year period was related to subtle declines in verbal episodic memory (Free and Cued Recall Total), visual episodic memory (Rivermead Picture Recognition), visuospatial construction (Block Design), and fine motor processing speed (Purdue Pegboard Single Hands). This pattern remained after controlling for chronological age; thus, an increase in global amyloid-β is related to decreased cognitive function in these areas beyond normative aging. After controlling for normative age-related declines, an increase in amyloid-β in the AVS was associated with declines in executive functioning (Cat Dog Switch Time) and visuospatial construction (VMI), in line with the role of the striatum in inhibiting responses, mental flexibility, and motor performance (Liljehom & O'Doherty, 2012; Mattfelt et al., 2011).

Given evidence from the general population (Villemagne et al., 2013) that amyloid-β accumulation may have little impact on cognitive decline prior to reaching a threshold level (i.e., PiB+), we also examined PiB retention as a dichotomous variable (PiB– versus PiB+). After controlling for chronological age, adults with DS who were consistently PiB+ demonstrated a worsening of performance in episodic memory – remembered less information (Free Recall Total) and made more recall errors (Cued Recall Intrusions) – whereas adults with DS who were consistently PiB– evidenced stable or improved performance. Thus, difficulties remembering newly learned information (e.g., what to buy at

store or who is visiting tomorrow) may be important early indicators that an adult with DS is on the pathway to clinical AD. Across the 3-years, six adults with DS converted from PiB− to PiB+ based on global amyloid-β (neocortical regions and striatum). This translates into a conversion rate of 19% (6 out of the 32 PiB− participants at Cycle 1) over three years. These participants exhibited a pattern that was in-between that of participants who were consistently PiB− and participants who were consistently PiB+.

Our longitudinal findings are consistent with findings in the general population showing a link between neocortical amyloid-β accumulation and memory and executive functioning declines (Mormino et al., 2009; Rowe et al., 2010). In addition, our findings are consistent with cross-sectional findings based on Cycle 1 using this sample (Hartley et al., 2014) in that both analyses indicated a negative association between global PiB retention and verbal and visual episodic memory and executive functioning performance. However, the current longitudinal findings did not indicate an association between expressive language declines and global amyloid-β accumulation. Although, there was an average-level decrease in expressive language (Expressive One Word) across the 3-years, this appeared to be a normative age-related decline. Similarly, in the current analyses, there were declines in adaptive behavior (Vineland), verbal fluency (Verbal Fluency Number), and fine motor processing (Purdue Pegboard) across the 3-years, but these also appeared to be normative age-related declines and were not associated with amyloid-β accumulation.

It is important to note that the large majority (15 of 17) of adults with DS in our sample who were PiB+ at both cycles of data collection remained pre-symptomatic for AD based both on clinical judgement and caregiver report. Indeed, only three adults with DS were deemed to have clinical AD at Cycle 2; two were consistently PiB+ and one converted from PiB− to PiB+. This highlights that declines in cognitive functioning were mild and did not have marked impacts on everyday lives. Yet, these declines may provide meaningful early markers of AD relevant for early screening and as outcomes of interest in therapeutic trials aimed at delaying or preventing clinical AD. Findings may also have relevance to other populations involving amyloid-β overproduction (e.g., autosomal dominant AD) or amyloid-β accumulation in the AVS (e.g., higher Braak neurofibrillary stages; Beach et al., 2012), which has also been shown to correlate with cognitive declines (Wolf et al., 1999).

