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Amyloid PET and cognitive decline in cognitively normal individuals: the SCIENCe project

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ABSTRACT

We examined the relationships between amyloid-β PET and concurrent and longitudinal cognitive performance in 107 cognitively normal individuals with subjective cognitive decline (age: 64 ± 8 years, 44% female, Mini-Mental State Examination score 29 ± 1). All underwent 90-minute dynamic [^{18}F]florbetapir PET scanning and longitudinal neuropsychological tests with a mean follow-up of 3.4 ± 3.0 years. Receptor parametric mapping was used to calculate [^{18}F]florbetapir binding potential (BP_{ND}), and we performed linear mixed models to assess the relationships between global [^{18}F]florbetapir BP_{ND} and neuropsychological performance. Higher [^{18}F]florbetapir BP_{ND} was related to lower concurrent Mini-Mental State Examination (β ± SE: −1.69 ± 0.63 $p < 0.01$) and to steeper rate of decline on tasks capturing memory (Rey Auditory Verbal Learning Task immediate [β ± SE −1.81 ± 0.81, $p < 0.05$] and delayed recall [β ± SE −1.19 ± 0.34, $p < 0.01$]), attention/executive functions (Stroop II [color] [β ± SE −0.02 ± 0.01, $p < 0.05$], Stroop III [word-color] [β ± SE −0.03 ± 0.02, $p < 0.05$]), and language (category fluency [β ± SE −0.04 ± 0.01, $p < 0.01$]). These findings suggest that higher amyloid-β load in cognitively normal individuals with subjective cognitive decline from a memory clinic is associated with lower concurrent global cognition and with faster rate of decline in a variety of cognitive domains.

1. Introduction

The pathological brain changes associated with Alzheimer's disease (AD) occur decades before the onset of dementia (Jack et al., 2013; Scheltens et al., 2016). AD symptoms can be staged across a continuum, including individuals who are cognitively unimpaired, but have biomarker evidence of amyloid-beta (Aβ) deposition and/or neurodegeneration (Jack et al., 2018; Sperling et al., 2011). Although cognitively normal individuals harboring Aβ pathology are at increased risk of developing AD dementia (Jansen et al., 2015), previous studies assessing the relationships between Aβ and cognition in cognitively normal individuals showed mixed results. Cross-sectional studies reported both an association between Aβ and cognitive impairment (Donohue et al., 2017; Sperling et al., 2013) and the absence of this relation (Jansen et al., 2018; Mielke et al., 2016). Longitudinal studies more robustly showed cognitive decline in controls with abnormal Aβ, but while some studies observed a relation with memory decline (Donohue et al., 2017; Lim et al., 2014b; Resnick et al., 2010), others observed decline in multiple cognitive domains (Doraiswamy et al., 2014; Petersen et al., 2016).

The aforementioned studies were based on community-dwelling cognitively normal individuals, hampering translation to clinical practice. By contrast, persons with subjective cognitive decline (SCD) seek medical help because of self-experienced deterioration in cognition, in the absence of objective cognitive deficits, and hence form a clinically relevant study population (Jessen et al., 2014). Furthermore, former studies often used dichotomous measures of

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Aβ or crude cognitive tests, possibly lacking sensitivity to detect subtle changes related to the first changes in AD.

In this study, we investigated individuals with SCD from a memory clinic cohort who underwent dynamic Aβ PET scanning to accurately quantify Aβ load and an extensive repeated neuropsychological test battery. We investigated the relationships between specific Aβ PET binding and 1) concurrent and 2) longitudinal cognitive performance in SCD.

2. Materials and methods

2.1. Participants

We included 107 participants with SCD from the ongoing Subjective Cognitive Impairment Cohort (SCIENCe) study within the Amsterdam Dementia Cohort at the Alzheimer Center Amsterdam (Slot et al., 2018). All participants underwent extensive diagnostic workup including neurological examination, neuropsychological assessment, laboratory tests, and brain magnetic resonance imaging (MRI) (van der Flier and Scheltens, 2018). In a consensus meeting, a diagnosis of SCD was made when cognitive functioning was within normal limits, and criteria for mild cognitive impairment (MCI), dementia, or any other neurological or psychiatric disorder likely to cause cognitive symptoms, were not met. Subsequently, participants with a diagnosis of SCD were invited to participate in SCIENCe, a prospective cohort study with annual neurological examinations and neuropsychological assessment. Education was evaluated using the Dutch Verhage system (ranging from 1 [low] to 7 [high]) (Verhage and Van Der Werff, 1964). At each follow-up visit, diagnosis was re-evaluated, and when progression to MCI or dementia was detected, participants were referred to the routine memory clinic follow-up. Exclusion criteria were abuse of alcohol or other substances, insufficient knowledge of the Dutch language, or abnormalities on MRI, likely to interfere with interpretation of amyloid PET. The Medical Ethics Review Committee of the VU University Medical Center, Amsterdam UMC approved this study. Written informed consent was obtained from all participants.

