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PET evidence of preclinical cerebellar amyloid plaque deposition in autosomal dominant Alzheimer's disease-causing Presenilin-1 E280A mutation carriers

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ABSTRACT

Background: In contrast to sporadic Alzheimer's disease, autosomal dominant Alzheimer's disease (ADAD) is associated with greater neuropathological evidence of cerebellar amyloid plaque (Aβ) deposition. In this study, we used positron emission tomography (PET) measurements of fibrillar Aβ burden to characterize the presence and age at onset of cerebellar Aβ deposition in cognitively unimpaired (CU) Presenilin-1 (PSEN1) E280A mutation carriers from the world's largest extended family with ADAD.

Methods: ^{18}F florbetapir and ^{11}C Pittsburgh compound B (PiB) PET data from two independent studies – API ADAD Colombia Trial (NCT01998841) and Colombia-Boston (COLBOS) longitudinal biomarker study were included. The tracers were selected independently by the respective sponsors prior to the start of each study and used exclusively throughout. Template-based cerebellar Aβ-SUVR (standard-uptake value ratios) using a known-to-be-spared pons reference region (cerebellar SUVR_pons), to a) compare 28–56-year-old CU carriers and non-carriers; b) estimate the age at which cerebellar SUVR_pons began to differ significantly in carrier and non-carrier groups; and c) characterize in carriers associations with age, cortical SUVR_pons, delayed recall memory, and API ADAD composite score.

Results: Florbetapir and PiB cerebellar SUVR_pons were significantly higher in carriers than non-carriers ($p < 0.0001$). Cerebellar SUVR_pons began to distinguish carriers from non-carriers at age 34, 10 years before the carriers' estimated age at mild cognitive impairment onset. Florbetapir and PiB cerebellar SUVR_pons in carriers were positively correlated with age ($r = 0.44$ & 0.69, $p < 0.001$), cortical SUVR_pons ($r = 0.55$ & 0.69, $p <$

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0.001), and negatively correlated with delayed recall memory ($r = -0.21$ & -0.50, $p < 0.05$, unadjusted for cortical SUVR_pons) and API ADAD composite ($r = -0.25$, $p < 0.01$, unadjusted for cortical SUVR_pons in florbetapir API ADAD cohort).

Conclusion: This PET study provides evidence of cerebellar Aβ plaque deposition in CU carriers starting about a decade before the clinical onset of ADAD. Additional studies are needed to clarify the impact of using a cerebellar versus pons reference region on the power to detect and track ADAD changes, even in preclinical stages of this disorder.

1. Introduction

Autosomal dominant genetic mutations explain a minority of Alzheimer's disease (ADAD) cases, with clinical onset typically before the age of 60 and evidence of amyloid-beta 42 (Aβ-42) overproduction nearly 20 years before clinical symptom onset (Lemere et al., 1996; Lopera et al., 1997). Since idiopathic (sporadic AD [sAD]) and ADAD have many features in common and there is limited availability of ADAD data, measurements and criteria based on neuropathological findings in sAD are often applied to ADAD. Although cerebellar Aβ plaques are well recognized in sAD, their presence is variable, and only rarely are they associated with dense core or fibrillar (neuritic) plaques (Dickson and Vickers, 2001; Jacobs et al., 2018; Joachim et al., 1989) in contrast, cerebellar plaques in ADAD are more abundant and associated with dense core and neuritic plaques (Larner, 1997; Larner and Doran, 2006; Lemere et al., 1996; Lopera et al., 1997; Mann et al., 2001; Sepulveda-Falla et al., 2014, 2012, 2011; Verkkoniemi et al., 2001). The cerebellum and the pons have generally been used as reference regions for positron emission tomography (PET) imaging studies in sAD and ADAD (Catafau et al., 2016; Clark et al., 2012; Edison et al., 2012; Gordon et al., 2018; Jacobs et al., 2018; Klunk et al., 2007; Minoshima et al., 1995; Schöll et al., 2015; Su et al., 2016). Interestingly, although cerebellar signs (i.e., cerebellar ataxia) are more common in carriers of ADAD mutations, limited data availability and phenotypic heterogeneity leave unclear whether these clinical signs correlate with cerebellar pathology (Larner and Doran, 2006; Mann et al., 2001; Sepulveda-Falla et al., 2014, 2012, 2011).

To date, we and our colleagues have comprehensively characterized a number of carriers of, ADAD mutations including the E280A mutation in the Presenilin-1 (PSEN1) gene from a single extended family in Medellín, Colombia (Fuller et al., 2019; Reiman et al., 2010, 2016; Rios-Romenets et al., 2017a, 2017b; Tariot et al., 2018). These include neuroimaging, clinical, and biofluid (cerebrospinal fluid and blood-based) biomarkers analyzed cross-sectionally (Bateman et al., 2012; Benzinger et al., 2013; Fleisher et al., 2012, 2015; Klunk et al., 2007; Knight et al., 2011; Quiroz et al., 2018, 2013, 2020; Rios-Romenets et al., 2017; Storandt et al., 2014; Su et al., 2016) and longitudinally (Babulal et al., 2019; Gordon et al., 2018; Preische et al., 2019; Sanchez et al., 2021; Su et al., 2019). Despite these efforts, there are still aspects of ADAD pathology that have not been elucidated fully, some of which may confound imaging and clinical endpoints that are frequently used in trials and observational studies (e.g., cortical standard uptake value ratios [SUVR], composite and delayed recall memory assessments). Neuroimaging studies using amyloid PET have relied on the cerebellum and the pons as a reference region based on the neuropathological finding that they are principally spared until final stages of the disease (Larner, 1997; Thal et al., 2006, 2002).

