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Amyloid- β and tau deposition influences cognitive and functional decline in Down syndrome

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ABSTRACT

This study investigates whether tau has (i) an independent effect from amyloid-β on changes in cognitive and functional performance and (ii) a synergistic relationship with amyloid-β in the exacerbation of decline in aging Down syndrome (DS).

105 participants with DS underwent baseline PET [^{18}F]-AV1451 and PET [^{11}C]PiB scans to quantify tau deposition in Braak regions II-VI and the Striatum and amyloid-β status respectively. Linear Mixed Effects models were implemented to assess how tau and amyloid-β deposition are related to change over three time points.

Tau was a significant independent predictor of cognitive and functional change. The three-way interaction between time, [^{11}C]PiB status and tau was significant in the models of episodic memory and visuospatial cognition.

Baseline tau is a significant predictor of cognitive and functional decline, over and above the effect of amyloid-β status. Results suggest a synergistic relationship between amyloid-β status and tau as predictors of change in memory and visuospatial cognition.

1. INTRODUCTION

Down Syndrome (DS) is the most common neurodevelopmental disorder caused by the presence of trisomy 21 (1:800 to 1:1000 live births worldwide). The extra copy of chromosome 21 is associated with a 4-5 fold overexpression of the amyloid precursor protein (APP) gene, increased accumulation of amyloid-β (Aβ) in the brain and subsequent neurofibrillary tangle (NFT) formation and neurodegeneration (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 decades later. Autopsy studies have revealed that at 35 years of age, almost all individuals with DS exhibit AD pathology (Head et al., 2015, Head et al., 2001).

The tracer [^{11}C]PiB has been successfully used for the imaging of amyloid-β deposits in the human brain (Klunk et al., 2004). The deposition of amyloid-β has been associated with reports of brain atrophy (Annus et al., 2017; Mak et al., 2019b) as well as hypoperfusion (Mak et al., 2021). Mimicking previous reports in sporadic AD, amyloid-β has also been linked with cognitive impairment in DS (Hartley et al., 2014). In one of the largest studies on the contri-

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butions of amyloid-β on cognitive impairment in DS, elevated neocortical [^{11}C]PiB retention was associated with decline in various cognitive domains (Hartley et al., 2014). However, in contrast to the well-characterised literature of amyloid-β burden in DS, the role of tau in DS has been less studied. Autopsy studies have shown that the progression of NFTs in adults with DS follows a similar Braak staging as found in AD in the non-DS population, initiating in the trans-entorhinal cortex, before spreading to the hippocampus, inferior temporal cortex, and neocortex (Mann et al., 1986). As seen in the non-DS population, tau distribution is generally concordant with the neurodegenerative pattern reflected by fluorodeoxyglucose (FDG)- PET and structural MRI, involving the medial temporal cortices and spreading posteriorly and dorsally into the parietal cortices (Rafii et al., 2017). The advent of the [^{18}F]-AV1451 tracer in AD and other neurodegenerative conditions has led to new opportunities to visualise the *in vivo* distributions of tau accumulation (Rafii et al., 2017), even at early stages of amyloid-β deposition (Zammit et al., 2021), and examine potential contributions to neurodegenerative changes and cognitive decline in DS (Lemoine et al., 2020). A previous case report has demonstrated a correspondence between temporo-parietal [^{18}F]-AV1451 deposition and longitudinal memory impairment (Mak et al., 2019a), in line with a previous pilot study showing that tau positivity was associated with cognitive and functional decline (Rafii et al., 2017).

However, our understanding of potential interactions between amyloid-β and tau deposition, as well as how such synergy may exacerbate trajectories of cognitive decline in DS, remains limited. Indeed, the presence of synergistic relationships could be anticipated from multiple lines of investigation: such as prior findings in non-DS AD patients (Pascoal et al., 2017), evidence of colocalization between both pathological phenomena in AD (Fein et al., 2008; Spires-Jones and Hyman, 2014) as well similar synergistic effects of amyloid-β and tau on dendritic spine loss in transgenic mice model of AD (Chabrier et al., 2014). A recent study further revealed that both amyloid-β and tau act in concert to cause dysregulated transcription of genes that are involved in synaptic function (Pickett et al., 2019). To the extent that synaptic function and dendritic arborisation are critical substrates of cognitive functioning (Colom-Cadena et al., 2020), it is hypothesised that cognitive decline in DS could be attributed to the interaction between amyloid-β and tau. At the molecular level the "tau axis hypothesis" suggests that increased concentrations of tau within the dendrites can make neurons more vulnerable to damage caused by amyloid-β in the postsynaptic dendrites (Ittner and Götz, 2011; Mietelska-Porowska et al., 2014). If confirmed, synergistic associations between amyloid-β and tau *in vivo* would have implications for the enrichment of disease-modifying clinical trials in AD with amyloid-β and tau imaging. A recent investigation (Hartley et al., 2021), drawing on data from the Neurodegeneration in Aging Down Syndrome (NiAD) research project, performed a cross-sectional analysis on the relationship between baseline tau, amyloid-β status and cognitive performance and their findings suggest that the presence of tau, but not Aβ alone, co-occurs with subtle episodic memory decline early on in the trajectory to AD in DS. The current study also draws on data collected by the NiAD study and extends Hartley et al. (2021)'s findings to a longitudinal dataset and to an extensive cognitive and functional outcomes battery. To our knowledge, this is the first published study to examine the effect of amyloid-β status and regional tau accumulation on cognitive change over time in people with Down syndrome.

