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Association of amyloid pathology with memory performance and cognitive complaints in cognitively normal older adults: a monozygotic twin study

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ABSTRACT

Amyloid pathology in cognitively normal older adults has been associated with low memory performance and cognitive complaints, but findings are conflicting. Using a monozygotic twin design, we further explored this relation. We investigated 199 cognitively normal older adults (96 twin pairs) and assessed cognitive performance, cognitive complaints, and amyloid pathology on positron emission tomography and in the cerebrospinal fluid (CSF). Participants were on average 70.5 (SD = 7.6) years and 114 (57%) were female. Amyloid–positron emission tomography abnormality on visual read and lower CSF amyloid-β 1-42/1-40 ratio were associated with lower Rey visuospatial memory performance (respectively, $\beta = -0.39$ [SE = 0.17], $p = 0.02$ and $\beta = 0.15$ [SE = 0.07], $p = 0.04$). Twin analyses showed that CSF amyloid-β 1-42/1-40 ratio in one twin of a pair could predict visuospatial memory performance in the cotwin (r = 0.20 [SE = 0.10], $p = 0.04$). Monozygotic twin discordance analyses further showed a probable effect of disease staging on face-name associative memory performance. Our results suggest amyloid aggregation to be associated with lower visuospatial and face-name–associated memory performance in cognitively normal older adults, supporting the view that amyloid pathology leads to memory dysfunction in very early stages of the disease.

1. Introduction

Alzheimer's disease (AD) is characterized by aggregation of amyloid beta in the brain, which may start up to 20 years before dementia onset (Jansen et al., 2015; Villemagne et al., 2013). Identification of cognitively normal individuals at risk for amyloid aggregation is important as this will help to select participants for treatment studies in a stage when neurodegeneration is still limited. Previous studies showed that amyloid pathology in cognitively normal individuals may be associated with low-normal memory performance and cognitive complaints, but findings have been conflicting (Chetelat et al., 2010; Jansen et al., 2017; Perrotin et al., 2012). This may be due to variability in memory tests and amyloid measures used. In particular, in cognitively normal older adults, cerebrospinal fluid (CSF) amyloid markers may be more sensitive for amyloid pathology than positron emission tomography (PET) amyloid markers (Palmqvist et al., 2016). Furthermore, it is not clear whether the relation between amyloid pathology and cognitive performance has a common underlying biology.

The aim of this study is to investigate the relation of amyloid pathology, assessed by dynamic [^{18}F]flutemetamol amyloid-PET scan and amyloid-β 1-42/1-40 ($A\beta_{42/40}$) ratio in CSF, with memory performance, assessed with 4 memory tests and degree of cognitive

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complaints in cognitively normal older adults using a monozygotic twin-pair approach. Monozygotic twins provide an unparalleled opportunity to explore the etiology of comorbidity among traits. Monozygotic twins share 100% of their genes. If 2 traits are influenced by the same genes, it follows that an across-participant association between traits will result in cross-trait association between twins from a pair. If amyloid pathology and memory dysfunction have a shared biology, we then expect that amyloid pathology in one twin will predict memory performance in the cotwin (De Moor et al., 2008; Vitaro F, 2009). In case within–twin-pair differences in amyloid markers correlate with within–twin-pair differences in memory function, this indicates that the relation between amyloid and memory is, at least partly, driven by nonshared environmental factors.

2. Methods

2.1. Participants

We selected 199 cognitively normal monozygotic twins (96 complete pairs and 7 twins of which the cotwin was not able to participate or did not have a measure for amyloid available) from the Netherlands Twin Register (Willemsen et al., 2013), who we enrolled in the European Information Framework for AD–PreclinAD study (Konijnenberg et al., 2018). Inclusion criteria were age $\geq$60 years, a delayed recall score > -1.5 SD of demographically adjusted normative data on the Consortium to Establish a Registry for Alzheimer's Disease 10 word list (Morris et al., 1989), a Telephone Interview for Cognitive Status modified score $\geq$23 (de Jager et al., 2003), a 15-item Geriatric Depression Scale score of $<$11 (Yesavage et al., 1982), and a Clinical Dementia Rating score of 0 (Morris, 1993). Exclusion criteria were any significant neurologic, systemic, or psychiatric disorder that could cause cognitive impairment. Twin zygosity was confirmed by buccal cell DNA analysis. Participants gave written informed consent. The Medical Ethics Review Committee of the VU University Medical Center approved the study. Research was performed according the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Participants Act and codes on "good use" of clinical data and biological samples as developed by the Dutch Federation of Medical Scientific Societies.