In this study we characterized the presence and age at onset of fibrillar-Aβ deposition in the cerebellum with the widely used ^{18}F-labeled ligand florbetapir, which binds with relatively high affinity to neuritic Aβ plaques, relatively low affinity to diffuse Aβ plaques and relatively high non-specific binding in white matter regions (Fleisher et al., 2011, 2012, 2015; Landau et al., 2013, 2014, 2015), and ^{11}C Pittsburgh Compound B (PiB), which binds with relatively high affinity to neuritic Aβ plaques, moderately high affinity to diffuse Aβ plaques, and less non-specific binding in white matter regions (Edison et al., 2012; Klunk et al., 2007; Knight et al., 2011; Su et al., 2019). Florbetapir and PiB PET data were collected from two independent studies in cognitively unimpaired (CU) PSEN1 E280A mutation carriers and non-carriers from the Colombian ADAD kindred. The tracers were selected independently by the respective sponsors prior to the start of each study and used exclusively throughout. Since the cerebellum is the region of interest, the pons was alternatively selected as the reference region because it is also spared of amyloid plaques and has been validated as a reference region for amyloid PET imaging in ADAD cohorts (Edison et al., 2012; Fleisher et al., 2012; Klunk et al., 2007; Knight et al., 2011). Other reference regions were also explored, and the results were consistent with what was shown using the cerebellum and the pons. Semi-quantitative and quantitative Aβ PET measurements using pons as the reference region (i.e., cerebellar SUVR_pons and distribution volume ratios [DVR] (Su et al., 2016) were used to provide evidence of cerebellar Aβ plaque deposition and its relationships with age, cortical measures of Aβ (i.e., cortical SUVR_pons and DVR_pons), delayed recall memory and API ADAD composite score prior to clinical onset in mutation carriers. We predicted in young CU carriers – higher cerebellar Aβ deposition relative to non-carriers, positive associations with age and cortical PET measurements, and no correlation with delayed recall memory score and API ADAD composite score (adjusted for cortical Aβ PET).

2. Methods

2.1. Study participants

Baseline florbetapir PET and magnetic resonance imaging (MRI) scans were acquired in 167 CU carriers and 75 non-carriers, ages 30–53, enrolled in the Alzheimer's Prevention Initiative (API) ADAD Colombia Trial (NCT01998841) (Data from 242 out of the 252 participants enrolled in the trial were used, to protect participant confidentiality) (Reiman et al., 2010; Rios-Romenets et al., 2017; Tariot et al., 2018). Baseline PiB PET and MRI scans were acquired in 21 CU carriers and 27 age-matched non-carriers, ages 28–56, who travelled from Antioquia, Colombia to Boston as part of the COLBOS project (Quiroz et al., 2018). Tracers were selected independently by the respective sponsors prior to the start of each study and used exclusively throughout. There was no overlap among research participants in the two studies. We analyzed cross-sectional florbetapir PET, PiB PET, API ADAD composite cognitive test score (composite score) and delayed word list recall score (delayed recall memory) from the Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) adapted for this population (Aguirre-Acevedo et al., 2007; Ayutyanont et al., 2014; Langbaum et al., 2014). Cognitive assessments were done within 1–3 months of the brain scans for the API ADAD cohort and two months for the COLBOS cohort (Quiroz et al., 2018). Details of baseline demographic, clinical, and cognitive characteristics for the API ADAD Colombia Trial are described in Rios-Romenets et al. (2020). Studies were approved by the University of Antioquia Ethics Committee in accordance with international ethics committee standards. The API ADAD Colombia Trial (Tariot et al., 2018) (https://clinicaltrials.gov/ct2/show/study/NCT01998841) was approved by the Colombian health authorities (Instituto Nacional de Vigilancia de Medicamentos y Alimentos) and the COLBOS study by Massachusetts General Hospital Institutional Review Board. All participants provided informed consent.

3. Brain imaging

Florbetapir scans were acquired in members of the API ADAD cohort on a Siemens Biograph mCT system, and PiB PET scans were acquired in members of the COLBOS study on a Siemens/CTI ECAT PET HR system. PET images were reconstructed using an OSEM algorithm and attenuation-corrected, frames were evaluated for adequate count statistics and absence of head motion (Fleisher et al., 2012; Quiroz et al., 2018).

Florbetapir PET scans were performed using an intravenous (IV) bolus injection of ~11 mCi (9.3–14.7 mCi) of florbetapir, a 50-minute radiotracer uptake-period, and a 20-minute dynamic emission scan in 4 frames (4 × 300 s). PiB PET scans were performed using an IV bolus injection of ~15 mCi (8.5–15.0 mCi) of PiB and a 60-minute dynamic acquisition in 39 frames (8 × 15 s, 4 × 60 s, 27 × 120 s). PiB PET SUVR were calculated using 10 frames collected between 40 and 60 min (10 × 120 s) (Becker et al., 2011; Quiroz et al., 2018).

High-resolution T1-weighted MRI scans from the API ADAD cohort were acquired on a 3 T Siemens Skyra system. The same type of MRI scans from the COLBOS cohort were acquired on a 3 T Siemens Tim Trio system (Quiroz et al., 2018). All images were visually reviewed for quality and motion artifacts.