Amyloid-β deposition is associated with increased tau deposition in Down syndrome (Tudorascu et al., 2020) and there is emerging evidence for a synergistic relationship between amyloid-β and tau in their contribution to cognitive performance at preclinical stage (Hartley et al., 2021). Thus, we aimed to determine if cognitive decline over time depends on the synergistic interaction between tau and amyloid-β. The present study extends the growing body of research examining *in vivo* contributions of amyloid-β deposition on the clinical course of AD (Esbensen et al., 2017; Hartley et al., 2014, 2020) by reporting novel evidence of tau-mediated cognitive decline in DS. Here, we test the hypothesis that longitudinal decline in cognition and adaptive functioning is predicted by interactions between tau and amyloid-β.

2. METHODS

2.1. Study design and participants

One hundred and five participants with Down syndrome were recruited across 3 study sites: University of Cambridge (n = 19), University of Wisconsin-Madison (n=45), and University of Pittsburgh (n = 41). The inclusion criteria included: Trisomy 21 confirmed by phenotyping; age above 25 years; baseline 'Mental Age' of 3 years or more on either the Stanford Binet Test (5th Ed, Roid, & Pomplun, 2012) or Peabody Picture Vocabulary Test (4th Ed, Dunn, & Dunn, 2007) as proxies; a reliable carer who is able to provide information about the participants' clinical symptoms and history; and cooperation with protocol procedures. The exclusion criteria included: no significant disease or unstable medical condition that could affect cognitive testing and no contraindication for MRI. All participants included in the analysis had completed at least two time points of cognitive and adaptive functioning assessments and 26 participants had three data points. The mean follow-up time between visit 1 and 2 was 17 months and the mean follow-up time between visits 1 and 3 was 32 months. All participants had baseline PET [^{11}C]PiB and PET [^{18}F]-AV1451 scans.

2.2. APOE genotype

All participants were genotyped for APOE polymorphisms using TaqMan SNP genotyping assays on a 7900HT Fast Real-Time PCR system (Applied Biosystems, Foster City, California). The APOE-ε4 variables was coded with three levels: ε2 for ε2/ε2 genotypes, ε3 for ε3/ε3 and ε3/ε2, ε4 for any genotype containing a ε4 allele.

2.3. Cognitive and functional outcome measures

The cognitive outcome measures comprised: Down Syndrome Mental Status Examination – DSMSE (Haxby, 1989), pictorial Cued Recall Test adapted from Buschke (1984), Cancellation subtest from the NEPSY (Developmental NEuroPSYchological Assessment) (Brooks et al., 2010), Stroop Cats and Dogs (Ball et al 2008), Wechsler Intelligence Scale for Children-IV Block Design (Wechsler, 2003) and the Haxby extension (Haxby, 1989), Purdue Pegboard Task (Tiffin & Asher, 1948). The Cued Recall task was used to extract two variables: i) Cued Recall is the sum of all recalled items and ii) Intrusions is the sum of incorrectly recalled items when given a cue. The scores from the WISC-IV Block Design and Haxby extension were summed to produce one Block Design outcome variable. The other four cognitive outcome variables were Stroop Cats and Dogs score, Cancellation score, DSMSE overall score, and Purdue Pegboard score, as derived from their corresponding outcome measures. All cognitive outcome variables were extracted consistently with previous research (see Table 1), in particular (Hartley et al., 2020)'s investigation on the same study cohort. The Block Design, Stroop Cats and Dogs, and the Cued Recall scores were previously demonstrated to be sensitive to amyloid-β load in people with Down Syndrome (Hartley et al., 2020). The DSMSE overall score is a reliable measure of cognitive decline (Krinsky-McHale et al., 2020). The functional outcome measures were administered to each participant's carer: Vineland Adaptive Behavior

Table 1
Summary of cognitive and functional assessments and their corresponding outcome variables used in the analysis.

