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Episodic memory and cortical amyloid pathology: PET study in cognitively discordant twin pairs

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ABSTRACT

We studied the association between episodic memory and cortical fibrillar β-amyloid pathology within twin pairs. Using telephone-administered cognitive screening of 1415 twin pairs in a population-based older Finnish Twin Cohort study, we identified 45 (mean [SD] age 72.9 [4.0] years, 40% women) cognitively discordant same-sex twin pairs (24 dizygotic and 21 monozygotic) without neurological or psychiatric disorders other than AD or mild cognitive impairment. In-person neuropsychological testing was conducted. Cortical amyloid was measured with carbon 11-labelled Pittsburgh compound B ([^{11}C]PiB) positron emission tomography imaging and quantified as the average standardized uptake value ratio in cortical regions affected in AD. Larger within-twin pair differences in verbal immediate (r = -0.42) and delayed free recall (r = -0.41), and visual delayed free recall (r = -0.46) were associated with larger within-twin pair differences in [^{11}C]PiB uptake (p's < 0.01). Correlations were not significantly different in dizygotic and monozygotic pairs suggesting that the episodic memory-cortical amyloid relationship is not confounded by genetic effects. However, larger samples are needed to draw more definitive conclusions.

1. Introduction

β-amyloid pathology (Aβ) and episodic memory (EM) impairment are biological and cognitive hallmarks of Alzheimer's disease (AD), respectively. Different levels of cortical Aβ as measured with positron emission tomography (PET) imaging are evident in preclinical AD, amnestic mild cognitive impairment (aMCI) and AD (Rowe and Villemagne, 2013). Similarly, EM performance differentiates people in the AD continuum (Belleville et al., 2017; Mortamais et al., 2017). Still, studies have documented a discrepancy between cortical amyloid pathology and EM with a substan-

tial proportion of amyloid positive individuals not showing EM impairment (Roberts et al., 2018).

Most studies on the Aβ-EM association have been conducted in unrelated individuals and hence, they cannot differentiate if this relationship is confounded by shared genetic effects. *Apolipoprotein E (APOE)* genotype is related to both amyloid accumulation and EM and may also modify the Aβ-EM relationship (Kantarci et al., 2012; Mormino et al., 2014). The Aβ-EM association may also be confounded by other genetic effects due to the polygenic nature of AD (Kunkle et al., 2019). Genetic association between Aβ and EM in late onset AD (LOAD) is supported by the fact that genetic variants affecting Aβ processing were associated with LOAD in a genome-wide association study where cases were determined based on clinical diagnosis that has a strong emphasis on EM impairment (Kunkle et al., 2019). Moreover, polygenic risk score of LOAD is associated with EM also earlier in the AD continuum before people have developed dementia (Elman et al., 2020). Studies in unrelated

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individuals can indeed evaluate the genetic associations but they are also limited because GWAS's / polygenic scores capture only part of the genetic variance of AD.

Here, twin studies are of great utility as it is possible to investigate the association between amyloid pathology and cognitive impairment by controlling for shared genetic effects even in the absence of any measured genes. Monozygotic (MZ) twins are genetically identical whereas dizygotic (DZ) twins share – like non-twin siblings – on average half of their segregating genes. The EM-Aβ relationship is not confounded by genetic effects if the associations of within-pair differences in EM and Aβ are similar in DZ and MZ twin pairs. An alternative scenario where the EM-Aβ association is attenuated, but still evident, within MZ pairs compared to DZ pairs would be suggestive of partial genetic confounding. If the EM-Aβ association is not evident in MZ twins then there occurs complete genetic confounding, in other words the association is fully mediated by shared genetic effects. In these twin analyses, no measured genes are needed but the level of genetic confounding can be interpreted from the differences in genetic relatedness between MZ and DZ twin pairs. This design also fully controls for shared environmental effects (i.e., all environmental effects that make twins similar). By design, differences in the magnitude of the EM-Aβ association between DZ and MZ twin pairs are due to genetic effects. The discordant twin approach is a quasi-experimental design that can inform more about causality of brain pathology-cognition associations than observational studies of unrelated individuals.