4. Image analysis

A unified pipeline based on Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/) and MATLAB 2013b (www.mathworks.com) was used to pre-process florbetapir PET, PiB PET, and T1 MRI scans. T1-weighted scans were normalized to the Montreal Neuroimaging Imaging Template (MNI) and forward deformation fields were recorded. Florbetapir and PiB PET scans were motion-corrected, summed, and co-registered to T1 scans. The co-registered summed images were transformed to MNI template space using the forward deformation fields. The template-based cerebellum was used as the target or region-of-interest (ROI) and the pons as the reference region to calculate a *cerebellar SUVR_pons* value. Whole cerebellum as defined in Joshi et. al. (2015) was used for florbetapir PET SUVR. The cerebellum ROI was provided by AVID which has been eroded/edited as the Joshi et al., 2015 publication describes. For PiB PET SUVR we used cerebellar crus as defined by the combined cerebellar crus 1 and 2 from the Automated Anatomic Labeling-2 (AAL-2) atlas (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002). We used the pons as defined in Joshi et al. (2015) for both tracers. For the association with cortical Aβ plaque measurements in CU carriers, we used previously established cortical ROIs and the pons reference region to calculate *cortical SUVR_pons*. Details, including list of cortical ROIs used, are described in the Supplementary document. Additionally, cortical SUVR and PiB DVR with a cerebellar reference region (i.e., cortical SUVR_cerebellar and cortical DVR_cerebellar) were generated and analyzed as supporting evidence in the Supplementary Table and Supplementary Figs. 1–3, details are described in the Supplementary Document. SPM12 and the MNI template was used for our initial analysis to permit direct comparisons with the approach we used to analyze other cortical SUVR_cerebellar data from this cohort (Fleisher et al., 2012). FreeSurfer was then used to reanalyze the same data in native space post hoc, leading to virtually identical findings.

4.1. Statistical analysis

Since all the statistical methods are not pre-specified and the results are not adjusted for multiplicity, the *p* values throughout this manuscript are unadjusted non-confirmatory *p* values; they need to be interpreted with caution. The terminology "statistical significance" throughout this manuscript is not type-I error controlled. Participant characteristics including age, sex, education, MMSE, delayed recall memory, API ADAD composite score, and cerebellar SUVR/DVR_pons shown in Table 1 were compared in CU carriers and non-carriers. The API ADAD composite score is the primary cognitive endpoint measure of the API ADAD Colombia trial (Tariot et al., 2018). Delayed recall memory was chosen because it has been our primary indicator of decline in cognitively unimpaired persons at genetic risk for >20 years, based on findings from our extensively characterized cognitively unimpaired APOE4 (apolipoprotein ε4) homozygotes, heterozygotes and non-carriers using AVLT long-term delayed recall (Caselli et al., 2009). Independent-samples *t*-tests were used to compare continuous variables. *Chi*-square tests were used to compare the proportion of men and women among CU carrier and non-carrier groups. Graphs and pairwise comparisons between CU mutation carrier and non-carrier groups from each cohort were performed using GraphPad Prism software (version 7).

Cerebellar SUVR_pons associations with age in CU carriers and non-carriers were characterized by non-parametric local regression (LOESS) with 95% confidence intervals (95% CIs) (Fox and Weisberg, 2019), and linear regression (95% CIs). Normal distribution was assessed in each cohort with Shapiro-Wilk Normality test. Linear regression with 95% CIs and Pearson *r* correlations were also used to assess associations with age, cortical SUVR_pons, composite score and delayed recall memory measurements (adjusted for cortical SUVR_pons — to help clarify the relationship with delayed recall memory and composite score independent from the effects of neocortical amyloid in CU carriers [since this is the marker that we know relates with cognitive decline in this ADAD population]; we did not covary for sex and years of education since they were not significantly different in either cohort). Pearson *r* correlations and curve fittings with LOESS and linear models were performed using R-software (version-3.4.1, www.r-project.org).

Additionally, to examine the impact of using a cerebellar versus a pons reference region on cortical PET measures of Aβ plaque deposition, effect-size comparisons using Cohen's *d* and 95% CIs (Lenhard and Lenhard, 2016) were performed as supporting evidence in the Supplementary Table and reported in detail in the Supplementary Document.

5. Results

5.1. Participant characteristics

As shown in Table 1, CU carriers from the API ADAD cohort were significantly younger (37 ± 5 years) than non-carriers (42 ± 6 years, $p < 0.001$). CU carriers and non-carriers had equivalent age ranges (30–53 years) and did not differ statistically in terms of sex and years of education ($p \geq 0.05$). CU carriers from the API ADAD cohort had lower scores on MMSE, delayed recall memory ($p < 0.01$), and API ADAD composite ($p \geq 0.05$), than non-carriers.

CU carriers from the COLBOS cohort did not differ statistically from corresponding non-carriers in terms of age, sex, and education ($p > 0.05$; Table 1). While MMSE and delayed recall memory in the COLBOS cohort were also lower in the CU carrier than non-carrier group, the differences did not reach statistical significance ($p \geq 0.05$; Table 1), perhaps due to the cohort's smaller sample size.