Outcome measure	Construct measured	Procedure	Outcome variable extraction
Peabody Picture Vocabulary-Fourth Edition - PPVT	Receptive vocabulary, used to represent level of intellectual functioning (Philips et al., 2014). Used as a measure of baseline cognitive ability.	Participants are given a word verbally while presented with 4 pictures and asked to select the picture representing the word.	De-meaned (sample mean is subtracted from each observation so that the mean is zero) equivalent age score.
Down Syndrome Mental Status Examination – DSMSE	Omnibus test of global cognitive functioning	Participants are tested on recall of personal information, orientation, memory, language, visuospatial function and praxis.	Overall DSMSE score (scoring method 2 – points are given for each correctly repeated word on the Verbal Repetition task)
Cued Recall Test (modified from the version developed for the typical population).	Episodic memory	After three practice trials, participants are asked to recall 12 pictures. Cues are given for any items not spontaneously recalled.	(i) Cued Recall: the sum of all items recalled at the three test trials (free recall + cued recall). (ii) Intrusions: number of words incorrectly recalled when given a cue.
Cancellation subtest - NEPSY (Developmental NEuroPSYchological Assessment).	Visual Attention	Participants cross out each instance of a target picture in an array comprised of targets and distractors.	Sum of correct cancellations minus commission errors consistent with Hartley et al. (2020).
Stroop Cats and Dogs	Executive function	For a string of 16 pictures (8 cats and 8 dogs), the participant is asked to name each picture rapidly, calling each cat - "dog", and each dog – "cat".	Number of correctly "reverse" named animals.
WISC-IV Block Design and the Haxby extension	Visuospatial ability	The participant copies designs using blocks with red/white surfaces.	All scores are added to produce a Total Block Design score.
Purdue Pegboard Task	Motor planning and speed	The participant places as many pegs as possible using either the left, the right or both hands simultaneously within a 30 second time limit.	Score obtained in the "both hands" trial, consistent with Hartley et al. (2020).
Vineland Adaptive Behavior Scale – 3	Adaptive behaviour in the areas of communication, activities of daily living and socialisation	Interview with a carer who knows the participant well.	Vineland Adaptive Behaviour Composite Score (ABC)
National Task Group Early Detection Screen for Dementia - NTG-EDSD	Dementia symptoms categorised according to onset: always present, always but worse, new symptom (more than 1 year), new symptom (less than 1 year).	Interview with a carer who knows the participant well.	The total number of reported new and worsening symptoms at each visit are summed.
Dementia Questionnaire for People with Learning Disabilities- DLD	Specific cognitive and functional deterioration as a result of dementia, sensory or psychiatric problems.	Interview with a carer who knows the participant well.	The Sum of Cognitive Scores and the Sum of Social Scores were used as separate variables. Higher scores indicate higher impairment in the relevant domain.

Scales – 3 (Sparrow et al., 2016), Dementia Questionnaire for People with Learning Disabilities- DLD (Evenhuis, 2007), and the National Task Group Early Detection Screen for Dementia - NTG-EDSD (Esralew et al., 2013). The DLD measure was used to extract two variables: i) DLD Cognitive is the sum of three cognitive subscales: short-term memory, long-term memory, and spatial and temporal orientation; ii) DLD Social is the sum of five social subscales: speech, practical skills, mood, activity and interest, and behavioural disturbance. The other two functional outcome variables were the Vineland Adaptive Behaviour Score (ABC) and the NTG symptoms, as derived from the corresponding outcome measures.

Table 1 summarises all outcome measures (cognitive and functional), their corresponding procedures and constructs measured as well as the way their corresponding outcome variables were extracted for the purposes of the current analysis.

2.4. Neuroimaging measures

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).

PET [^{11}C]PiB:

PET [^{11}C]PiB scans were acquired and pre-processed via protocols described in previous publications (Hartley et al., 2020). Thresholds for [^{11}C]PiB (Aβ+/Aβ-) classification are detailed in (Hartley et al., 2020).

^{18}F-flortaucipir (AV-1451) PET image processing:

PET-MR [^{18}F]-AV1451images were acquired over a range of time that included 80-100 minutes post injection. The processing procedure was the same as that for PET [^{11}C]PiB with the difference that Freesurfer regions grouped into Braak regions were used for generating the standardized uptake value ratios (SUVR). The Striatum was excluded from Braak V because it is a known region for off-target binding for [^{18}F]-AV1451. The Striatum was considered separately and was parcellated using the CIC (Tudorascu et al., 2018; Tziortzi et al., 2011) atlas due to its finer segmentation. Figure 1 visualises the Braak stages.

2.5. Statistical Analysis

For all outcome variables, except NTG symptoms, Linear Mixed Effects models (LME) were implemented with the lmer function from the lme4 package in R (Bates et al., 2015). In order to address any data contamination and the influence of outliers, all models were refitted using the rlmer function from the robustlmm pack-