2.2. [^{18}F]Florbetapir synthesis

[^{18}F]Florbetapir was prepared according to Avid Radiopharmaceuticals methodology and specifications at the good manufacturing practices tracer production facility of the department of Radiology & Nuclear Medicine at the VU University Medical Center. The radiochemical purity of all batches was >95% and the molar activity >18.5 GBq/μmol.

2.3. Scanning procedures

Dynamic emission scans of 90 minutes were started at the time of an intravenous [^{18}F]florbetapir tracer injection of approximately 370 MBq. PET scans were acquired on a PET/CT Ingenuity TF (n = 60) or Gemini TF (n = 47) scanner (Philips, Best, the Netherlands). Participants were instructed to lie still and their heads were immobilized with a special foam head fixation together with a headband. The protocol included a low-dose CT scan for attenuation correction of PET scans. During scans, movement was checked using laser beams and head position was corrected if necessary. Listmode data were reconstructed into 22 frames using 3D RAMLA reconstruction algorithm and included all standard corrections for scatter, randoms, attenuation, decay, and dead time, which resulted into images with a matrix size of 128 × 128 × 90 and a voxel size of 2 × 2 × 2 mm^3.

All participants underwent structural MRI including 3D T1-weighted images (3T Philips Ingenuity TF PET/MR system, n = 57; 3T GE Discovery MR750w, n = 36; 3T Toshiba Vantage Titan n = 8; 3.0 T GE Signa HDxt, n = 3; 1.5 T GE Signa HDxt, n = 2; 1.5 T Siemens Sonata n = 1).

2.4. Image analysis

With the use of Vinci software (Max Planck Institute, Cologne, Germany), T1-weighted MR images were coregistered to PET images. Voxelwise parametric images were created using receptor parametric mapping (RPM) (Gunn et al., 1997), applied to the full dynamic (90 minutes) PET data using cerebellar gray matter as reference region. Previously, our group identified RPM as the best simplified parametric reference method compared with full kinetic modeling for [^{18}F]florbetapir (Golla et al., 2018). The outcome measure of RPM is binding potential (BP_{ND}), which reflects the ratio of specifically bound tracer to nondisplaceable tracer in tissue at equilibrium (Lammertsma, 2017). Regions of interest (ROIs), based on MRI, were delineated using the Hammers template (Hammers et al., 2003) in PVElab (Svarer et al., 2005) and projected onto PET images in native space. BP_{ND} values were obtained for volume-weighted global cortex. In addition, for sensitivity analyses, we created 2 alternative amyloid measures. First, native space parametric BP_{ND} images were warped to Montreal Neurological Institute (MNI152) space using coregistered T1-weighted MR images. All warped images were checked manually for transformation errors. We then extracted an AD-specific ROI using the MarsBar package implemented in SPM. This AD-specific ROI, adapted from Villeneuve et al. (Villeneuve et al., 2015), consisted of medial frontal cortex, precuneus, lateral frontal, and parietal lobes. Second, native space standardized uptake value ($SUV_{50–70}$) images were visually read by an experienced nuclear physician (BvB) to assess amyloid status ("negative" or "positive") according to guidelines provided by Avid Radiopharmaceuticals.

2.5. Neuropsychological assessment

A standardized neuropsychological test battery was conducted to assess performance in 4 cognitive domains (van Loenhoud et al., 2017). For memory, Visual Association Test (VAT, part B), immediate and delayed recall on the Dutch version of Rey Auditory Verbal Learning Task (RAVLT) were performed. For attention, we used Digit Span Forward, Trail Making Test (TMT) part A, Stroop task 1 (word) and 2 (color). To assess executive functioning, we used Digit Span Backward, TMT-B, Stroop task 3 (word-color) and Letter Fluency (sum of letters D, A, & T). Category fluency (animals, 1 minute) and VAT naming condition were used to assess the domain of language. In addition, we used Mini-Mental State Examination (MMSE) as an indication of global cognitive performance. Raw test scores for TMT and Stroop were inverted, so that lower test scores indicate worse performance. TMT, Stroop, and category fluency test scores were log-transformed because of their non-normal distribution. For other neuropsychological tests, actual observed test scores were used. In addition, we combined individual neuropsychological tests into cognitive domain scores for memory (VAT, RAVLT immediate and delayed recall), attention (Digit Span Forward, TMT part A, Stroop task 1 (word) and 2 (color), executive functions (Digit Span Backward, TMT part B, Stroop task 3 (word-color), and Letter Fluency), and language (Category Fluency and VAT naming) (Groot et al., 2018). To this end, raw test scores were converted to Z scores, using mean and SD of the equivalent neuropsychological tests administered most closely to the PET. Next, we created composite scores by averaging Z scores for the corresponding tests per domain. If less than 2 tests per domain were available, no composite scores were created. To avoid