6. Associations with age

Associations with age and cerebellar SUVR and DVR values are illustrated in Fig. 1 and Supplementary Fig. 1, using a LOESS fit and 95% CIs (wider 95% CIs at the oldest ages are partially due to fewer participants at those ages). Age estimates for the onset of cerebellar Aβ deposition with LOESS were 34 years for the API ADAD florbetapir PET SUVR sample and 37 years for the COLBOS PiB PET sample (both SUVR and DVR values).

Table 2 shows the average age at which cerebellar SUVR/DVR_pons values became significantly higher in CU carrier than non-carrier groups with each underlying model. The linear model had the closest estimates among the two cohorts (~1 year difference in age estimate vs ~3 year difference with LOESS), and generated the earliest age estimates between the two cohorts (33–34 years). Age was positively correlated with

Table 1
Participant characteristics in preclinical cognitively unimpaired PSEN1 E280A mutation carriers & non-carriers.

	API ADAD cohort (Florbetapir)			COLBOS cohort (PiB)		
	Carriers n = 167	Non-carriers n = 75	*p*	Carriers n = 21	Non-carriers n = 27	*p*
Age (range)	37 ± 5 (30–53)	42 ± 6 (30–53)	<0.001	37 ± 5 (29–47)	38 ± 7 (28–56)	0.49
Female % (No.)	60% (101)	67% (50)	0.36	57% (12)	56% (15)	0.91
Education	8.8 ± 4.1	8.5 ± 4.4	0.64	9.7 ± 4.3	10 ± 4.3	0.79
MMSE	28.8 ± 1.4	29.2 ± 1.0	0.01	28.3 ± 1.0	28.9 ± 0.9	0.06
API ADAD Composite	81.2 ± 10.2	84.0 ± 10.0	0.05	–	–	–
CERAD delayed recall memory	6.9 ± 2.2	7.7 ± 1.9	0.01	6.3 ± 2.3	7.3 ± 1.1	0.05
Cerebellar SUVR_pons	0.77 ± 0.07	0.72 ± 0.04	<0.0001	0.60 ± 0.08	0.52 ± 0.04	<0.0001
Cerebellar DVR_pons	–	–	–	0.79 ± 0.06	0.73 ± 0.04	<0.0001

Independent-samples *t*-test were used to compare continuous variables and *Chi*-square tests to compare proportion of men and women in CU carrier and non-carrier groups from the API ADAD and COLBOS cohorts. Means ± SD and *p*-values are reported.
Abbreviations: Aβ, amyloid-beta; MMSE, Mini-Mental State Exam; API, Alzheimer's Prevention Initiative; ADAD, autosomal dominant Alzheimer's disease; CERAD, consortium to establish a registry for Alzheimer's Disease; SUVR, standard uptake value ratio; DVR, distribution volume ratio; CU, cognitively unimpaired.