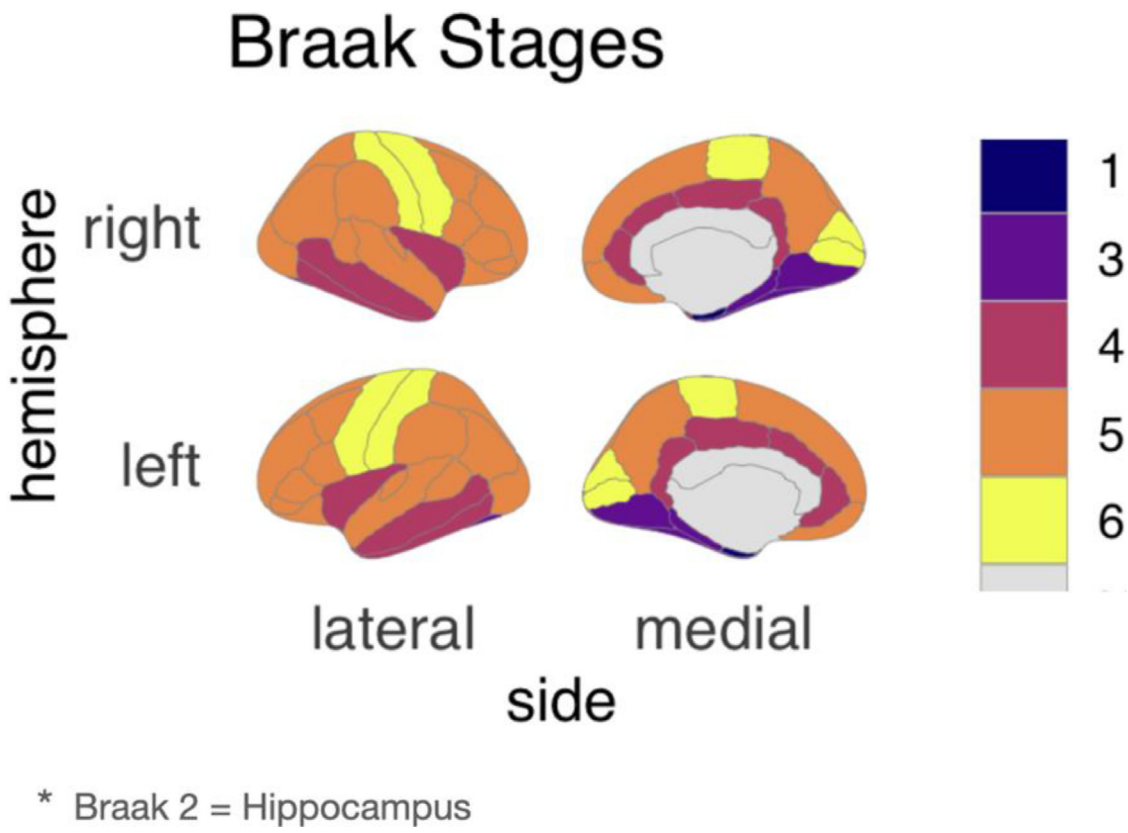

Figure 1. Braak stages I to VI.

age in R (Koller, 2016). The robust t-values from the rlmer models and the degrees of freedom from the corresponding non-robust models, were used to derive robust p-values. The LME models included a random intercept for each participant. As 75% of the participants in the sample had only 2 time points, a random slope model was not considered appropriate and would lead to convergence failures. To account for the count nature of the three NTG outcome variables, a Generalised Linear Mixed Effects model (glmer function in the lme4 package in R) with a specified Poisson distribution and a logarithmic link function was used instead of the LME model. Residual distributions were assessed for each model and in order to address the observed deviations from normal distribution, the variable Stroop Cats and Dogs was log-transformed.

Six models were constructed sequentially to address the primary objectives of the study: (1) we assessed whether the outcome variables show a significant change over time by specifying the following fixed effects (i) the centred mean age of each participant as a control for between-subject differences in age; (ii) the de-meaned age of each participant at each time point as a within-subject measure of time between each visit; (iii) biological sex; (iv) de-meaned PPVT equivalent age score as a measure of baseline cognitive ability (v) site ID; (2) the interaction between time and amyloid-β status was added to the above models to assess whether change over time is differentially affected by amyloid-β accumulation. APOE genotype was added as a covariate in this model and all subsequent models; (3) to assess how baseline tau accumulation affects cognitive and functional change over time, the de-meaned [18F]-AV1451 SUVR was added to model 1 and interacted with time; (4) we explored three-way interactions between [18F]-AV1451 SUVR, [^{11}C]PiB status and time to investigate whether tau and amyloid together have synergistic effects on longitudinal decline in cognitive or functional capacity. To correct for separately assessing the effect of multiple Braak regions on each of the outcome variables, the p-values were adjusted within each outcome variable via the False Discovery Rate (FDR) method through the p.adjust function in *R*; (5) to evaluate whether the synergistic relationship between tau and amyloid-β is independent of brain volume, we conducted sensitivity analysis on the three-way interaction models which survived FDR correction. Grey matter volume for the ROI of interest was added to each model and interacted with time; (6) to assess whether tau or amyloid status is better at predicting change over time in cognitive function, a model with the two-way interactions between time and amyloid-β status and time and ROI tau was explored. The full model equations for each step of the analysis (1-6) can be found in the Supplement. For all models, participants with missing outcome variables were excluded from the analysis for that particular outcome variable only.

3. RESULTS

3.1. Preliminary analysis

Table 2 shows the sample statistics and the characteristics of the participants' scores on each cognitive and adaptive functioning outcome variable at baseline according to [^{11}C]PiB (Aβ+/Aβ-) status.

3.2. Cognitive and functional change over time

The following outcome variables showed a significant effect of time: Cued Recall (t (127.84) = -6.09, $p < 0.01$), Intrusions (t (130.17) =3.19, $p < 0.01$) and NTG (z (132.16) =5.33, $p = 0$).. Results

Table 2
Participant characteristics.