There were strengths to the current study. We included a relatively large sample of adults with DS and a rigorous neuropsychological evaluation to capture fine-grained declines and understand the specific domains of cognition affected by amyloid-β accumulation. We conducted analyses with and without controlling for chronological age in order to separate normative age-related declines from those associated with the early stages of AD. There were also limitations. An alpha value of .05 was used for significance to allow for the detection of mild cognitive declines. This strategy increases risk of type 2 errors; findings from current study are exploratory until replicated. The current study is not representative of adults with DS who are non-verbal or who have a mental age equivalent of less than 2.5 years. Moreover, floor level effects occurred in some of the neuropsychological measures in a subset of participants (4.1% – 17.9%), meaning it was not possible to detect potential declines across cycles for these participants. Longer-term longitudinal studies with multiple data collection cycles are needed to tease apart time-order causal pathways, and are currently

ongoing. Future studies should examine change in brain structure in relation to declining cognitive functioning and amyloid-β accumulation. Moreover, studies should examine whether increased amyloid-β accumulation is associated with subtle changes in emotional and behavioral functioning in AD, as there is evidence that these domains are also altered in the earliest stages of AD in DS (Ball et al., 2006). In the current study, anti-depressant medication usage increased (29% to 41%) in participants who were consistently PiB+, potentially signaling increased depressive symptoms.

In summary, the current study provides the first longitudinal investigation of early change in biomarkers of amyloid-β accumulation in adults with DS who initially did not have clinical AD. Findings provide important information about the association between early AD neuropathology and cognitive decline, beyond the effects of chronological age. Findings also identify cognitive measures that are sensitive to AD biomarkers in the early preclinical AD stage, and thus may be useful outcomes for therapeutic trials or early AD screening tools in DS.

Acknowledgments

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Highlights

- Amyloid-β increased throughout neocortex and in striatum

- Increased global amyloid-β related to decline in cognitive functioning across 3 years

- PET PiB relevant biomarker of early, preclinical decline in cognitive functioning in DS.
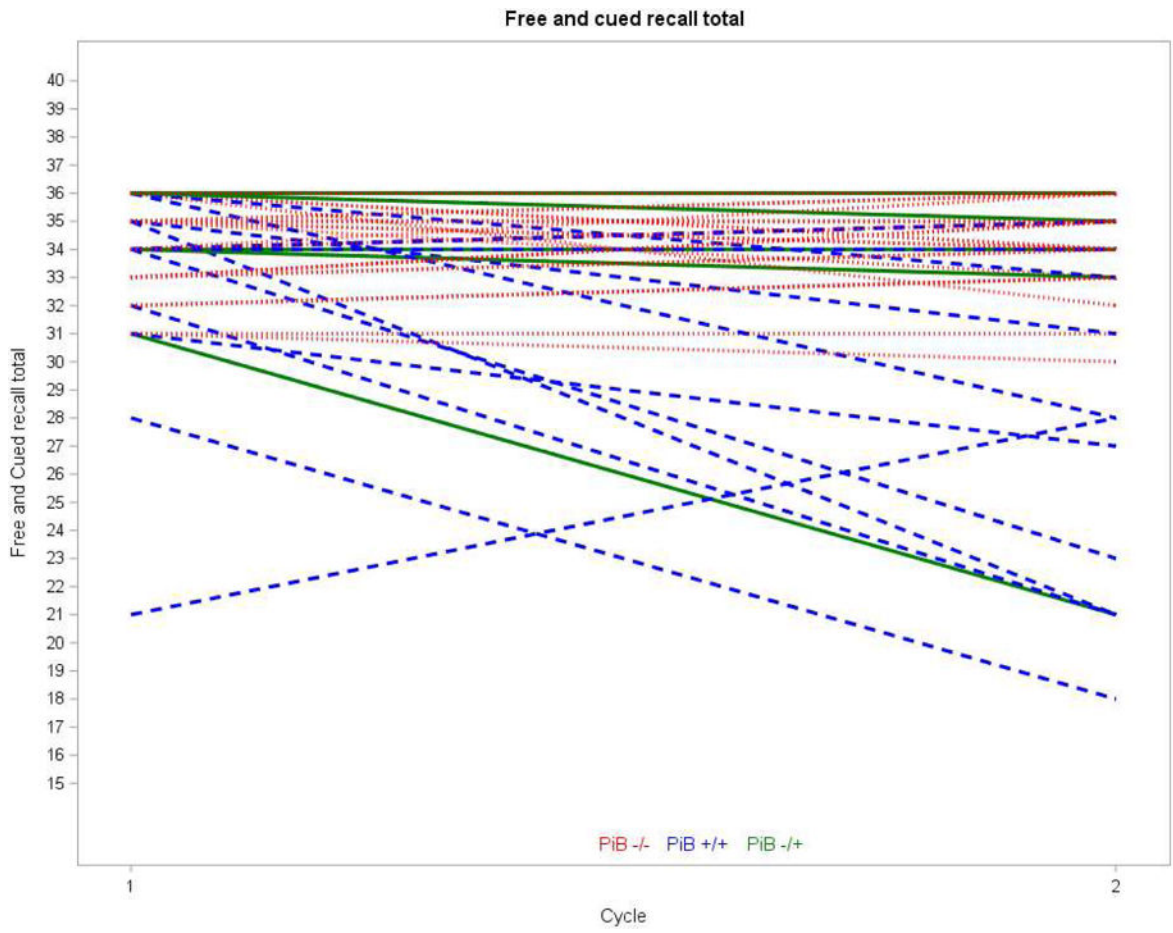
Figure 1.
Change from Cycle 1 to Cycle 2 in Free and Cued Recall Total score by PiB Categorization group. The one participant who had a floor level (i.e., lowest possible score) score at Cycle 1 was removed.