2.2. Assessment of memory performance and cognitive complaints

Cognitive complaints were assessed using the Cognitive Complaints Index (CCI), consisting of 20 questions on memory performance compared to 5 years ago (Rattanabannakit et al., 2016). We used this self-reported score because in cognitively normal adults, self-reported complaints are supposed to best reflect actual disease (Buckley et al., 2015). We selected 4 memory tests that differed in type of material presented (verbal vs. visual) and learning paradigm (unrelated items vs. association between items), which were previously associated with amyloid pathology: the Rey complex figure 3-minute recall (visuospatial memory) (Meyers et al., 1996; Snitz et al., 2013), total score from the face-name–Associated Memory Examination–names delayed recall (face-name associative memory) (Papp et al., 2014; Rentz et al., 2011), Cambridge Neuropsychological Test Automated Battery Paired Associate Learning total errors adjusted (visual associative memory) (Reijs et al., 2017; Robbins et al., 1994), and the Rey auditory verbal learning task delayed recall (verbal memory) (Rey, 1964; Tolboom et al., 2009a). Face-name associative memory data were missing in 22 of 199 participants mainly because of refusal or lack of time as this test was performed at the end of the neuropsychological test battery. Participants with missing face-name scores were older, more often had a positive amyloid-PET scan (32% vs. 14%, $p = 0.01$), and showed worse performance on Mini-Mental State Examination, Rey visuospatial memory, and paired associative learning compared with participants who completed the test.

2.3. Amyloid markers

2.3.1. Cerebrospinal fluid collection

Up to 20 mL CSF was obtained by lumbar puncture in 126 (62%) participants, between 10 AM and 2 PM, after at least 2 hours of fasting. CSF was collected in Sarstedt polypropylene syringes using a Spinocan 25 Gauge needle in intervertebral spaces between L3 and S1. Samples were centrifuged at 1300–2000 g at 4 °C for 10 minutes and supernatants were stored in aliquots of 0.5 mL at −80 °C until analysis. A maximum of 2 hours was allowed between lumbar puncture and freezing (del Campo et al., 2012). Levels of $A\beta_{42/40}$ were analyzed using kits from the same batch according to manufacturer instructions (ADx Neurosciences/Euroimmun) (De Vos et al., 2015).

2.3.2. Positron emission tomography scanning

Dynamic [^{18}F]flutemetamol amyloid-PET scans were performed on a Philips Ingenuity PET–magnetic resonance imaging (MRI) scanner at VU University Medical Center. PET scans were acquired for 30 minutes under standard resting conditions (eyes closed, dimmed ambient light), immediately after a manual injection of 185 MBq ($\pm$10%) [^{18}F]flutemetamol (Nelissen et al., 2009). After an interval of 60 minutes, in which the patient was taken from the scanner bed, a second scan of 20 minutes was acquired, starting 90 minutes after injection. Before each part of the PET scan, a dedicated MR sequence was obtained for attenuation correction. PET scans were reconstructed using the LOR-RAMLA dedicated Philips reconstruction algorithm for the brain into 18 frames of increasing length ($6 \times 5, 3 \times 10, 4 \times 60, 2 \times 150, 2 \times 300, 1 \times 600$ seconds) and into 4 frames of 300 s each. Data from 2 scans were combined into a single image data set after coregistration using Vinci Software 2.56 and in-house built software for decay correction of the second part. Regions of interest were automatically delineated based on the T1-MRI images using the Hammers atlas as implemented in PVElab (Hammers et al., 2003; Svarer et al., 2005). Parametric nondisplaceable binding potential (BP_{ND}) images were generated from the entire image set using the receptor parametric mapping and cerebellar gray matter as reference tissue (Gunn et al., 1997; Wu and Carson, 2002). Global cortical BP_{ND} was calculated as the average BP_{ND} of 22 regions located within frontal, parietal, temporal, posterior cingulate, and medial temporal lobes (Tolboom et al., 2009b). Visual read on the dynamic BP_{ND} [^{18}F] flutemetamol images as negative or positive was applied by the consensus of 3 readers, blinded to the clinical and demographic data.