	Aβ- (N=62)	Aβ+ (N=43)	Overall (N=105)
Age			
Mean (SD)	34.9 (5.70)	46.3 (7.31)	39.6 (8.52)
Median [Min, Max]	34.8 [24.6, 53.4]	48.2 [27.8, 57.1]	37.9 [24.6, 57.1]
PPVT equivalent age			
Mean (SD)	8.02 (2.63)	7.46 (2.91)	7.79 (2.75)
Median [Min, Max]	7.46 [3.42, 15.3]	6.75 [2.50, 13.8]	7.17 [2.50, 15.3]
Missing	0 (0%)	0 (0%)	0 (0%)
Diagnosis			
No MCI & no Dementia	60 (96.8%)	32 (74.4%)	92 (87.6%)
MCI	0 (0%)	5 (11.6%)	5 (4.8%)
Dementia	0 (0%)	4 (9.3%)	4 (3.8%)
Unable to determine	2 (3.2%)	2 (4.7%)	4 (3.8%)
APOE genotype			
E2	8 (12.9%)	8 (18.6%)	16 (15.2%)
E3	41 (66.1%)	27 (62.8%)	68 (64.8%)
E4	8 (12.9%)	8 (18.6%)	16 (15.2%)
Missing	5 (8.1%)	0 (0%)	5 (4.8%)
Biological sex			
male	31 (50.0%)	20 (46.5%)	51 (48.6%)
female	31 (50.0%)	23 (53.5%)	54 (51.4%)
DSMSE			
Mean (SD)	66.1 (11.1)	62.9 (12.0)	64.8 (11.5)
Median [Min, Max]	68.5 [33.5, 84.0]	66.0 [39.5, 82.0]	67.0 [33.5, 84.0]
Missing	0 (0%)	0 (0%)	0 (0%)
Block Design			
Mean (SD)	26.4 (10.2)	26.6 (11.4)	26.5 (10.7)
Median [Min, Max]	26.0 [0, 55.0]	27.0 [2.00, 67.0]	26.0 [0, 67.0]
Missing	0 (0%)	1 (2.3%)	1 (1.0%)
Cancellation			
Mean (SD)	17.1 (8.09)	16.4 (6.15)	16.8 (7.33)
Median [Min, Max]	19.0 [-42.0, 20.0]	18.0 [-13.0, 20.0]	19.0 [-42.0, 20.0]
Missing	0 (0%)	0 (0%)	0 (0%)
Stroop Cats and Dogs			
Mean (SD)	14.6 (3.19)	12.8 (5.62)	13.9 (4.39)
Median [Min, Max]	16.0 [0, 16.0]	16.0 [0, 16.0]	16.0 [0, 16.0]
Missing	0 (0%)	2 (4.7%)	2 (1.9%)
Cued Recall			
Mean (SD)	33.8 (3.09)	30.1 (7.01)	32.4 (5.31)
Median [Min, Max]	35.0 [20.0, 36.0]	34.0 [13.0, 36.0]	34.0 [13.0, 36.0]
Missing	0 (0%)	2 (4.7%)	2 (1.9%)
Intrusions			
Mean (SD)	1.65 (2.23)	4.71 (6.22)	2.86 (4.52)
Median [Min, Max]	1.00 [0, 12.0]	2.00 [0, 22.0]	1.00 [0, 22.0]
Missing	0 (0%)	2 (4.7%)	2 (1.9%)
Purdue Pegboard			
Mean (SD)	9.47 (3.37)	8.00 (3.35)	8.85 (3.43)
Median [Min, Max]	10.0 [2.00, 16.0]	8.00 [2.00, 14.0]	8.00 [2.00, 16.0]
Missing	2 (3.2%)	0 (0%)	2 (1.9%)
DLD Cognitive			
Mean (SD)	2.66 (4.52)	4.86 (6.31)	3.56 (5.41)
Median [Min, Max]	1.00 [0, 26.0]	2.00 [0, 27.0]	1.00 [0, 27.0]
Missing	0 (0%)	0 (0%)	0 (0%)
DLD Social			
Mean (SD)	3.45 (3.79)	4.28 (4.92)	3.79 (4.28)
Median [Min, Max]	3.00 [0, 17.0]	3.00 [0, 22.0]	3.00 [0, 22.0]
Missing	0 (0%)	0 (0%)	0 (0%)
Vineland ABC			
Mean (SD)	53.8 (19.3)	48.0 (16.6)	51.5 (18.4)
Median [Min, Max]	55.0 [20.0, 95.0]	51.0 [20.0, 76.0]	53.0 [20.0, 95.0]
Missing	0 (0%)	2 (4.7%)	2 (1.9%)

for all outcome variables are presented in Table S1 in the Supplement. These results correspond to model equation 1.

3.3. Baseline amyloid-β status as a predictor of cognitive and functional change over time

The two-way interaction between amyloid-β status and time was significant for the Cued Recall (t (120) = -4.58, p <0.01), Block Design (t (122.7) = -2.29, p < 0.01), and Stroop Cats and Dogs (t (118.6) = -2.05, p < 0.01) outcome variables only. Results for all outcome variables are presented in Table S2 in the Supplement. These results correspond to model equation 2.