Cued intrusions total
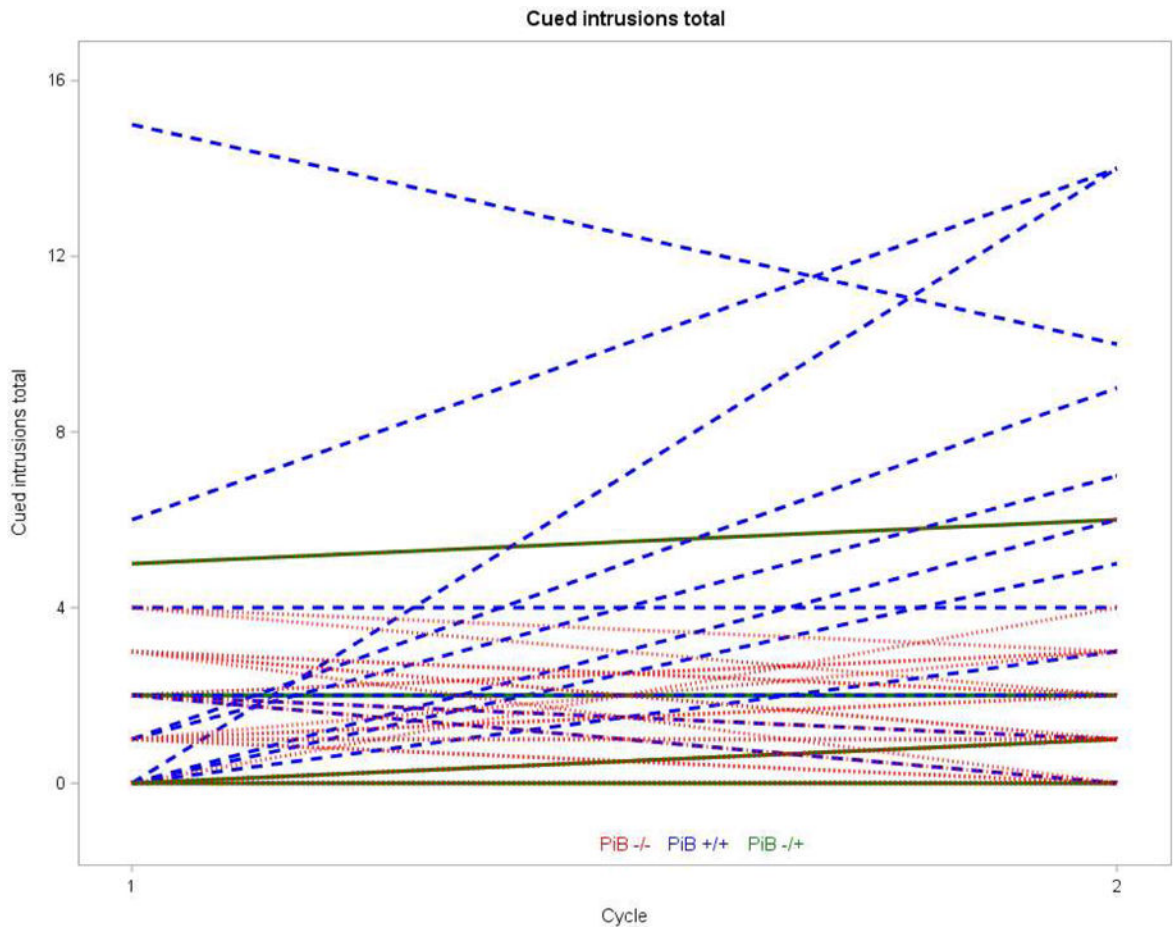
Figure 2.
Change from Cycle 1 to Cycle 2 in Cued Intrusions Total score by PiB Categorization group.