differences in domain scores over time to be caused by differences in number of tests available at follow-up for a given subject, we created composite scores based on tests that were available on all time points. Each subject underwent at least one neuropsychological examination, and the same neuropsychological test battery was repeated during annual follow-up. The 107 participants underwent a total of 369 neuropsychological evaluations, conducted both in the years before and after PET scanning procedures. For 97 participants, at least 2 neuropsychological assessments were available, and 10 participants only underwent one neuropsychological evaluation. The number of missing evaluations was limited and ranged from 0.3% (RAVLT total learning) to 5.8% (digit span backward). We therefore did not perform multiple imputation of missing data.

2.6. Statistics

We assessed the relationships between Aβ and i) concurrent cognitive performance and ii) rate of cognitive decline over time with linear mixed models. The advantage of a linear mixed model is that it allows for different numbers of assessments and for variability in time intervals between assessments, enabling reliable estimates of slopes. The models included terms for [^{18}F]florbetapir BP_{ND} (global cortical ROI; continuous), time, and the interaction term [^{18}F]florbetapir BP_{ND}*time. We computed the time variable as the time difference between [^{18}F]florbetapir PET scan and neuropsychological test. The association between [^{18}F]florbetapir BP_{ND} and neuropsychological performance most closely to the [^{18}F]florbetapir scan was set as time = 0 (i.e., concurrent cognition). In this model, the effect of "[^{18}F]florbetapir BP_{ND}" reflects the effect of [^{18}F]florbetapir BP_{ND} on concurrent cognition (i.e., when time = 0). The interaction term "[^{18}F]florbetapir BP_{ND} * time" refers to the extra effect of [^{18}F]florbetapir BP_{ND} for each time unit, that is, the estimated effect of [^{18}F]florbetapir BP_{ND} on annual decline in cognition. For all models, we used type III sum of squares, an unstructured variance type, and a random slope and random intercept, to account for individual changes in baseline scores and slope. All analyses were adjusted for age at PET scan, sex, and education. Data are presented as β (SE), indicating I) effect of [^{18}F]florbetapir BP_{ND} on concurrent neuropsychological performance (main effect [^{18}F]florbetapir BP_{ND}), II) annual change in neuropsychological test score ([^{18}F]florbetapir BP_{ND}*time). We repeated analyses with each specific cognitive test as dependent variable. Results are reported at a threshold of $p < 0.05$, both without and with correction for multiple comparisons using the Benjamini-Hochberg procedure with a false discovery rate (FDR) Q value of 5%. We used SPSS version 22 for all statistical analyses.

2.6.1. Sensitivity analyses

We performed sensitivity analyses to assess relationships between a) regions where amyloid tends to accumulate first and b) binary classification of PET (e.g., positive vs. negative) and cognition. We repeated linear mixed models with [^{18}F]florbetapir BP_{ND} in an AD-specific ROI and visual read of [^{18}F]florbetapir PET as predictors. Because sex differences in AD symptomatology and biomarkers have been found (Ferretti et al., 2018), we repeated linear mixed models with global [^{18}F]florbetapir BP_{ND} as predictor and cognitive domain scores as dependent variable, stratified for sex. Furthermore, we assessed the relationship between yearly change in RAVLT delayed recall and voxelwise [^{18}F]florbetapir BP_{ND}, corrected for age, sex, and education, using regression analysis in SPM version 12. Finally, to investigate the effect of including both retrospective and prospective data in our model, we repeated analyses restricted to concurrent neuropsychological data (obtained within one year from PET) and further on.

3. Results

3.1. Demographics

Demographics are shown in Table 1. At the time of [^{18}F]florbetapir PET, all participants had a diagnosis of SCD, and a mean MMSE score of 28.9 ± 1.2. Participants were on average 64 ± 8 years old, 47 (44%) were female and 24 (22%) participants had a positive [^{18}F]florbetapir PET scan on visual assessment. Global [^{18}F]florbetapir BP_{ND} was 0.18 ± 0.15. Mean follow-up time was 3.4 ± 3.0 years. Supplementary Table 1 provides the number of neuropsychological evaluations available for different follow-up time intervals. Participants scored below cutoff points on questionnaires assessing depression (Center for Epidemiologic Studies Depression Scale) (Radloff, 1991) and anxiety (Hospital Anxiety and Depression Scale, anxiety subscale) (Bjelland et al., 2002), but did report worse cognitive functioning compared with 1 year before (Subjective Cognitive Functioning Scale) (Aalten et al., 2014). Five participants (4.7 %) showed clinical progression to MCI during follow-up. Supplementary Table 2 shows the characteristics of these individuals.