3.4. Baseline tau as a predictor of cognitive and functional change over time

Before FDR correction, all outcome variables were associated with a significant two-way interaction between time and tau in at

least one region of interest (ROI). After FDR correction, the same two-way interaction was significant for nine out of the eleven outcome variables, which indicates that longitudinal change in these outcome variables is significantly associated with baseline tau accumulation. For the NTG symptoms outcome variable, there was a significant interaction between time and tau in all ROIs, with the strongest association in Braak VI ($z\ (130.24) = 3.46$, $p < 0.01$). Longitudinal change in DSMSE scores was significantly associated with tau accumulation in Braak III ($t\ (119.20) = -2.78$, $p = 0.01$), Braak IV ($t\ (119.20) = -3.21$, $p = 0.01$), and Braak V ($t\ (119.20) = -2.97$, $p = 0.01$). Change in the DLD Cognitive was significantly associated with tau in all ROIs, with the strongest interaction between time and tau observed in Braak V ($t\ (117.08) = 6.91$, $p < 0.01$). For DLD Social there wasn't a significant interaction between tau and time in any of the ROIs after FDR correction. For the Vineland ABC score, there was a significant interaction between time and tau in Braak II ($t\ (115.47) = -2.30$, $p = 0.03$), Braak III ($t\ (115.58) = -3.84$, < 0.01), Braak IV ($t\ (115.47) = -3.20$, $p < 0.01$), Braak V ($t\ (115.50) = -3.91$, $p < 0.01$) and Braak VI ($t\ (115.35) = -3.85$, $p < 0.01$). For the Block Design task, there was a significant interaction between time and tau in all ROIs, with the strongest association in Braak III ($t\ (120.1) = -4.45$, $p < 0.01$). For the Cancellation task, there was a significant interaction between time and tau in the Striatum, ($t\ (123.69) = -3.21$, $p < 0.01$), Braak III ($t\ (125.1) = -2.59$, $p = 0.02$) and Braak VI ($t\ (124.29) = -5.65$, $p < 0.01$). Cued Recall was also associated with significant time and tau interactions in all ROIs, with the strongest association in Braak III ($t\ (118.99) = -7.93$, $p < 0.01$). Results from all models are presented in Table S3 in the Supplement. These results correspond to model equation 3.

3.5. Interaction between baseline tau and amyloid-β status in predicting cognitive and functional decline

After FDR correction, the Cued Recall and Block Design outcome variables were associated with a significant three-way interaction between time, amyloid-β status and tau. For the Block Design variable, there was a significant interaction between time, amyloid-β and tau in Braak V ($t\ (117.10) = -2.74$, $p = 0.02$) and Braak VI ($t\ (117.57) = -3.22$, $p = 0.01$). For the Cued Recall variable, there was a significant three-way interaction between amyloid-β status, time and tau accumulation in the Striatum ($t\ (123.16) = -4.27$, $p < 0.01$). Figure 2 visualises these findings for each participant. No other cognitive measure and none of the functional measures were associated with a significant three-way interaction between time, amyloid-β status and tau. Results from all models are presented in Table S4 in the Supplement. These results correspond to model equation 4.

3.6. Sensitivity analysis

The results from the sensitivity analysis are summarised in Table 3 and are in relation to model equation 5 in the Supplement. These follow-up analyses showed that the observed relationship between amyloid-β and tau is independent of the interaction between ROI volume and time.

3.7. Comparing independent effects of tau and amyloid-β on cognitive change

After FDR correction, the interaction between tau and time was significant for almost all the outcome variables: NTG symptoms (all Braak regions), DSMSE (Braak II, III, IV, and V), DLD Cognitive (all Braak regions), Vineland ABC score (Braak III, IV, V, VI), Block Design (all Braak regions), Cancellation (Braak III, VI and the Striatum), Stroop Cats and Dogs (Braak III, IV, V), Purdue Pegboard (Braak III, IV, V, VI), and Cued Recall (Braak III, IV, V, VI). Interestingly, the interaction between time and striatal tau as a predictor of Cued Recall was not significant ($t(121.62) = -1.73$, $p = 0.09$). The only models for which the interaction between time and amyloid-β status was significant, were the models with Cued Recall outcome variable for all Braak regions and the Striatum. The strongest amyloid-β status and time interaction was in the model accounting for the striatal tau ($t(119.61) = -4.15$, $p < 0.01$). All results from these models are presented in Tables S5 and S6 in the Supplement. These results correspond to model equation 6.

4. DISCUSSION

Previous research has suggested that there is a significant association between amyloid-β deposition and cognitive decline in Down Syndrome (Hartley et al., 2020). Given the significant relationship between *in vivo* amyloid-β and tau pathology where amyloid-β deposition is associated with increased tau deposition (Tudorascu et al., 2020), the potential interaction between tau, amyloid-β and cognitive decline requires to be addressed as it could have implications for the design and targets of Alzheimer's disease (AD) clinical trials. A recent cross-sectional study (Hartley et al., 2021) has shown that the presence of tau, but not Aβ alone, co-occurs with subtle episodic memory decline early in the trajectory to AD in DS. We have extended these findings to a longitudinal dataset with an extensive cognitive and functional outcomes battery by demonstrating a strong relationship between baseline tau and longitudinal change in cognition. Our main findings are (a) the interaction between tau and time is significant for most cognitive (DSMSE, Cancellation, Stroop Cats and Dogs, Purdue Pegboard, Cued Recall) and functional outcome variables (NTG, DLD Cognitive, DLD Social, Vineland ABC score) while the interaction between amyloid-β status and time is not significant in the same models, (b) there is a significant three-way interaction between amyloid-β status, tau and time as predictors of change in episodic memory and visuospatial construction and this suggests a synergistic relationship between the two biomarkers.