2.4. Apolipoprotein E genotype

Apolipoprotein E (*APOE*) genotype was assessed based on 2 single-nucleotide polymorphisms (rs429358 and rs7412) genotyped on the Affymetrix Axiom array (Ehli et al., 2017); for 2 participants, APOE data were missing.

2.5. Statistical analysis

Statistical analyses were performed in SPSS version 23 for Windows and RStudio version 3.3.1 (http://www.r-project.org/). Amyloid-PET BP_{ND} values were skewed; therefore, log-transformation was used to normalize the data. Z-scores were used for all markers obtained as standardized variables with a mean of 0 and a standard deviation of 1 (using the sample mean and standard deviation). Across-participant associations were assessed using Generalized Estimating Equations with PET (dichotomous and continuous) or the CSF $A\beta_{42/40}$ ratio (continuous) as predictors

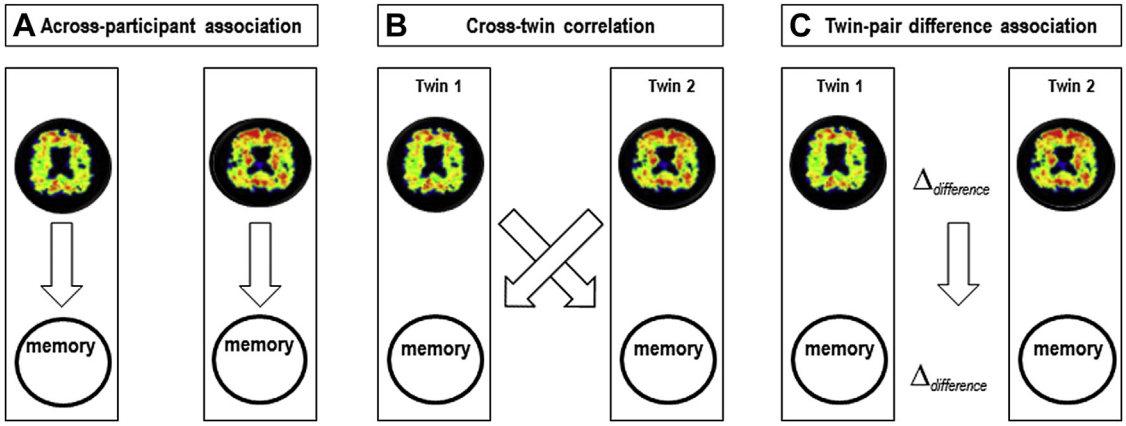

Fig. 1. Twin analyses on relation between amyloid markers and memory illustration of analyses performed. (A) association between amyloid measures and memory in total group; (B) cross-twin cross-trait analysis: amyloid measure in one twin is correlated with memory score in the cotwin, a significant cross-twin correlation indicates that the relation is in part driven by common genetic and/or environmental factors; (C) within–twin-pair difference analysis: within–twin-pair difference in amyloid measures is associated with within–twin-pair difference in memory score; a significant within–twin-pair difference association indicates that the relation is partly driven by unique environmental factors.

and memory performance or CCI as outcome variables adjusted for clustering of twins within pairs (model 1) and for clustering of twins within pairs, age, gender, and education (model 2) (Minica et al., 2014). When observing a significant effect for a covariate, we subsequently tested for an interaction.