3.2. Neuropsychology

Cross-sectional neuropsychological test scores and estimated annual changes are reported in Table 2. Linear mixed models adjusted for age, sex, and education showed that on average, participants improved over time on tests for memory (RAVLT delayed recall: β 0.35 ± 0.13, $p < 0.01$) and executive functioning (Stroop III [color-word]: β 6.41 ± 1.73, $p < 0.001$; Letter Fluency: β 1.19 ± 0.15, $p < 0.001$), while performance on other tests remained stable.

3.3. Relationships between Aβ and concurrent cognition

Higher [^{18}F]florbetapir BP_{ND} was associated with higher age (standardized β 0.28, $p < 0.01$), but not with sex ($p = 0.81$) or education ($p = 0.17$). To assess the effects of Aβ load on cognition, we used linear mixed models with [^{18}F]florbetapir BP_{ND}, time, and the interaction between [^{18}F]florbetapir BP_{ND} and time as factors, while adjusting for age, sex, and education. Mean time lag between [^{18}F]florbetapir PET and concurrent neuropsychological evaluation was 0.13 ± 0.33 years. Higher [^{18}F]florbetapir BP_{ND} was not associated with lower concurrent cognitive domain scores (Table 3). Table 4 and Fig. 1 show the cross-sectional and longitudinal associations between [^{18}F]florbetapir BP_{ND} and neuropsychological tests. Higher global [^{18}F]florbetapir BP_{ND} was associated with lower concurrent MMSE scores (β −1.69 ± 0.63, $p < 0.01$), but this association did not survive FDR correction. There

Table 1
Demographics

	Total group (n = 107)
Male/female	60/47
Age, y	64 ± 8
Education (Verhage scale), median (IQR)	6 (2)
Follow-up duration, y	3.4 ± 3.0
Global [^{18}F]florbetapir BP_{ND}	0.18 ± 0.15
Positive [^{18}F]florbetapir PET on visual read, n(%)	24 (22%)
Center for Epidemiologic Studies Depression Scale (CES-D) (≥16)	8.6 ± 7.0
Hospital Anxiety and Depression Scale (HADS)—anxiety subscale (≥8)	3.9 ± 3.2
Subjective cognitive functioning (SCF) scale (≥0)	−1.5 ± 2.9

Values are represented as mean ± SD, unless otherwise indicated.
Education was rated using Verhage's scale (Verhage and Van Der Werff, 1964).
Key: BP_{ND}, nondisplaceable binding potential; IQR, interquartile range.

Table 2
Neuropsychological baseline data and annual change.

Global cognition	Mean ± SD	*p*
MMSE (30)	28.9 ± 1.2	
Annual change, β ± SE	**0.12 ± 0.03**	***p* = 0.001**
Memory		
VAT (12)	10.8 ± 1.2	
Annual change, β ± SE	−0.05 ± 0.03	$p = 0.082$
RAVLT immediate recall (75)	45.1 ± 8.9	
Annual change, β ± SE	**0.35 ± 0.13**	***p* = 0.006**
RAVLT delayed recall (15)	9.1 ± 3.2	
Annual change, β ± SE	0.06 ± 0.06	$p = 0.302$
Attention		
Digit Span Forward (21)	13.5 ± 3.1	
Annual change, β ± SE	−0.09 ± 0.0	$p = 0.063$
TMT-A (360 s)	33.3 ± 11.0	
Annual change[a,b], β ± SE	1.7 ± 2.0	$p = 0.382$
Stroop I (word)	42.6 ± 6.8	
Annual change[a,b], β ± SE	−0.5 ± 0.9	$p = 0.626$
Stroop II (color)	57.7 ± 10.4	
Annual change[a,b], β ± SE	2.1 ± 1.1	$p = 0.054$
Executive		
Digit Span Backward (21)	9.7 ± 2.7	
Annual change, β ± SE	−0.0 ± 0.0	$p = 0.801$
TMT-B (500 s)	74.8 ± 27.7	
Annual change[a,b], β ± SE	1.1 ± 2.0	$p = 0.577$
Stroop III (color-word)	91.8 ± 22.6	
Annual change[a,b], β ± SE	**6.4 ± 1.7**	***p* < 0.001**
Letter Fluency	23.4 ± 5.8	
Annual change[a], β ± SE	**1.2 ± 0.2**	***p* < 0.001**
Language		
Category Fluency (animals, 1 min)	1.4 ± 0.1	
Annual change, β ± SE	−1.4 ± 1.7	$p = 0.419$
VAT naming	12.0 ± 0.2	
Annual change, β ± SE	−0.0 ± 0.0	$p = 0.647$