The findings of this study present *in vivo* evidence that tau could potentiate the relationship between amyloid-β status and cognitive decline. This potentiation, revealed by the synergistic interaction between regional tau and amyloid-β status, was associated with more severe cognitive decline of episodic memory and visuospatial construction and was particularly pronounced in the Striatum. Preclinical AD in DS has been associated with a distinct pattern of increased bilateral striatal amyloid-β deposition (Cohen et al., 2018). The literature on sporadic AD in the non-DS population (Pascoal et al., 2017), has already suggested that a synergistic rather than an additive effect between Aβ and p-tau determines greater cognitive decline and clinical progression in amnestic MCI individuals. Furthermore, (Pascoal et al., 2017) demonstrated that the lateral and basal temporal and inferior parietal cortices are the brain regions where the synergistic effect between Aβ and p-tau determined the increased likelihood of progression from amnestic MCI to AD dementia in the general population. In this study, we demonstrated such a relationship between amyloid-β status and tau accumulation in the stratum as well as in Braak V and VI. We considered the possibility that brain atrophy is a confounding variable, however, our analyses did not find an association between regional brain volume and cognitive change over time. In addition, the interaction between amyloid-β and tau on cognition remained significant, indicating that brain volume does not account for the observed effects. An investigation of regional amyloid-β accumulation rather than global amyloid-β

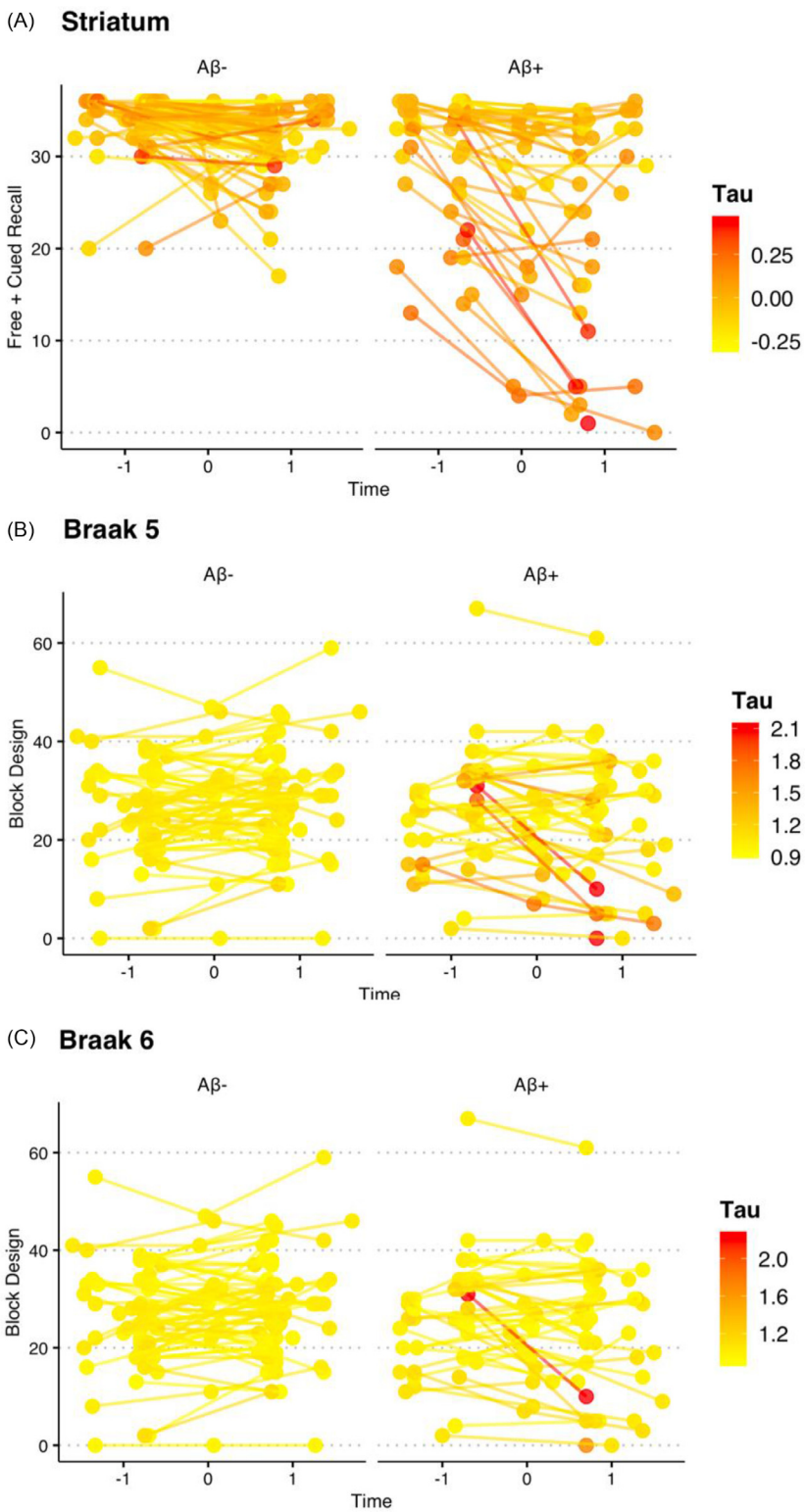

Figure 2. A, Baseline striatal tau and Cued Recall change in performance within Aβ+ and Aβ- individuals. B, Baseline Braak V tau and Block Design change in performance within Aβ+ and Aβ- individuals. C, Baseline Braak VI tau and Block Design change in performance within Aβ+ and Aβ- individuals.

status and its interaction with regional tau deposition would further confirm these findings in the DS population.