When a significant (Bonferroni-corrected $p = 0.05/(5 \text{ tasks}^*2 \text{ amyloid measures}) = 0.005$) across-participant association was found, we further examined whether amyloid in one twin could predict memory or CCI in its cotwin, by estimating the cross-twin cross-trait correlations in OpenMx in R (Fig. 1B) (Boker et al., 2011). We used the monozygotic within–twin-pair difference model (De Moor et al., 2008) to test whether our data support a direct relation between amyloid, memory, and CCI. In monozygotic twin pairs, the variances and covariances of difference scores are a function of unique environmental factors that influence the 2 traits and the correlation between these environmental factors. A significant relation between difference scores implies a correlation between unique environmental factors; that also is compatible with a direct influence of one trait on the other trait (Boomsma et al., 2005). For this analysis, we regressed within–twin-pair differences in memory performance or CCI on within–twin-pair differences in amyloid load (Fig. 1C). We used a monozygotic twin discordance model based on amyloid aggregation as measured by visual read of the PET scan and tested whether twin pairs concordant for having an amyloid-negative PET scan (referred to as concordant negative/control group) differ from discordant twin pairs where one twin has an amyloid-negative PET scan (discordant negative group) and the cotwin has an amyloid-positive PET scan (discordant positive group) and twin pairs concordant for having an amyloid-positive PET scan (concordant positive group). This model can function as a disease stage model, where twins discordant for amyloid pathology might be in an earlier amyloid stage compared with twins with both amyloid pathologies. We tested whether group status (concordant negative, discordant negative, discordant positive, and concordant positive) was associated with memory performance or CCI, adjusted for clustering of twins within pairs, age, gender, and education using Generalized Estimating Equations.

3. Results

3.1. Sample characteristics

We included 199 participants of which 196 had a PET visual read, 188 had dynamic PET BP_{ND} data, and 126 had CSF available. Participants were on average 70.5 years, 57% was female, and 33% carried at least one APOE-ε4 allele. The subgroup of 118 participants with both dynamic PET and CSF data was younger compared with participants with PET only (Table 1).

Table 1
Sample characteristics

	Whole sample	Subgroup with CSF and PET data
N	199	118
Complete MZ pairs[a]	96	49
Concordant pairs with positive visual amyloid-PET BP_{ND} read	6	5
Concordant pairs with negative visual amyloid-PET BP_{ND} read	74	36
Discordant pairs for visual amyloid-PET BP_{ND} read	14	8
Twins with missing amyloid data for cotwin	7	20[b]
Age, mean (SD)	70.5 (7.6)	68.9 (6.7)[e]
Years of education, mean (SD)	11.5 (2.6)	11.3 (2.7)
Female, n (%)	114 (57)	64 (54)
APOE ε4 carrier, n (%)[c]	65 (33)	40 (34)
Family history with dementia, n (%)	92 (45)	59 (50)
MMSE, mean (SD)	29.0 (1.0)	28.9 (1.1)
RCF recall 3 min, mean (SD)	18.4 (5.4)	18.9 (5.5)
FNAME delayed recall subscore names, mean (SD)	19.8 (10.0)	20.2 (10.3)
PAL total errors adjusted, mean (SD)	28 (16)	28 (16)
RAVLT delayed recall, mean (SD)	8.4 (2.9)	8.3 (2.9)
CCI, median (IQR)	21 (20–24)	21 (20–24)
Positive amyloid-PET (visual read BP_{ND} images), n (%)[d]	28 (14)	16 (14)
PET global cortical BP_{ND}, mean (SD)	0.16 (0.12)	0.17 (0.14)
CSF available, n (%)	126 (63)	118 (100)
CSF ratio amyloid-β 1-42/1-40, mean (SD)	-	0.10 (0.03)

Key: MZ, monozygotic; PET, positron emission tomography; BP_{ND}, nondisplaceable binding potential; IQR, interquartile range; SD, standard deviation; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; RCF, Rey complex figure; FNAME, face-name–associated memory examination; PAL, paired associate learning; RAVLT, Rey auditory verbal learning task; CCI, cognitive change index self-reported; CSF, cerebrospinal fluid.

[a] In 2 twin-pairs, PET was not performed in both twins.
[b] Twins with cotwin with either missing CSF or PET data.
[c] Two participants missing.
[d] Three participants missing.
[e] $p < 0.0001$ difference between subgroup with CSF and PET vs. subgroup with PET only.

3.2. Across-participant association between amyloid aggregation and memory performance

Participants with a positive amyloid-PET scan on visual read (n = 24) had lower scores on the Rey visuospatial memory test (Supplementary Table 1). A lower CSF $A\beta_{42/40}$ ratio was also associated with lower Rey visuospatial memory scores ($\beta = 0.15$, $p = 0.04$, Fig. 2A, Table 2). Age showed a significant negative association with Rey visuospatial memory scores, but the interaction of age with the CSF $A\beta_{42/40}$ ratio or amyloid-PET visual read on Rey visuospatial memory was not statistically significant ($p > 0.44$). We found no association between the CSF $A\beta_{42/40}$ ratio and other memory test scores or between amyloid-PET BP_{ND}/visual read and memory performance. None of the amyloid measures or memory tests were associated with the CCI. When analyses were repeated without participants with missing face-name associative memory scores (n = 22), findings remained the same.