Neuropsychological data are presented as mean ± SD and annual change as β ± SE, as estimated by linear mixed models, corrected for age, sex, and education.
The baseline is defined as the neuropsychological assessment most closely to the [^{18}F]florbetapir scan.
Mean or β values marked in bold indicates significant ($p < 0.05$) results.
Key: MMSE, mini-mental state examination; VAT, visual association test; RAVLT, rey auditory visual learning test; TMT, trail making test.
[a] TMT, Stroop, and category fluency test scores are log-transformed and then multiplied by 1000.
[b] TMT and Stroop test scores are inversed.

were no associations between [^{18}F]florbetapir BP_{ND} and concurrent performance on tests of attention, executive functioning, or language (all $p > 0.05$, Table 4). In sensitivity analyses, we observed no associations between [^{18}F]florbetapir in the amyloid-specific ROI and concurrent MMSE. Lower concurrent MMSE scores were associated with a positive [^{18}F]florbetapir PET. There were no associations between [^{18}F]florbetapir in the amyloid-specific ROI or visual read of [^{18}F]florbetapir and concurrent performance on tests of attention, executive functioning, or language.

Table 3
Relationships between global [^{18}F]florbetapir BP_{ND} and I) concurrent cognition and II) annual cognitive change on domain scores

	Global BP_{ND}	
	Concurrent	Annual change
Memory	−0.67 (0.47)	**−0.29 (0.09)**[b,c]
Attention	−0.29 (0.47)	**−0.18 (0.09)**[a]
Executive functions	−0.33 (0.46)	**−0.19 (0.08)**[a,c]
Language	0.21 (0.46)	−0.14 (0.12)

Neuropsychological data are represented as β (SE), as estimated by linear mixed models.
Mean or β values marked in bold indicates significant ($p < 0.05$) results.
Key: BP_{ND}, nondisplaceable binding potential; FDR, false discovery rate.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] FDR corrected.

3.4. Relationships between Aβ load and cognitive trajectories

When we analyzed cognitive changes over time in relation to Aβ load, we found that higher global [^{18}F]florbetapir BP_{ND} was associated with steeper decline on cognitive domain scores for memory (β −0.29 ± 0.09, $p < 0.05_{FDR}$), attention (β −0.18 ± 0.09, $p < 0.05$), and executive functions (β −0.19 ± 0.08, $p < 0.05_{FDR}$) (Table 3). When we subsequently analyzed specific tests, higher global [^{18}F]florbetapir BP_{ND} was associated with steeper decline on RAVLT immediate recall (β −1.81 ± 0.81, $p < 0.05$) and RAVLT delayed recall (β −1.19 ± 0.34, $p < 0.01$) (Table 4). In addition, higher global [^{18}F]florbetapir BP_{ND} was associated with a steeper rate of decline in performance on Stroop II (color; attention), Stroop III (word/color; executive functions), and category fluency over time. Associations between [^{18}F]florbetapir BP_{ND} and RAVLT delayed recall survived FDR correction. Sensitivity analyses showed that higher [^{18}F]florbetapir BP_{ND} in the AD-specific ROI and a positive [^{18}F]florbetapir PET scan were associated with decline in RAVLT immediate recall, RAVLT delayed recall, Stroop II (color), and category fluency, but not with decline in Stroop III (word/color) (Supplementary Table 3). When repeating linear mixed models stratified for sex, we observed no significant associations between higher [^{18}F]florbetapir BP_{ND} and concurrent or longitudinal cognitive domain scores, possibly due to a reduction in sample size (Supplementary Table 4). Furthermore, higher [^{18}F]florbetapir BP_{ND} in frontal, parietal, temporal, and occipital lobes was associated with decline in RAVLT delayed recall (yearly change) (Fig. 2). When we restricted analyses to neuropsychological data obtained within one year from PET and further on, associations between higher [^{18}F]florbetapir BP_{ND} and decline in cognitive domain scores remained comparable(Supplementary Table 5).

4. Discussion

In this study, we demonstrated that cognitively normal participants with SCD with higher specific [^{18}F]florbetapir binding had subtly poorer concurrent cognitive performance. Moreover, higher Aβ load was associated with more rapid decline on memory, attention, executive functioning, and language tests.