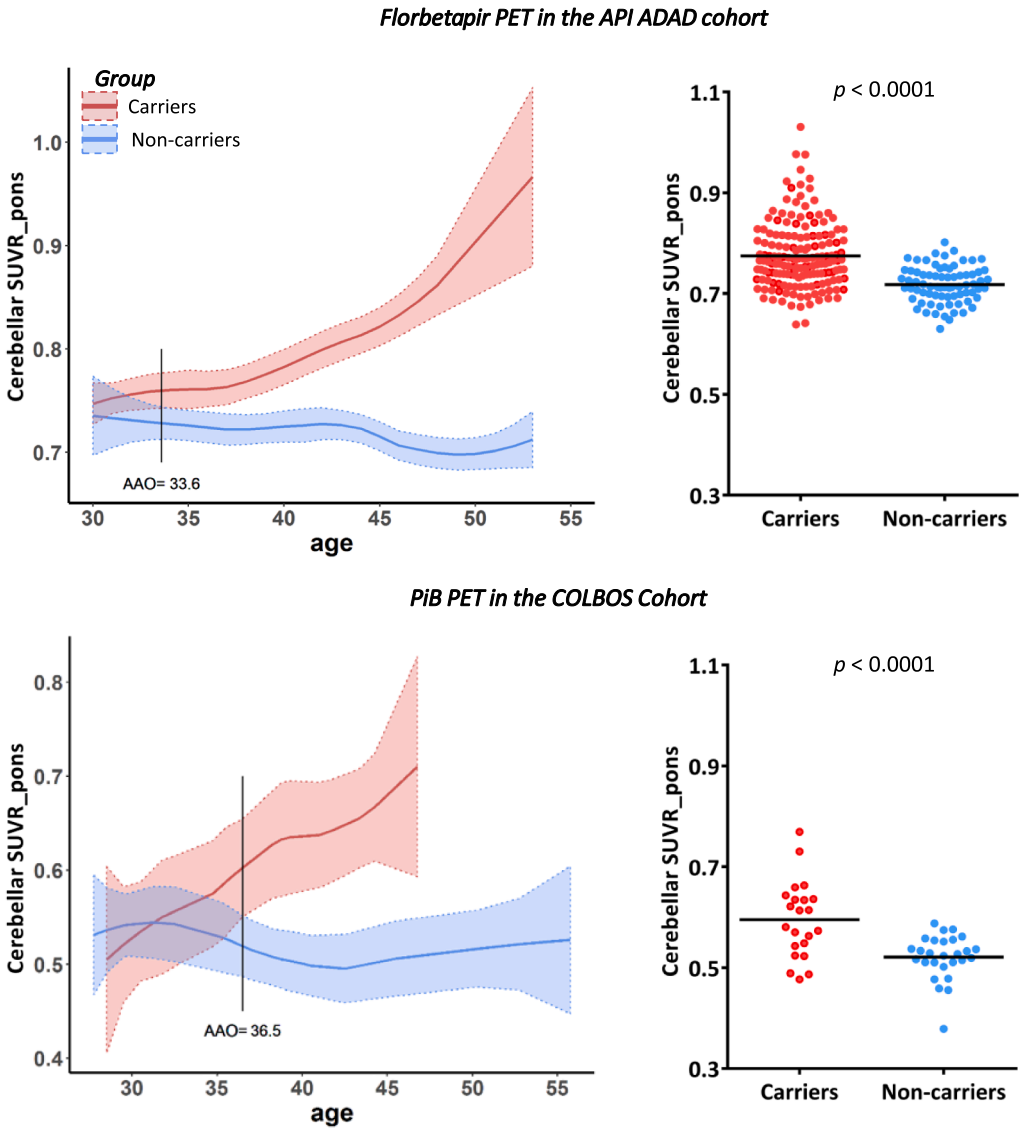

Fig. 1. Relationships between cerebellar Aβ PET SUVRs and age in preclinical cognitively unimpaired PSEN1 E280A carriers and non-carriers. Cerebellar SUVR_pons and age associations with LOESS (95% CIs) (left) and unpaired *t*-test (right). Age estimates (AAO), means, and p-values are reported. Abbreviations: Aβ, amyloid beta; AAO, average age of biomarker onset; LOESS, non-parametric local regression; SUVR, standard uptake value ratio; CIs, confidence intervals.

Table 2
Age estimates of cerebellar Aβ deposition onset in cognitively unimpaired PSEN1 E280A carriers & non-carriers.

	API ADAD cohort (Florbetapir)	COLBOS cohort (PiB)	
	Cerebellar SUVR N = 242	Cerebellar SUVR N = 48	Cerebellar DVR N = 48
LOESS (adjusted age & education)	34 (35)	37 (37)	37 (37)
Linear (adjusted age & education)	33 (33)	34 (34)	34 (34)

Age estimates in years at which cerebellar amyloid PET SUVR and DVR values became significantly greater in CU carriers than non-carriers using LOESS or linear models. Adjusted estimates for age and education were approximately the same as the unadjusted values reported and are shown in parenthesis.
Abbreviations: Aβ, amyloid beta; API, Alzheimer's Prevention Initiative; ADAD, autosomal dominant Alzheimer's disease; LOESS, non-parametric local regression; SUVR, standard uptake value ratio; DVR, distribution volume ratio.

florbetapir and PiB PET cerebellar SUVR_pons in CU carriers from the API ADAD and COLBOS cohorts ($r = 0.44$, $p < 0.0001$ & $r = 0.69$, $p < 0.001$, respectively). Data from both cohorts were normally distributed (Shapiro-Wilk Normality Test, $p > 0.05$). Table 3 shows the average age at which cortical SUVRs and DVRs with a pons reference region became significantly greater in CU carrier than non-carrier groups, before and after adjustments for age and education, using each regression model.

7. Brain imaging biomarker findings

CU carriers in the API ADAD and COLBOS cohorts had significantly higher florbetapir and PiB PET cerebellar SUVR/DVR_pons compared with respective non-carriers ($p < 0.0001$; Table 1, Fig. 1, & Supplementary Fig. 1). Linear regression with 95% CIs in Fig. 2 illustrates the associations with cortical SUVR_pons, delayed recall memory, and composite score (for the API ADAD cohort only) in CU carriers. Florbetapir and PiB cerebellar SUVR_pons in CU carriers were positively correlated with cortical SUVR_pons and negatively correlated with delayed recall memory and composite score in Fig. 2 (Fig. 2a. cortical SUVR_pons, $r = 0.55$ & 0.69, $p < 0.01$ in API ADAD & COLBOS, respectively; Fig. 2b. delayed recall memory, $r = -0.21$ & -0.50, $t = -2.76$ & -2.49, AIC = 731.5 & 93.8, $p < 0.05$, in API ADAD & COLBOS, respectively; Fig. 2c. API ADAD composite score, $r = -0.25$, $t = -3.30$, AIC = 1228.2, $p < 0.01$, in API ADAD cohort only). Cerebellar SUVR_pons was no longer significantly correlated with delayed recall memory after adjustment for cortical SUVR_pons ($r = -0.05$ & $r = -0.22$, $t = -0.59$ & -0.98, AIC = 722.7 & 94.2, $p > 0.05$, in API ADAD & COLBOS, respectively). API ADAD composite score correlation remained negatively correlated with cerebellar SUVR_pons in CU carriers even after adjusting for cortical SUVR_pons ($r = -0.16$, $t = -2.00$, AIC = 1228.14, $p < 0.05$, in API ADAD cohort only).

Accompanying linear regression with 95% CIs in Supplementary Fig. 2 illustrates the associations with cortical DVR_pons and delayed recall memory from the COLBOS cohort. PiB cerebellar DVR_pons was also positively correlated with cortical DVR_pons and negatively correlated with delayed recall memory ($r = 0.64$ & -0.55, $p < 0.01$, respectively, Supplementary Fig. 2). Correlations with CERAD delayed recall after adjustments for cortical DVR_pons were no longer significant ($r = -0.32$, $t = -1.45$, AIC = 92.9, $p > 0.05$). In addition, cortical comparisons were significantly higher in CU carriers than non-carriers ($p < 0.0001$, for both cohorts; Supplementary Table).