3.3. Cross–twin-pair correlation between amyloid aggregation and memory performance

Because we observed a significant relation between amyloid aggregation with Rey visuospatial memory performance, we further tested the influence of shared genetic/environmental factors. We found that CSF $A\beta_{42/40}$ ratio in one twin could predict Rey visuospatial memory score in the cotwin (r = 0.20, $p = 0.04$), but this association was not statistically significant after correction for age (r = 0.08, $p = 0.41$). This suggests that the relation between amyloid aggregation and visual memory performance is partly driven by factors that are shared within identical twin pairs (genes/environment).

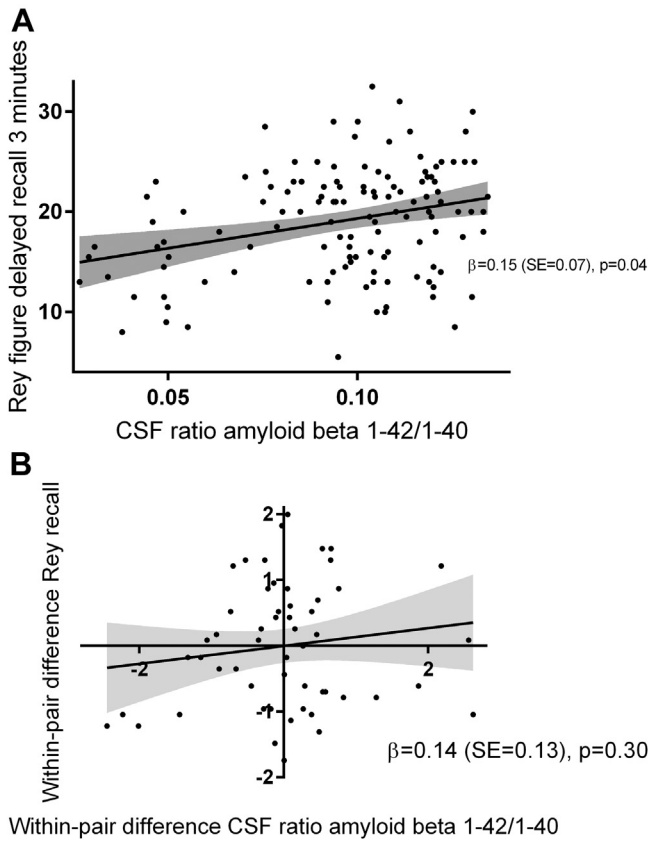

Fig. 2. Association between CSF $A\beta_{42/40}$ ratio and Rey visuospatial memory (A) Across-participant association: Generalized estimating equations are shown adjusted for age, APOE ε4, and gender. Analysis includes random effect for twin status. A standardized beta is shown, calculated with z-scores. Each dot represents one participant. Amyloid aggregation is reflected by lower CSF amyloid-β 1-42/1-40 ratio. (B) Within twin-pair difference association: Linear regression result is shown for the relation between the standardized difference scores (z-scores) within a twin-pair for CSF Aβ42/40 ratio with the Rey figure recall score. Each dot represents one twin pair. Abbreviations: APOE, apolipoprotein E; CSF, cerebrospinal fluid.

Table 2
Associations between memory performance, cognitive complaints, and amyloid pathology