Table 1

Socio-demographics of Adults with Down syndrome at Cycle 1 and Cycle 2

	Cycle 1			Cycle 2		
	Total N = 58*	PiB– N = 39	PiB+ N = 17	Total N = 58*	PiB– N = 32	PiB+ N = 22
Sex						
Male n (%)	30(51.7)	17(43.6)	11(64.7)	30(51.7)	16(50.0)	11(50.0)
Age in years, M (SD)	37.6(6.8)	34.6(5.4)	44.6(4.2)	40.5(7.1)	36.4(5.4)	45.9(4.8)
Race/Ethnicity, n (%)						
White	57(98.3)	39(100)	16(94.1)	56(98.2)	32(100)	20(95.2)
American Indian/Alaska Native	1(1.7)	0(0)	1(5.9)	1(1.7)	0(0)	1(4.8)
Residence, n (%)						
Family	37(63.8)	25(64.1)	10(58.8)	36(62.1)	19(59.4)	14(63.6)
Group home	7(12.1)	3(7.7)	4(23.5)	6(10.3)	2(6.3)	4(18.2)
Supported apartment	9(15.5)	7(17.9)	2(11.8)	8(13.8)	6(18.8)	2(9.1)
Independently	4(6.9)	3(7.7)	1(5.9)	5(8.6)	4(12.5)	0(0)
Other	1 (1.7)	1(2.6)	0(0)	3(5.2)	1(3.1)	2(9.1)
Employment, n (%)						
Full or part time	19(32.8)	13(33.3)	5(29.4)	20(34.5)	10(31.3)	9(40.9)
Full or part time with support	13(22.4)	10(25.6)	3(17.6)	11(19.0)	9(28.1)	1(4.5)
Supported workshop	14(24.1)	8(20.5)	5(29.4)	13(22.4)	7(21.9)	4(18.2)
Volunteer	6(10.3)	3 (7.7)	3(17.6)	5(8.6)	2(6.3)	3(13.6)
Day treatment or not employed	6(10.3)	5(12.8)	1 (5.9)	9(15.5)	4(12.5)	5(22.7)
Mental Age in years, M (SD)	5.5 (1.3)	5.6(1.1)	5.5(1.6)	5.8(2.7)	6.4(3.3)	5.1(1.4)
Dementia Symptoms						
DSDS - CCS, n (%) 3 or above	2(3.4%)	1(2.6%)	1(5.9%)	5(8.6%)*	1(3.1)	3(13.6)
Medications						
Hypothyroidism	31(53.4)	23(59.0)	7(41.2)	36(63.2)	22(71.0)	11(50.0)
Hypertension	3(5.2)	2(5.1)	1(5.9)	4(6.9)	2(6.3)	2(9.1)
Antipsychotic	7(12.1)	3(7.7)	4(23.5)	6(10.3)	2(6.3)	4(18.2)
Antidepressant/anti-anxiety	16 (27.6)	11(28.2)	5(29.4)	18(31.0)	8(25.0)	9(40.9)