Illustrated in Supplementary Figure 3 are side-by-side comparisons of cortical SUVR and DVR measurements using the pons or the cerebellum as the reference region (i.e., cortical SUVR/DVR_*pons* & cortical SUVR/DVR_*cerebellar*) in CU carriers and non-carriers from both cohorts. Both pons and cerebellar reference regions significantly distinguish cortical Aβ deposition in CU carriers from non-carriers ($p < 0.0001$, Supplementary Fig. 3 & Supplementary Table).

Table 3
Age estimates of cortical Aβ deposition onset in cognitively unimpaired PSEN1 E280A carriers & non-carriers.

	API ADAD cohort (Florbetapir) Cortical SUVR N = 242	COLBOS cohort (PiB)	
		Cortical SUVR N = 48	Cortical DVR N = 48
LOESS (adjusted age & education)	30 (30)	31 (32)	30 (30)
Linear (adjusted age & education)	–	31 (31)	30 (30)

Age estimates (years) at which cortical amyloid PET SUVR and DVR values became significantly greater in cognitively unimpaired carriers than non-carriers using LOESS or linear models. Adjusted estimates for age and education were approximately the same as the unadjusted values reported and are shown in parenthesis.
Abbreviations: Aβ, amyloid beta; API, Alzheimer's Prevention Initiative; ADAD, autosomal dominant Alzheimer's disease; LOESS, non-parametric local regression; SUVR, standard uptake value ratio; DVR, distribution volume ratio.

8. Discussion

This study provides evidence of cerebellar Aβ plaque deposition and its association with memory decline prior to the clinical onset of AD in CU carriers and non-carriers from an ADAD kindred. Florbetapir cerebellar SUVR_pons and PiB cerebellar SUVR/DVR_pons were significantly higher in CU PSEN1 E280A carriers than non-carriers. Cerebellar amyloid measurements were also associated with age, cortical Aβ plaque deposition, delayed recall memory, and API ADAD composite score in carriers. Cerebellar SUVR/DVR_pons measurements in the unimpaired carriers were distinguished from those in the non-carriers starting at age 34, approximately 10 years before their estimated median age at MCI (mild cognitive impairment) onset (Rios-Romenets et al., 2017). Cortical amyloid deposition preceded cerebellar deposition by 3–7 years, before and after adjustment for age and education, depending on the regression model. Florbetapir cerebellar SUVR_pons correlated with API ADAD composite score decline even after controlling for cortical SUVR_pons. Additional studies are needed to clarify the impact of using pons versus a cerebellar reference region on the statistical power to detect and track ADAD changes, even in preclinical stages of this disorder.

Since the cerebellum is relatively spared in neuropathological studies of sAD, a cerebellar reference region is used commonly to provide SUVR or DVR measurements of Aβ plaque deposition in the cerebral cortex (Braak et al., 1989; Fleisher et al., 2011; Larner, 1997; Thal et al., 2002). Aside from the relatively sparse Aβ plaque pathology in advanced sAD, other reasons for using a cerebellar reference region include size, ability to distinguish between CU and MCI groups, and its grey and white matter composition which is well-defined allowing more accurate parcellation of grey and white matter and the different cerebellar nuclei. We did test cerebellar grey and white matter SUVR_pons with FreeSurfer ROIs to detect if the signal came from cerebellar grey matter or white matter in PiB PET scans from the COLBOS cohort; only cerebellar grey matter was significantly different between CU groups. In contrast, the pons is much smaller with part of the ROI involving the brainstem and a more interlaced grey and white matter composition (Edison et al., 2012). The cerebellum has since been used to generate neuropathologically validated thresholds to determine Aβ positivity such as the 1.17 SUVR cutoff for florbetapir of moderate to frequent plaque deposition in sAD (Fleisher et al., 2011). However, decades before amyloid PET tracers, functional tracers such as FDG (2-[^{18}F]fluoro-2-Deoxy-D-glucose) used pons as an alternative reference region in imaging studies (Greve et al., 2016; Minoshima et al., 1995). Even though neuropathological studies suggest that the cerebellum is affected in the