Predictor	Dependent	Model 1 B (SE)	*p*-value	Model 2 B (SE)	*p*-value
PET global cortical BP_{ND}	FNAME delayed recall subscore names	−0.06 (0.06)	0.29	−0.02 (0.05)	0.69
PET global cortical BP_{ND}	RCF recall 3 min	−0.12 (0.08)	0.13	−0.05 (0.07)	0.49
PET global cortical BP_{ND}	PAL total errors adjusted	0.10 (0.07)	0.11	0.04 (0.06)	0.51
PET global cortical BP_{ND}	RAVLT delayed recall	−0.10 (0.07)	0.12	−0.02 (0.06)	0.74
PET global cortical BP_{ND}	CCI	−0.0 (0.08)	0.49	−0.10 (0.07)	0.16
Ratio CSF amyloid-β 1-42/1-40	FNAME delayed recall subscore names	0.11 (0.08)	0.17	0.06 (0.08)	0.51
Ratio CSF amyloid-β 1-42/1-40	RCF recall 3 min	0.26 (0.08)	0.001*	0.15 (0.07)	0.04
Ratio CSF amyloid-β 1-42/1-40	PAL total errors adjusted	−0.11 (0.09)	0.24	−0.04 (0.09)	0.65
Ratio CSF amyloid-β 1-42/1-40	RAVLT delayed recall	0.10 (0.09)	0.27	0.06 (0.09)	0.52
Ratio CSF amyloid-β 1-42/1-40	CCI	0.0 (0.10)	0.54	0.12 (0.10)	0.22
FNAME delayed recall subscore names	CCI	−0.09 (0.07)	0.19	0.01 (0.08)	0.93
RCF recall 3 min	CCI	−0.11 (0.07)	0.14	−0.05 (0.08)	0.50
PAL total errors adjusted	CCI	−0.01 (0.07)	0.85	−0.06 (0.07)	0.38
RAVLT delayed recall	CCI	−0.15 (0.09)	0.08	−0.10 (0.11)	0.36

Key: PET, positron emission tomography; BP_{ND}, nondisplaceable binding potential; FNAME, face-name–associated memory examination; RCF, Rey complex figure; PAL, paired associate learning; RAVLT, Rey auditory verbal learning task; CCI, cognitive change index self-reported; CSF, cerebrospinal fluid.
Generalized estimating equations are shown unadjusted (model 1) and covariate unadjusted (age, gender, and education [model 2]). *significant after correction for multiple testing (Bonferroni-corrected $p < 0.05 = 0.05/10 = 0.005$). All models included random effect for twin status. Beta is z-scores of standardized residuals. A higher PET BP_{ND} and a lower CSF amyloid β 1-42/1-40 ratio indicate higher amyloid load.

3.4. Within–twin-pair difference association between amyloid aggregation and memory performance

We also tested the influence of nonshared environmental factors on the relation between amyloid aggregation and Rey visuospatial memory performance by twin-pair difference analysis but did not observe a significant association between twin-pair difference in amyloid aggregation and twin-pair difference Rey visuospatial memory performance, suggesting nonshared environmental factors do not contribute to the observed association (Fig. 2B).

3.5. Monozygotic twin discordance analysis—disease stage model

Finally, we tested possible effects of disease staging using the twin discordance model. This model can be used as a staging model