We observed associations between Aβ load and changes in cognition over time across all domains, but only modest associations with concurrent cognition. This suggests that while immediate effects of Aβ are subtle, long-term exposure to Aβ may have a negative effect on cognitive changes over time, even in individuals with normal cognition. Aβ-related decline was most pronounced in the memory domain, with the strongest effects on a delayed recall episodic memory task. However, the longitudinal effects of Aβ extended beyond the memory domain, as changes over time in tests covering attention, executive functions, and language were also observed. The presence of associations between Aβ and both cross-sectional cognition and rate of cognitive decline are largely in line with current literature in cognitive normal populations. A recent meta-analysis showed that Aβ-related cognitive impairment was present for both cross-sectional cognition (episodic memory, executive functioning, processing speed, visuospatial function, and global cognition) and longitudinal cognitive decline (episodic memory, semantic memory, visuospatial function, and global cognition), with comparable effect sizes for cross-sectional and longitudinal data (Baker et al., 2017). Sensitivity analyses showed that associations between Aβ and cognition were largely consistent when using an AD-specific ROI or visual read of Aβ PET, suggesting that the presence of Aβ, rather than the accumulation in a specific region, is related to cognition.

Although investigating the relationship between Aβ and cognition is important for our understanding of the origin and evolution

Table 4
Relationships between global [^{18}F]florbetapir BP_{ND} and I) concurrent cognition and II) annual cognitive change

	Global BP_{ND}			
	Concurrent		Annual change	
	β (SE)	t	β (SE)	t
Global cognition				
MMSE	**−1.69 (0.63)**[b]	−2.82	−0.36 (0.27)	−1.17
Memory				
VAT	−0.56 (0.71)	−0.78	−0.33 (0.20)	−1.61
RAVLT	−4.02 (5.05)	−0.80	**−1.81 (0.81)**[a]	−2.23
RAVLT recall	−3.09 (1.77)	−1.75	**−1.19 (0.34)**[b,c]	−3.48
Attention				
Digit Span Forward	−1.90 (1.92)	−0.99	−0.13 (0.29)	−0.47
TMT-A[d,e]	0.04 (0.08)	0.54	−0.02 (0.01)	−1.26
Stroop I (word)[d,e]	−0.05 (0.04)	−1.25	−0.01 (0.01)	−1.76
Stroop II (color)[d,e]	−0.03 (0.05)	−0.63	**−0.02 (0.01)**[a]	−2.51
Executive functions				
Digit Span Backward	0.32 (1.48)	0.22	−0.25 (0.25)	−1.02
TMT-B[d,e]	−0.09 (0.08)	−1.09	−0.02 (0.01)	−1.47
Stroop III (word-color)[d,e]	−0.04 (0.05)	−0.69	**−0.03 (0.02)**[a]	−2.21
Letter Fluency	2.03 (6.65)	0.31	−1.07 (1.14)	−0.94
Language				
Category Fluency[d]	−0.05 (0.06)	−0.89	**−0.04 (0.01)**[b,c]	−3.21
VAT naming	−0.03 (0.10)	−0.32	−0.06 (0.04)	−1.40

Neuropsychological data are represented as β (SE), as estimated by linear mixed models.
Mean or β values marked in bold indicates significant ($p < 0.05$) results.
Key: BP_{ND}, nondisplaceable binding potential; FDR, false discovery rate; MMSE, mini-mental state examination; RAVLT, rey auditory visual learning test; TMT, trail making test; VAT, visual association test.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] FDR corrected.
[d] TMT, Stroop, and category fluency test scores are log transformed.
[e] TMT and Stroop test scores are inversed.

of AD, these results do not allow causal inferences about the role of Aβ on cognitive decline. Moreover, in cognitively normal individuals, the presence of both Aβ and neurodegeneration is more predictive for future cognitive decline than Aβ alone (Amariglio et al., 2015; Mormino et al., 2009; van Harten et al., 2013). It could be possible that Aβ triggers the more downstream neurodegenerative processes such as accumulation of tau neurofibrillary tangles and brain atrophy, which in turn cause cognitive decline. Alternatively, the accumulation of Aβ and neurodegeneration could be seen as independent processes and lead to cognitive dysfunction independently (Jagust, 2016), for instance by altering functional connectivity networks in cognitively normal individuals (Lim et al., 2014a, Mormino et al., 2011). Moreover, when combined, Aβ and neurodegeneration could cause synergistic harmful effects.