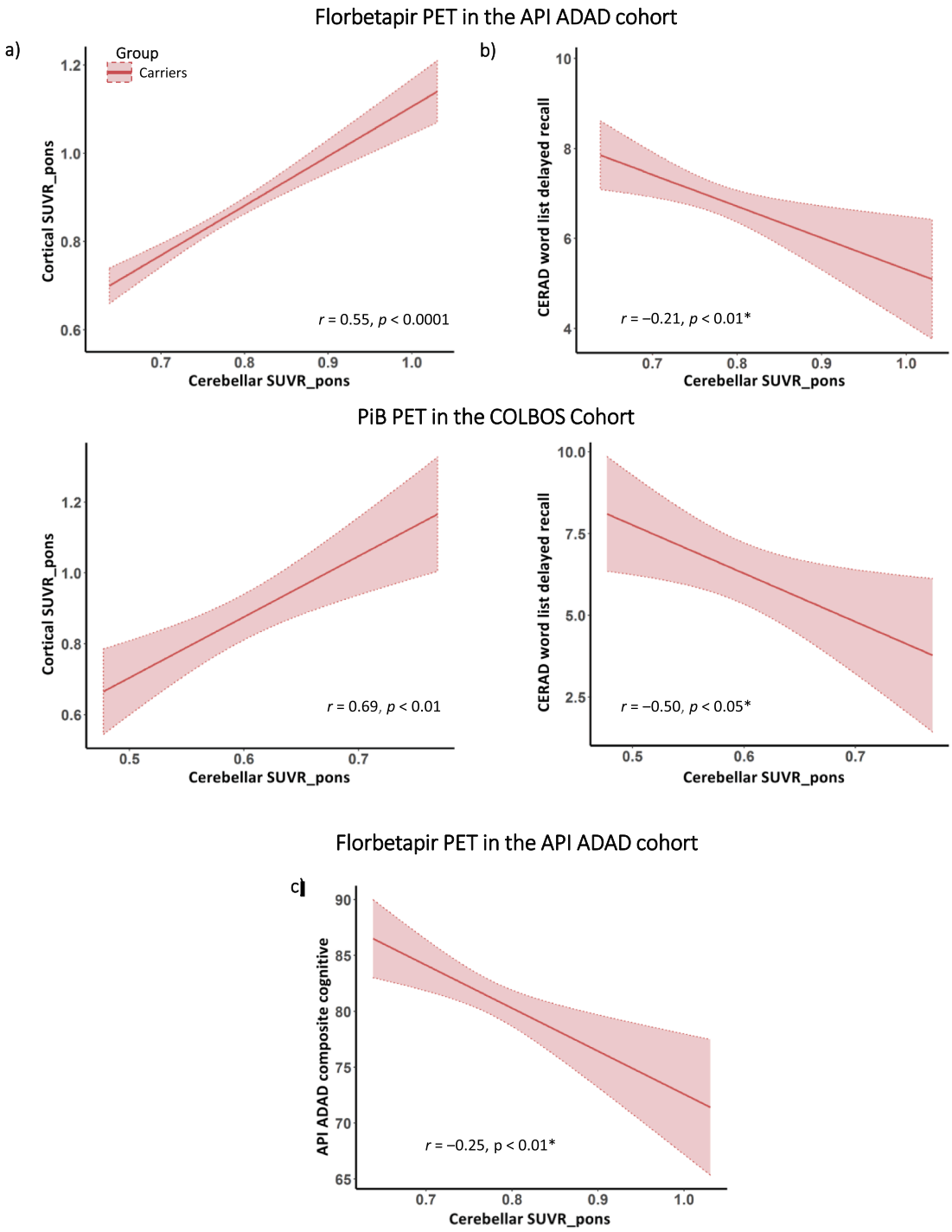

Fig. 2. a-b. Cortical Aβ PET SUVRs and CERAD delayed recall associations with cerebellar Aβ PET SUVRs in PSEN1 E280A carriers Linear-fitted curves (95% CIs) and Pearson r correlations for (a) cortical SUVR_pons and (b) CERAD delayed recall in cognitively unimpaired carriers. *Pearson r correlations and p-values unadjusted for cortical SUVR_pons are reported for delayed recall correlations, similar findings were seen with CERAD total recall. Abbreviations: Aβ, amyloid beta; SUVR, standard uptake value ratio; CERAD, consortium to establish a registry for Alzheimer's Disease; CIs, confidence intervals. Fig. 2c. Cerebellar Aβ PET SUVR associations with API ADAD composite score in PSEN1 E280A carriers Linear-fitted curves with 95% CIs and Pearson r correlations for (c) API ADAD composite cognitive score in cognitively unimpaired carriers. *Pearson r correlation and p-value unadjusted for cortical SUVR_pons are reported. Abbreviations: Aβ, amyloid beta; API, Alzheimer's Prevention Initiative; SUVR, standard uptake value ratio; CIs, confidence intervals.

advanced clinical stages of sAD (i.e. Thal stage >5), use of a cerebellar reference region could lead to underestimations of cortical Aβ deposition in the detection and tracking of ADAD. This study provides PET evidence of *in vivo* cerebellar Aβ deposition in CU ADAD mutation carriers and suggests that these changes begin about a decade prior to the estimated onset of MCI. Since cerebellar SUVR were associated with API ADAD composite score decline even after controlling for associated cortical SUVR, this study raises the possibility cerebellar Aβ contributes to subtle cognitive decline in the preclinical stages of AD.

This study capitalized on PET measurements in a large number of CU PSEN1 E280A carriers and non-carriers from an exceptionally large ADAD kindred with well-established median ages at MCI and dementia

onset. In addition, it capitalized on the use of pons as a reference region in the computation of both cerebral and cerebellar SUVRs, since this region is relatively spared in the clinical stages of both sAD and ADAD (Larner, 1997; Thal et al., 2002). Finally, it demonstrated the generalizability of our findings using two different Aβ PET ligands.