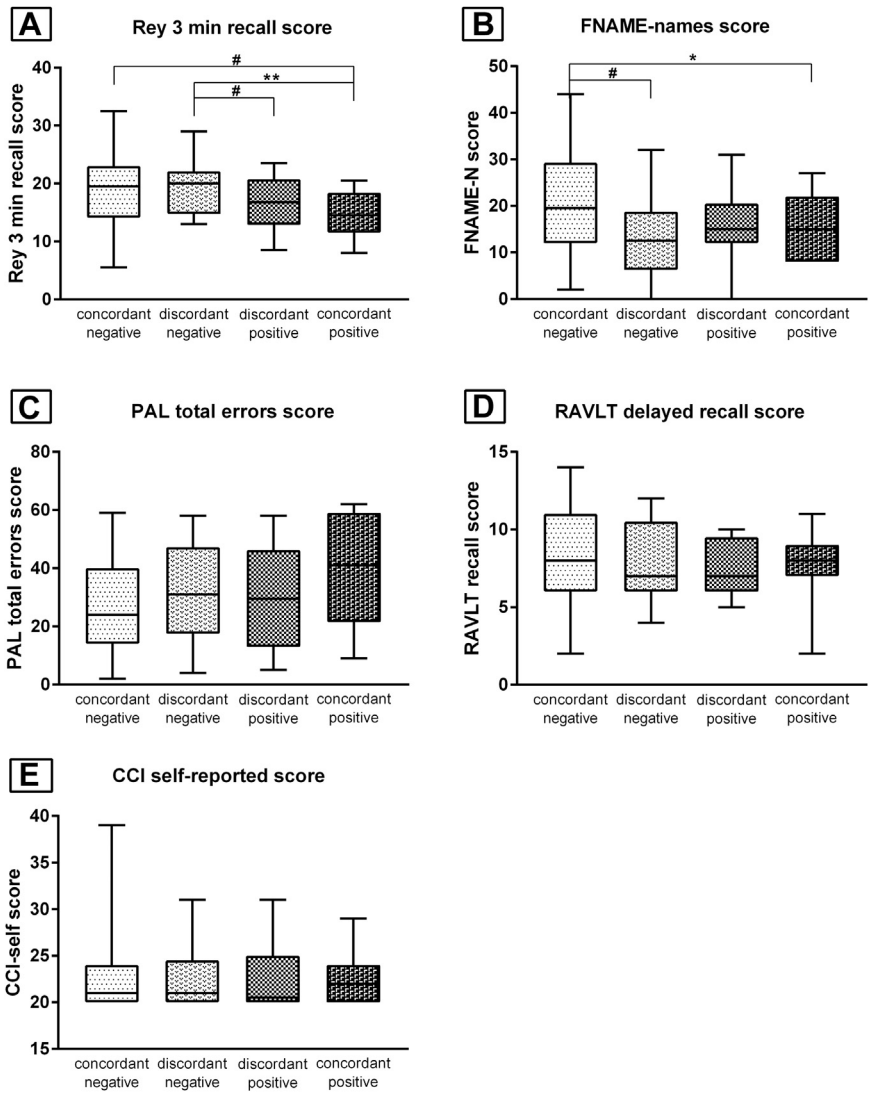

Fig. 3. Memory and complaints score according to amyloid-PET twin discordance/concordance status. Boxplots show Rey 3 minutes recall scores (A), FNAME-name subscore (B), PAL total errors score (C), RAVLT delayed recall score (D), and CCI self-reported score (E) for twins from pairs that have both a negative amyloid-PET scan (concordant negative, $N_{pairs} = 74$), twin from a discordant pair with negative amyloid-PET scan (discordant negative, n = 14), twin from a discordant pair with positive amyloid-PET scan (discordant positive, n = 14), and twins from pairs that have both a positive PET scan (concordant positive $N_{pairs} = 6$). For tests that showed overall significance, we indicated which group comparisons were significant $^{**}p < 0.01$, $^{*}p < 0.05$, or showed a trend $^{\#}p < 0.10$ (corrected for age, gender, and education). Abbreviations: CCI, cognitive change index self-reported; FNAME, face-name–associated memory examination; PAL, paired associate learning; RAVLT, Rey auditory verbal learning task.

for amyloid pathology, with concordant negative twin pairs being the control group, discordant twins with a negative amyloid-PET scan in a preamyloid stage, followed by discordant cotwins with a positive amyloid-PET scan, and twin pairs concordant for having a positive amyloid-PET scan reflecting a more advanced stage of the disease. Fourteen twin pairs were discordant (one twin had a negative amyloid-PET scan and its cotwin had a positive amyloid-PET scan), in 74 twin pairs, both twins had negative amyloid-PET scans (concordant negative), and in 6 pairs, both twins had positive amyloid-PET scans (concordant positive) (Fig. 3, Supplementary Table 2). Discordant amyloid-negative twins had a higher PET BP_{ND} than concordant amyloid-negative twins (Supplementary Table 2). Discordant twins with positive amyloid-PET scan tended to show lower Rey visuospatial memory scores compared with their cotwins with a negative amyloid-PET scan ($p = 0.08$). Concordant positive twins performed worse on the Rey visuospatial memory task compared with discordant negative twins ($p = 0.009$) and compared with concordant negative twins at trend level ($p = 0.08$). Compared with concordant amyloid-negative twins, the face-name associative memory score was lower in concordant positive twins ($p = 0.02$) and tended to be lower in twins with negative amyloid-PET scan from a discordant pair ($p = 0.07$). Concordant and discordant twins did not differ from each other on paired associative memory, Rey verbal memory performance, and CCI scores.

4. Discussion

We found amyloid pathology to be associated with lower visual memory performance in cognitively normal older adults. Participants with higher levels of amyloid aggregation, measured with both PET and in CSF, showed worse visuospatial memory performance (Rey complex figure). We found no association between verbal memory performance and amyloid pathology, cognitive complaints, and amyloid pathology or between cognitive complaints and memory performance.