Recent neuroimaging studies with people with Down syndrome have shown that tau pathology is increased in regions associated with significant amyloid-β pathology (Tudorascu et al., 2020). There is also accumulating literature on the effects of tau at the intracellular level and the possible biological mechanisms that could explain the observed synergistic relationship between tau and amyloid-β in predicting change at the cognitive and functional level, as demonstrated in the current study. The most rec-

Table 3
Interaction between [^{11}C]PiB status, tau and Time and interaction between the corresponding ROI volume and Time, for each of the ROIs and outcome variables which showed a significant three-way [^{11}C]PiB status x tau x Time interaction.

Outcome Variable	ROI	Standard Error	Degrees of Freedom	T-statistic	P-values
[^{11}C]PiB x Tau x Time:					
Block Design	Braak 5 no STR	8.14		-2.71	0.01
			116.2		
Block Design	Braak 6	8.39		-3.09	0.00
			116.6		
Cued Recall	Striatum	3.38		-4.53‘	0.00
			122.3		
ROI volume x Time:					
Block Design	Braak 5 no STR	0.02		0.28	0.78
			118.3		
Block Design	Braak 6	0.06		0.36	0.72
			117.2		
Cued Recall	Striatum	0.11		-0.86	0.39
			118.5		

ognized functions of tau include promoting microtubule formation and maintaining their stability (Kadavath et al., 2015). However, the mechanism by which it might promote neurodegeneration is less clear. Excessively phosphorylated tau aggregates in neurons, forming neurofibrillary tangles. Research in mice has demonstrated that intracellular accumulation of tau can block axonal transport and cause synapse and memory deficits (Yin et al., 2016). In the past decade, clinical trials in the general population have focused on therapeutic interventions for amyloid-β, led by the framework of the amyloid cascade hypothesis. However, given their limited success, there is an argument to be made for the possible interaction between the tau and amyloid-β proteins in causing neurodegeneration and cognitive decline. The “tau axis hypothesis” incorporates the essential role of tau by suggesting that amyloid-β and tau target different components of the same system, amplifying each other’s toxic effects (Ittner and Götz, 2011; Mietelska-Porowska et al., 2014). This synergistic relationship between tau and amyloid-β is corroborated by research in mice (Busche et al., 2019; Mietelska-Porowska et al., 2014). The development of tau and amyloid-β PET neuroimaging methods in humans allows us to investigate this synergistic relationship *in vivo*. Such research in sporadic AD indeed suggests that cognitive decline in AD is driven by a synergistic rather than an additive relationship between tau and amyloid-β (Pascoal et al., 2017). The current study is the largest one to date to look at the relationship between tau accumulation and global amyloid-β status and their effect on cognitive and functional decline over time in people with Down syndrome and our results suggest that such a synergistic relationship might exist in this unique population as well.

Our study warrants further investigation using follow-up PET imaging of both amyloid and tau, given that longitudinal changes in tau deposition were found to correlate more strongly with cognitive decline compared to cross-sectional measures (Hanseeuw et al., 2019). All DS cases may not follow the same temporal progression, and larger studies are thus required to evaluate interindividual variations in biomarkers trajectories. Additional observations will help delineate the delay separating the trajectories of amyloid-β, tau, and cognition. Furthermore, while the current study followed up 105 participants for 16 months, only 26 provided three data points. This did not allow us to use random slopes in the models and thus account for interindividual variability in the rate of change over time. Finally, investigating both tau and amyloid-β as continuous variables in the same regions of interest would further help to disentangle their effect on cognitive decline with respect to distinct cognitive and functional outcomes.

5. Conclusions

Our results contribute to an emerging framework in which the elevated risk of developing dementia involves mechanisms associated with both amyloid-β and tau aggregation. While amyloid-β plaques and NFTs are the main pathological markers of AD, it is postulated that amyloid-β accumulation is insufficient to cause cognitive deterioration directly in the general population, whereas tau, which occurs downstream of amyloid-β, is more closely related to cognitive decline in the general population. This is supported by our finding that when including the two-way interactions between amyloid-β status and time and regional tau and time in the same model, tau seems to be a more significant predictor of cognitive change over time than amyloid-β status. Furthermore, the observed synergistic relationship between tau and amyloid-β status suggests that amyloid-β and tau work together to potentiate cognitive decline and this has implications for future disease-modifying therapeutic trials targeting amyloid-β or tau pathologies.

Author Contributions

Conceptualisation, analysis and writing, M.G. and E.M; investigation, all authors; imaging data curation, C.L, D.T.; review and editing, all authors; funding acquisition, B.H., B.C., A.C, B.A, W.K, and S.Z. All authors have read and agreed to the published version of the manuscript. The authors present this work on behalf of the Neurodegeneration in Aging Down Study (NiAD) project.

Declaration of Competing Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript or in the decision to publish the results.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.07.003.

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