	Cycle 1			Cycle 2		
	Total N = 58*	PiB– N = 39	PiB+ N = 17	Total N = 58*	PiB– N = 32	PiB+ N = 22
Mood/Behavior stabilizer	1 (1.7)	0(0)	1(5.9)	2(3.4)	0(0.0)	2(9.1)
Narcotic Pain reliever	1 (1.7)	0(0)	1(5.9)	2(3.4)	1(3.1)	1(4.5)
Cholesterol	7(12.1)	3(7.7)	3(17.6)	8(13.8)	2(6.3)	4(18.2)
Memory enhancer/Alzheimer's	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Other	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

Note.

*
Total number does not equal sum of PiB– and PiB+ given that PiB status could only be determined on 56 participants at Cycle 1 and 54 participants at Cycle 2. Mental age was assessed using the Stanford-Binet, Fifth Edition Abbreviated Battery (Roid, 2003), DSDS-CCS = Down Syndrome Dementia Scale (Gedye, 1995) – Cognitive Cutoff.

Table 2

Means and Standard Deviation for regional PiB retention

	Cycle 1		Cycle 2		Cycle 1 –Cycle 2 Difference
	Mean	SD	Mean	SD	p-Value
Anterior Ventral Striatum	1.41	0.49	1.59	0.60	0.00
Anterior Cingulate Gyrus	1.45	0.31	1.51	0.39	0.007
Frontal Cortex	1.39	0.31	1.43	0.40	0.067
Lateral Temporal Cortex	1.34	0.22	1.36	0.30	0.389
Precuneus Cortex	1.35	0.29	1.45	0.38	0.000
Parietal Cortex	1.31	0.23	1.37	0.32	0.002
Global	1.37	0.29	1.45	0.38	0.000

Note. See Cohen et al., 2013 for information about cutoffs. Global is the average of the 6 separate regions of interest volumes.

Table 3

Change in Neuropsychological Measures From Cycle 1 to Cycle 2 in Adults with Down syndrome

Measure	No Control for Age			Controlling for Age	
	Cycle 1 Mean (SD)	Cycle 2 Mean (SD)	t - value	Estimate (SE)	t - value
Vineland	183.67 (47.65)	170.17 (49.81)	-3.67**	-15.61 (3.96)	-3.94***
Free Recall	16.57 (6.15)	17.81 (6.47)	1.54	0.25 (0.70)	0.35
Free and Cued Recall	33.02 (5.37)	31.73 (5.34)	-1.76	-1.94 (0.63)	-3.08**
Cued Recall Intrusions	2.21 (3.29)	3.19 (3.81)	2.00*	1.57 (0.45)	3.52***
Block Design	27.43 (9.08)	26.79 (9.88)	-0.74	-1.63 (0.86)	-1.90+
Severe Impairment Battery	46.64 (3.62)	46.38 (4.29)	-0.57	-0.48 (0.49)	-0.99
Visual Attention Time	82.59 (41.49)	86.50 (49.81)	0.70	10.18 (5.46)	1.86+
Visual Attention Accuracy	18.00 (3.14)	18.09 (3.08)	0.16	-0.29 (0.42)	-0.69
Verbal Fluency Number	24.25 (9.06)	20.80 (9.15)	-2.93**	-4.30 (1.10)	-3.92***
Verbal Fluency Repetition	2.49 (2.53)	3.05 (3.37)	1.33	0.43 (0.44)	0.97
Purdue Pegboard - Single Hands	14.93 (3.41)	13.93 (3.73)	-2.70**	-1.55 (0.33)	-4.97***
Purdue Pegboard - Both Hands	5.43 (1.94)	4.56 (1.89)	-4.25***	-1.02 (0.20)	-5.12***
Story Recall Initial	2.25 (2.07)	2.64 (2.26)	1.68	0.17 (0.23)	0.73
Story Recall Initial - Delayed	3.25 (2.79)	3.52 (3.06)	0.55	0.17 (0.28)	0.61
Expressive One Word	75.73 (24.18)	72. 89 (24.59)	-1.93+	-4.70 (1.42)	-3.31**
PPVT age equivalent	97.14 (40.13)	94.39 (39.11)	-0.90	-4.33 (3.10)	-1.40
Rivermead Picture Recognition	6.06 (3.27)	5.79 (3.50)	-0.68	-0.57 (0.41)	-1.39
VMI	17.36 (2.89)	16.89 (2.88)	-1.36	-0.68 (0.32)	-2.10*
Cat Dog Switch Errors	2.02 (3.79)	2.07 (3.75)	0.10	0.48 (0.46)	1.04
Cat Dog Switch Time	10.04 (8.45)	9.69 (9.57)	-0.22	-0.55 (1.38)	-040
Corsi Forward	11.93 (7.98)	12.32 (7.95)	0.38	-0.25 (0.96)	-0.26
Corsi Backward	4.04 (4.13)	3.75 (4.65)	-0.53	-0.68 (0.70)	-0.97
Digits Span Forward	11.63 (6.99)	11.89 (7.65)	0.36	-0.25 (0.76)	-0.34
Digits Span Backward	4.89 (4.98)	4.96 (5.61)	0.13	0.35 (0.73)	0.48