Limitations of this study include the relatively small number of mutation carriers with PiB PET scans, absence of the longer dynamic florbetapir PET scans needed to quantify DVR, and our inability to characterize the generalizability of our findings to persons with other ADAD mutations. Since CU mutation carriers in our two cohorts were close to the mutation carriers' estimated median age at MCI onset and since some of their cognitive scores were significantly or non-significantly lower than those in non-carriers, cerebellar amyloid-beta findings appear to be particularly relevant to the late preclinical stages of ADAD. Please note cerebellar SUVR_pons are sometimes <1.0 due to more non-specific binding in this reference region, not unlike one has seen using cortical-to-white matter reference regions for florbetapir PET using a white matter reference region with high non-specific binding (Chen et al., 2015). We wish to point out that there are potential limitations to the use of the pons as a reference region for the computation of DVRs using the Logan method or similar quantitative measurements using other dynamic models and that those limitations may have contributed to the finding that cerebellar DVR_pons values were lower, rather than higher than the corresponding SUVRs. Despite this limitation, ages at onset of cerebellar-to-pons DVR and SUVR increases in mutation carriers were quite similar. We found these findings of cerebellar to pons accumulation with two different tracers, we showed that both reference regions are still quite good at distinguishing cases and control in comparison to cortical reference regions and the extent to which the distinction between cases and controls can be studied by cortical to cerebellar or pons SUVRs dependance on the cortical regions of interest need to be addressed in other studies. Studies in a larger number of participants, with greater statistical power, and in different ADAD mutations will be needed to clarify whether the observed relationship between cerebellar Aβ PET measurements and delayed recall memory and cerebellar Aβ PET measurements and composite score are solely attributable to associated increases in cortical Aβ PET measurements.

9. Conclusion

This study provides PET evidence of cerebellar Aβ plaque deposition in the preclinical stages of ADAD, suggesting it may start about 10 years before the estimated MCI onset in this particular kindred mutation. Our ongoing longitudinal and prevention studies in this kindred hold promise to further clarify the impact of cerebellar, pons and other (e.g., white matter) reference regions on our power to detect and track preclinical changes and evaluate prevention therapies. Additional studies are still needed to clarify the optimal reference region to detect and track ADAD changes and evaluate ADAD prevention therapies with optimal statistical power.

Declaration of Competing Interest

V.G., D.D.G., H.D.P., M.H.M-A., Y.C., V.D., J.L., W.L., C. T. B., A.B., Y. B., E.G.V., E.P.D., C.V.C., J.T.F-F., and S.A. report no disclosures. J.B.L. is a consultant to Alector. N.H., and D.C. are full-time employees of Genentech, Inc., a member of the Roche Group. R.G.T. obtained research support from NIH (U01 AG010483) and consultant fees from Toyama and vTv. Y.T.Q. was supported by grants from the NIA/NIH, Alzheimer's Association, and Massachusetts General Hospital Executive Committee on Research (ECOR). S.R.R. received grant and contract support from the NIA, Roche/Genentech, and an anonymous international foundation to help conduct the API ADAD Trial in Colombia. F.L reports participation in other projects financed by NIH, Roche, Comité para el Desarrollo de la Investigación (CODI- U de A), and COLCIENCIAS. K.C. and Y.S are consultants for Green Valley Pharmaceuticals. P.N.T. received personal compensation for consulting, serving on scientific advisory board, speaking, or other activities with AbbVie, Acadia, AC Immune, Acadia, Auspex, Axsome, BioExcel, Boehringer Ingelheim, Chase Pharmaceuticals, Corium, Cotexyme, Eisai, GliaCure, INSYS Therapeutics, Pfizer, T3D, AstraZeneca, Avanir, Biogen, Brain Test, Inc., Eli Lilly, H. Lundbeck A/S, Merck and Company, Otsuka & Astex, Roche and Syneos; is listed on a patent application from the University of Rochester; holds stock and/or stock options in Adamas; received research support from AbbVie, AstraZeneca, Avanir, Biogen, Cortexyme, Eli Lilly, H. Lundbeck A/S, Merck and Company, Roche, Amgen, Avid, Functional Neuromodulation, GE Healthcare, Genentech, Novartis, Takeda, and Targacept. E.M.R. is a scientific advisor to Alkahest, Alzheon, Aural Analytics, Biogen, Denali, Green Valley, MagQ, Takeda & United Neuroscience, and Roche/Roche Diagnostics (expenses only). He is a principal investigator of prevention trials that include research agreements with Genentech/Roche and Novartis/Amgen, PET studies that include research agreements with Avid/Lilly, and several NIH and foundation supported research studies. He is the inventor of a patent owned by Banner Health in which biomarkers are used to accelerate the evaluation of AD prevention therapies. He is also the co-founder of ALZPath, a startup company that is intended to help develop and support the use of blood-based biomarkers for Alzheimer's disease and related disorders in research, drug development and clinical settings. E.M.R., F.L., and P.N.T are principal investigators of the Alzheimer's Prevention Initiative (API) Autosomal Dominant AD Trial.

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Author contributions

VG, FL, YTQ, and EMR conceived and designed the study. PNT, YTQ, FL, JBL, and EMR provided study supervision and funding. SA, AB, YB, AE, NAB, MMG, SRR, and the API ADAD Colombia Trial group contributed to the acquisition of brain imaging, cognitive, and other relevant data. DDG, HDP, VD, JL, and WL contributed to the analysis of anonymized PET and MRI data. VG, DDG, HDP, MHMA, YC, RGT, NH, DC, KC, and YS contributed to the analysis of data and interpretation of findings. VG, EMR, FL, and YTQ, contributed to the preparation of the manuscript, reviewed the manuscript, and the other authors reviewed the manuscript and provided input. YC, EGV, EPD, CVC, and JTFF contributed in the preparation of figures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102749.

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