Individuals with SCD represent an important subset of cognitively normal individuals because they are worried about their cognitive function and seek help (Jessen et al., 2014). Previous studies showed that SCD is associated with an increased prevalence of abnormal AD biomarkers, such as decreased hippocampal volumes (Meiberth et al., 2015; Saykin et al., 2006; van der Flier et al., 2004), glucose hypometabolism (Mosconi et al., 2008; Scheef et al., 2012), altered brain connectivity (Verfaillie et al., 2018; Wang et al., 2013), and deposition of Aβ and tau proteins (Amariglio et al., 2012; Buckley et al., 2017; Perrotin et al., 2012; Snitz et al., 2015). Studies focusing on Aβ and cognition in SCD are scarce. The present results are partially in line with 2 recent studies that focused on the effects of both Aβ and SCD on cognition. In the first study, for a mean follow-up of 4 years, Aβ-PET–positive cognitively normal individuals with high

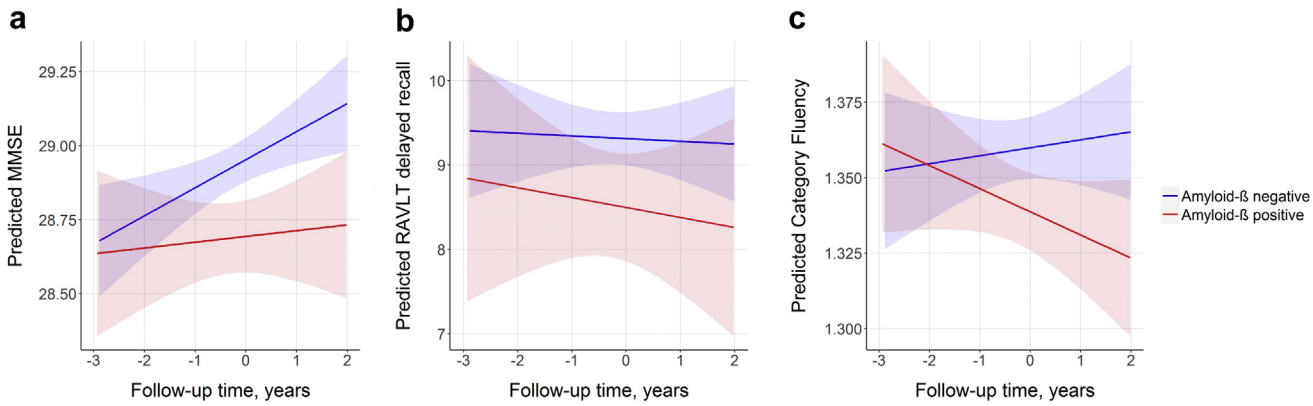

Fig. 1. Concurrent (panel A) and longitudinal (panel B and C) relationships between amyloid-β load and cognitive functioning. Results of linear mixed models with global [^{18}F] florbetapir BP_{ND}, time, age, gender, and global [^{18}F]florbetapir BP_{ND} * time as predictor, and neuropsychological tests as dependent variable. For visualization purposes, results are binarized for amyloid-β–positive and amyloid-β–negative subjects. Abbreviations: BP_{ND}, nondisplaceable binding potential; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Visual Learning Test. Category fluency test scores are log transformed.

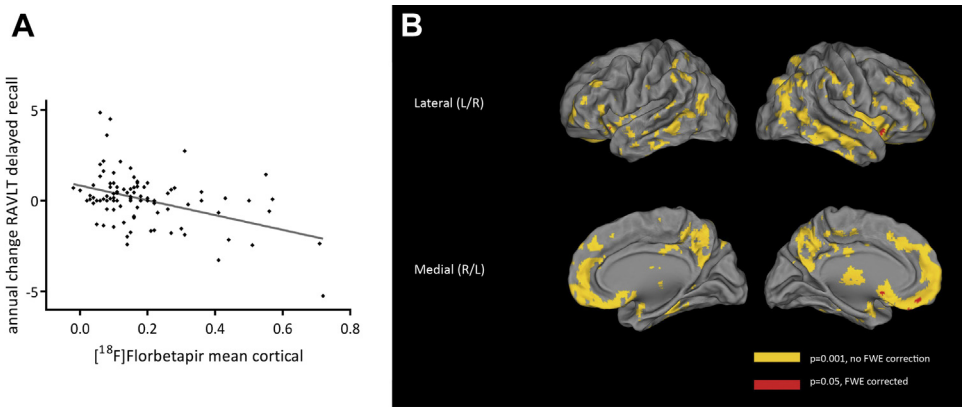

Fig. 2. Relationships between yearly change RAVLT delayed recall and global [^{18}F]florbetapir BP_{ND} (A) and voxelwise [^{18}F]florbetapir BP_{ND} (B). Displayed are the results of voxelwise regression analyses (B) between yearly change in RAVLT delayed recall as dependent and [^{18}F]florbetapir BP_{ND} images as independent variables. We calculated yearly change on RAVLT delayed recall (the only test surviving FDR correction in main analyses) by subtracting last from first test score and dividing it by the time difference in years between measurements. Analyses are adjusted for age, sex, and education. *p*-values are set at 0.05, familywize error corrected (red) and with a more liberal threshold of $p < 0.001$ (uncorrected for multiple comparisons, yellow). Abbreviations: BP_{ND}, nondisplaceable binding potential; FDR, false discovery rate; RAVLT, Rey Auditory Visual Learning Test. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