Note.

+
p < .10;

*
p .05;

**
p .10;

***
p .001. When controlling for chronological age, estimate represents change for a participant at age 40 years with mean Cycle 1 score. As follow-up, analyses were re-run excluding individuals with floor level (i.e., lowest possible score) scores at Cycle 1 as these individuals would not be able to show decline. The pattern of significant results remained the same.

Table 4

Associations between Cycle 1 to Cycle 2 Change in Neuropsychological Measures and Change in PiB Retention

	Striatum Change			Global Change		
	No Control for Age	Controlling for Age		No Control for Age	Controlling for Age	
	r	Estimate (SE)	t-value	r	Estimate (SE)	t-value
Vineland	0.01	0.85 (21.83)	0.04	−0.11	−45.21 (31.81)	−1.42
Free Recall	−0.24[+]	2.26 (3.64)	0.62	−0.21	−2.49 (4.97)	−0.50
Free and Cued Recall	−0.20	0.08 (3.33)	0.02	−0.34[*]	−10.93 (4.22)	−2.59[**]
Cued Recall Intrusions	0.16	1.16 (2.43)	0.48	0.35[**]	10.27 (2.96)	3.47[***]
Block Design	−0.23	−3.77 (4.81)	−0.78	−0.32[*]	−14.30 (6.17)	−2.32[*]
Severe Impairment Battery	−0.05	0.63 (2.76)	0.23	−0.14	−3.70 (3.66)	−1.01
Visual Attention Time	0.02	4.18 (28.01)	0.15	−0.07	10.62 (39.26)	0.27
Visual Attention Accuracy	−0.07	1.06 (2.61)	0.41	−0.10	−2.28 (3.53)	0.27
Verbal Fluency Number	−0.22	−7.51 (6.38)	−1.18	−0.10	−7.68 (8.62)	−0.89
Verbal Fluency Repetition	−0.05	2.50 (2.51)	1.00	−0.04	5.68 (3.32)	1.71[+]
Purdue Pegboard - Single Hands	−0.36[**]	−1.80 (1.79)	−1.00	−0.43[**]	−5.20 (2.34)	−2.23[*]
Purdue Pegboard - Both Hands	0.05	1.29 (1.15)	1.12	−0.01	0.17 (1.60)	0.10
Story Recall Initial	−0.11	−0.04 (1.41)	−0.03	−0.03	−0.01 (1.96)	−0.01
Story Recall Initial – Delayed	−0.15	−2.94 (2.54)	−1.16	−0.13	−3.64 (3.33)	−1.09
Expressive One Word	−0.17	−4.92 (8.43)	−0.58	−0.19	−8.85 (11.38)	−0.78
PPVT age equivalent	0.02	−8.37 (18.68)	−0.45	−0.03	−17.11 (25.18)	−0.68
Rivermead Picture Recognition	−0.22	0.21 (2.13)	0.10	−0.33[*]	−5.46 (2.65)	−2.06[*]
VMI	−0.19	−3.40 (1.64)	−2.07[*]	−0.14	−3.69 (2.25)	−1.64
Cat Dog Switch Errors	0.14	−2.24 (2.57)	−0.87	0.13	1.74 (3.46)	0.50
Cat Dog Switch Time	0.24[+]	17.40 (8.10)	2.15[*]	0.13	10.55 (11.32)	0.93
Corsi Forward	0.18	9.04 (5.84)	1.55	0.18	11.89 (7.81)	1.52
Corsi Backward	−0.10	−4.31 (4.29)	−1.00	−0.00	−0.82 (5.24)	−0.16
Digits Forward	0.03	2.57 (4.80)	0.54	−0.13	−3.73 (6.27)	−0.59
Digits Backward	−0.02	−5.07 (4.01)	−1.27	0.06	−1.16 (5.20)	−0.22