4.1. Amyloid aggregation and memory performance

4.1.1. Visuospatial memory

The Rey complex figure (visuospatial memory) task was found to be associated with amyloid pathology both on PET (visual read) and in CSF ($A\beta_{42/40}$ ratio). These results are in line with a previous study showing decline in Rey visuospatial memory performance to be associated with amyloid pathology at follow-up (Snitz et al., 2013). Our monozygotic twin-pair analysis showed that CSF $A\beta_{42/40}$ ratio in one twin could predict Rey visuospatial memory scores in the genetically identical cotwin, suggesting this relation to be driven by factors that are shared within these twin pairs (genes/environment). However, as the association was no longer present after correction for age, it is possible that the association resulted from the fact that both amyloid aggregation and memory dysfunction increase with age in a parallel way (Jansen et al., 2017). Using amyloid-PET status of monozygotic amyloid discordant and concordant twins as a disease staging model for amyloid pathology, we found that Rey visuospatial memory scores in concordant amyloid-positive twins were worse relative to concordant and discordant amyloid-negative twins, which may suggest that Rey visuospatial memory is impaired in a relatively late stage of amyloid aggregation.

The fact that the relation between Rey visuospatial memory performance and amyloid abnormality on PET imaging was only found for a visual read of the PET scan, but not with the continuous amyloid-PET BP_{ND}, may be explained by the low variability in PET BP_{ND} values, as the large majority of the sample showed low BP_{ND} levels.

4.1.2. Visual associative memory

Although visual associative memory was not associated with amyloid aggregation in the total group, monozygotic twin amyloid discordance analysis showed a possible effect of disease staging on visual associative memory with a trend for lower face-name associative memory scores in amyloid-PET discordant negative twins and lower scores for amyloid-PET concordant positive twin pairs compared with concordant negative twin pairs. Contrary to Rentz et al., we did not find that amyloid aggregation was associated with face-name associative memory in the total group. This may be explained by differences in amyloid quantification (global binding in our study vs. regional binding in the other study). The absence of the association may also be due to selective dropout as participants who did not complete the face-name associative memory task were older and had lower cognitive scores.

4.2. Cognitive complaints and amyloid aggregation

Amyloid measures did not correlate with cognitive complaints. One other study in community-dwelling cognitively normal older adults showed that cognitive complaints were associated with higher amyloid load (Perrotin et al., 2017), which may be due to differences in definition of cognitive complaints and exclusion criteria used. Cognitive complaints may be more strongly associated with amyloid aggregation in a memory clinic setting (Molinuevo et al., 2017). We found no relation between CCI and memory performance, in line with previous studies (Alegret et al., 2015; Snitz et al., 2015).

4.3. Strengths and limitations

A strength of this study is the large sample size of cognitively normal older monozygotic twins with amyloid biomarker data on PET and in a substantial subsample in CSF as well. Possible limitations are the inclusion and exclusion criteria applied in our study, as these reduced the range of memory performance and CCI scores, which may have limited the ability to detect associations. Our population was relatively healthy with a low prevalence of positive amyloid-PET scans (14%), which may have also limited power to detect differences in the continuous PET analyses in relation to memory performance. The number of concordant amyloid-positive twin-pairs was relatively small, which limited statistical power. By design, we only included monozygotic twin pairs and we could therefore not discriminate between the contribution of shared genetics and shared environment to the association between memory and amyloid pathology. However, shared environment is most often not involved, in twin correlations for brain aging markers in older adults (Blokland et al., 2012; Lee et al., 2010).

5. Conclusions

Visuospatial memory and face-name associative memory are among the types of memory sensitive for early AD. Our monozygotic twin study provides a useful approach to clarify mechanisms behind early amyloid pathology and memory loss in AD.

Disclosure

EK, MK, AB, JT, MY, SDM, AAL, DLB, PS, PJV report no competing interests. CT has functioned in advisory boards of Fujirebio and Roche, received nonfinancial support in the form of research consumables from ADx Neurosciences and Euroimmun, and performed contract research or received grants from Janssen prevention center, Boehringer, Brainsonline, Axon Neurosciences, EIP Pharma, Roche. BNMvB is a trainer for the visual interpretation of [^{18}F]flutemetamol PET scans. He does not receive personal compensation for this.

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Appendix A. Supplementary data

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