SCD scores showed steeper decline in episodic memory and global cognition than cognitively normal individuals without high SCD scores and/or Aβ (Vogel et al., 2017). The second study showed that among Aβ-PET−positive participants, higher SCD scores at the baseline predicted cognitive decline on a cognitive composite test; whereas this association was absent for Aβ-PET−negative participants (Amariglio et al., 2018). Previously, our group reported that individuals with SCD and abnormal Aβ levels in CSF showed steeper decline in memory, executive, and global composite scores over 2 years (van Harten et al., 2013). The current work was based on a different Aβ modality, had a longer follow-up time, and focused on individual neuropsychological tests rather than cognitive domain scores only.

In contrast to aforementioned studies, individuals with SCD with positive and negative Aβ PET did not differ in cognition at the baseline or at 30 months follow-up in a recent large observational study (Dubois et al., 2018). The absence of this correlation could be due to short follow-up duration. Another important issue to take into account when studying SCD is the recruitment method. The SCD participants in the latter cohort were recruited from the community, as opposed to SCD participants in our sample, who were recruited from a memory clinic, seeking medical help for their problems. It is hypothesized that participants with SCD from a memory clinic are further along the AD trajectory because memory-clinic participants with SCD are more likely to progress to MCI (Abdelnour et al., 2017; Snitz et al., 2018) and have lower gray matter volumes (Perrotin et al., 2017) than individuals with SCD in the general population. However, the associations between medical help seeking and increased risk of AD are not straightforward because other studies report no differences in conversion rate (Mitchell et al., 2014), cognition, or Aβ positivity between community-dwelling and memory clinic SCD (La Joie et al., 2016; Perrotin et al., 2017). With a mean age of 64 ± 8 years, our cohort is approximately 10 years younger than other large community-dwelling cohorts studying SCD (Amariglio et al., 2018; Dubois et al., 2018; Vogel et al., 2017). Because it is known that the prevalence of amyloid positivity increases with age, it could be argued that this cohort is at lower risk for incipient AD.

Among the strengths of this study is the combination of quantitative Aβ PET and extensive repeated neuropsychological testing in a clinically relevant SCD cohort. We quantified Aβ load using dynamic scans with binding potential (BP_{ND}), a measure of specific binding to Aβ. This validated method takes into account differences in tracer delivery and washout between individuals, and therefore, more accurately captures actual Aβ load compared with, for example, standardized uptake value ratio measurements, which may overestimate true binding (Lammertsma, 2017; van Berckel et al., 2013).

The study also has some limitations. First, we included neuropsychological test results both retrospectively and prospectively from Aβ-PET scan procedures. As a consequence, we cannot make specific statements about the predictive value of baseline PET, but this approach has the important advantage that it allows for precise estimation of cognitive slopes as all available data points have been included. When we restricted analyses to concurrent and prospective data, associations between higher Aβ-PET and steeper decline in cognition remained comparable. Second, even though we excluded participants with a major depression, subthreshold depressive or anxiety symptoms could have affected neuropsychological test scores. The relationship between depression and cognition in the context of AD is complicated. It remains unclear whether depressive and anxiety symptoms are a prodromal manifestation of AD, a reaction to self-perceived cognitive decline or whether depressed participants simply over-report the cognitive decline they experience (Ismail et al., 2016; Rabin et al., 2017).

Although SCD is associated with an increased risk of clinical progression to dementia (Buckley et al., 2016; Jessen et al., 2010; Ronnlund et al., 2015), not all individuals with SCD are in the AD continuum. This is emphasized in the most recent research framework proposed by the NIA-AA (Jack et al., 2018), where SCD is incorporated into the "syndromal" categorical cognitive staging scheme of cognition (irrespective of biomarker status) and in the "numeric" clinical staging scheme (including only Aβ-positive and/or tau biomarker−positive individuals, which are considered to be in the "AD continuum"). In the numeric clinical staging scheme, stage 2 reflects a transitional stage between cognitively normal and MCI, which may be established through a subjective report of cognitive decline. The presence of both SCD and Aβ-positivity may thus increase the risk for future objective decline, which could be used as an enrichment strategy for clinical trials. Our present study could be interpreted as a validation of the numeric clinical staging scheme in the NIA-AA research framework, as we find that higher amyloid load in individuals presenting clinically with a stage 2 syndrome, is indeed related to steeper rate of cognitive decline over time.

Disclosure

TT, RO, SCJV, CWJvdW, RERS, LMPW, ADW, EEW, MY, NDP, and AAL report no disclosure.

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Data statement

Data not provided in the article and additional information on methods and materials may be shared on request.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.02.020.

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