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Note.

$^+$ = p < .10;

* = p .05;

** p .01;

*** p .001. As follow-up, analyses were re-run excluding individuals with floor level (i.e., lowest possible score) scores at Cycle 1 as these individuals would not be able to show decline. The pattern of significant results remained the same.

Table 5

Change in Cognitive Functioning by PiB Category Group (consistently PiB−, consistently PiB+, and converted PiB− to PiB+) from Cycle 1 to Cycle 2.

| Measure | PiB − to PiB − | | | PiB + to PiB+ | | | PiB − to PiB + | | | No Control for Age | Controlling for Age |
	N	Cycle 1 Mean (SD)	Cycle 2 Mean (SD)	N	Cycle 1 Mean (SD)	Cycle 2 Mean (SD)	N	Cycle 1 Mean (SD)	Cycle 2 Mean (SD)	F value	F value
Vineland	31	190.97 (49.00)	181.29 (48.78)	13	171.77 (43.85)	159.69 (54.89)	6	164.17 (26.70)	141.50 (25.87)	0.71	0.81
Free Recall	31	17.68 (6.15)	20.13 (5.17)	12	14.17 (5.25)	12.50 (6.67)	6	14.00 (6.90)	18.00 (7.43)	3.39*	1.78
Free and Cued recall	31	33.19 (6.36)	33.87 (3.00)	12	32.50 (4.27)	27.83 (5.97)	5	34.20 (2.05)	31.80 (6.14)	6.13**	5.69**
Cued Recall intrusion	31	1.94 (3.15)	1.65 (1.96)	12	2.75 (4.27)	6.25 (4.71)	5	1.80 (2.05)	2.20 (2.28)	6.44**	5.84**
Block Design Total	31	29.77 (9.61)	30.45 (8.90)	14	27.29 (7.73)	23.29 (9.08)	6	22.33 (7.17)	25.83 (8.38)	4.77**	2.33+
Severe Impairment Battery	31	47.10 (3.38)	47.32 (3.02)	14	45.71 (3.58)	45.14 (5.35)	6	47.17 (4.07)	47.33 (3.08)	0.26	0.27
Visual Attention Time	31	71.06 (34.70)	71.87 (43.42)	14	104.57 (43.22)	110.21 (43.08)	6	87.33 (47.31)	81.33 (37.76)	0.26	0.28
Visual Attention Accuracy	31	18.16 (3.08)	18.65 (1.52)	14	17.36 (4.07)	16.86 (5.48)	6	19.50 (0.84)	18.50 (1.87)	0.47	0.17
Verbal Fluency Number	31	24.84 (8.29)	22.94 (8.97)	13	21.38 (8.35)	18.00 (8.91)	6	27.33 (12.61)	19.00 (7.27)	1.46	0.65
Verbal Fluency Repetitions	31	2.35 (2.43)	2.71 (2.75)	13	2.69 (3.15)	3.46 (4.98)	6	3.00 (2.53)	3.33 (1.51)	0.09	1.12
Purdue Pegboard - Single Hands	30	15.37 (3.74)	15.23 (3.11)	13	14.54 (2.47)	12.46 (3.38)	6	15.67 (3.83)	14.00 (3.29)	3.23*	0.42
Purdue Pegboard - Both Hands	30	5.93 (1.89)	4.90 (1.84)	13	5.15 (1.86)	4.23 (1.88)	6	5.17 (1.60)	4.83 (1.72)	0.54	1.03
Story Recall Initial	31	2.58 (2.17)	3.16 (1.90)	14	1.57 (2.06)	1.71 (2.13)	6	2.50 (1.52)	3.00 (2.68)	0.34	0.03
Story Recall Initial - Delayed	31	3.68 (2.96)	3.94 (2.98)	14	3.00 (2.88)	2.71 (3.02)	6	2.83 (1.72)	3.50 (2.59)	0.18	0.00
Expressive One Word	31	80.77 (25.18)	80.58 (22.33)	14	68.00 (22.05)	63.07 (25.16)	6	68.83 (18.16)	63.17 (21.48)	1.37	0.39
PPVT age equivalent	31	104.68 (46.84)	104.13 (43.08)	14	90.43 (28.17)	85.93 (32.42)	6	93.00 (27.48)	84.50 (34.60)	0.37	0.35
Rivermed Picture Recognition	31	6.45 (3.42)	5.97 (3.55)	14	4.29 (3.24)	4.14 (3.44)	6	7.33 (3.08)	6.17 (3.66)	0.38	0.82
VMI	31	17.87 (3.03)	17.71 (2.84)	14	17.21 (2.99)	16.21 (2.49)	6	16.17 (1.47)	15.33 (1.51)	0.79	2.06
Cat Dog Switch Errors	30	1.00 (2.39)	0.83 (1.98)	14	2.29 (4.03)	3.21 (5.77)	6	4.33 (6.74)	1.50 (1.76)	1.78	0.86
Cat Dog Switch Time	30	9.63 (8.11)	9.50 (9.80)	14	13.07 (10.47)	9.71 (11.13)	6	7.83 (6.49)	12.50 (7.18)	1.00	0.40
Corsi Forward	31	13.58 (8.76)	14.71 (7.28)	14	12.21 (7.08)	9.43 (6.56)	6	6.83 (6.37)	13.50 (11.64)	3.28*	1.74
Corsi Backward	31	4.26 (3.93)	5.06 (5.38)	13	4.31 (4.33)	2.38 (2.43)	6	4.00 (6.20)	2.33 (4.08)	2.43+	2.83+
Digits Forward	31	13.00 (7.65)	14.03 (8.51)	14	11.00 (6.42)	9.86 (5.45)	6	7.67 (3.83)	10.17 (7.08)	1.12	0.43
Digits Backward	31	5.94 (5.40)	5.97 (6.49)	14	3.57 (4.88)	3.64 (3.59)	6	4.33 (3.20)	5.83 (5.31)	0.31	1.92

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Note.

$^+$ = p < .10;

* = p .05;

** p .01;

*** p .001.

F values for overall ANOVA or ANCOVA using the three groups for change in neuropsychological measure across cycles. Bonferroni pairwise post-hoc comparisons indicated PiB− to PiB− group differed from PiB+ to PiB+ group at p <.05 in all significant analyses. As a follow-up, analyses were re-run excluding individuals with floor level (i.e., lowest possible score) scores at Cycle 1 as these individuals would not be able to show decline. The pattern of significant results remained the same.