One study including only MZ twins looked at 96 cognitively normal twin pairs and did not find statistically significant differences between 14 amyloid-PET positive and negative co-twins in two EM measures (Konijnenberg et al., 2019). However, it should be noted that there is only a weak amyloid-EM correlation in cognitively normal individuals (Baker et al., 2017; Hedden et al., 2013). Another approach utilizing twins is to purposefully investigate pairs where the two twins differ cognitively, that is, are discordant. By studying cognitively discordant twin pairs it is possible to test if cognitively impaired co-twins differ in amyloid pathology from their cognitively healthy co-twins or from non-twin cognitively healthy controls. Using this approach, we have earlier reported that 9 cognitively preserved monozygotic – but not dizygotic – co-twins of cognitively impaired probands had increased cortical carbon 11-labelled Pittsburgh compound B ([^{11}C]PiB) uptake compared to 9 cognitively healthy non-twin controls (Scheinin et al., 2011). Taken together, these earlier twin studies suggest genetic confounding in the Aβ-EM association.

The primary aim of this case-control study was to investigate if within-twin pair differences in EM are related to within-twin pair differences in cortical amyloid pathology. We identified cognitively discordant twin pairs from a population-based sample and measured EM with in-person neuropsychological testing and amyloid pathology with [^{11}C]PiB PET. We used both, continuous EM score and binary case-control – a co-twin with poorer versus a co-twin with better EM performance – approaches when studying within-twin pair differences in amyloid pathology. The hypothesis was that twins with poorer EM have more cortical amyloid pathology compared to their co-twins with better EM and that we would see this in both DZ and MZ twin pairs. If the association would be stronger within DZ pairs compared to MZ pairs, this would suggest that the association between EM and cortical amyloid pathology would be confounded by shared genetic effects because DZ twins differ in approximately half of their segregating genes. Our secondary aim was to test if cognitively normal DZ or MZ twins with EM impaired co-twins have greater cor-

tical amyloid pathology compared to cognitive normal non-twin controls.

2. Methods

2.1. Study design and participants

The participants were recruited from the older Finnish Twin Cohort (FTC) which was established in 1975 and consisted of 13888 same-sex twin pairs born before 1958 (Kaprio et al., 2019; Kaprio and Koskenvuo, 2002). Twins who were ≥65 years were asked to participate in a telephone interview: those born before 1938 during 1999–2007 (Project I, participation rate 73%) and those born in 1938–1944 during 2013–2017 (Project II, participation rate 61%) (Lindgren et al., 2018). Of these, 62% (1415 / 2296) of full twin pairs participated including 560 MZ and 849 DZ pairs and 6 pairs with unknown zygosity (Fig. 1). In addition to twins, non-twin cognitively healthy controls were recruited through open invitation.

The telephone interview protocol consisted of the telephone assessment for dementia (Gatz et al., 2002), and the Telephone Interview for Cognitive Status (Brandt et al., 1988) - both validated in Finnish for the detection of dementia (Järvenpää et al., 2002). Cognitively discordant twin pairs, as defined by the telephone interview or a diagnosis of AD or memory impairment in one twin sibling, were asked to participate in brain imaging and in-person neuropsychological testing at the Turku PET Centre, Finland. Exclusion criteria included neurological and psychiatric disorders other than AD or mild cognitive impairment, including history of major stroke or head trauma, significant medical conditions affecting the ability to undergo the study and contraindications for brain scanning. Telephone interview included four questions about independence in activities of daily living: (1) Are you able to take care of your household? (2) Are you able to get around outside? (3) Are you able to do shopping? (4) Are you able to dress and undress yourself? Participants self-reported if they were able to perform the activity independently, with the help from others or were not able to perform the activity.

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants. We followed Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for case-control studies.

In Project I, 30 twin pairs (16 MZ, 14 DZ) and 12 healthy non-twin controls who were over 65 years old, and an additional 57-year-old DZ pair discordant for a diagnosis of AD, participated in both [^{11}C]PiB PET and MR imaging. In Project II, 17 twin pairs (8 MZ, 9 DZ) and 8 healthy non-twin controls who were over 65 years old participated (Fig. 1). A subgroup of Project I participants were included in an earlier report (Scheinin et al., 2011), but new preprocessing and analysis of PET data for these participants was done in the present study. Zygosity was based on genotyping multiple polymorphic markers (Sarna et al., 1978).

2.2. APOE genotyping

APOE genotype was determined by directly genotyping two single-nucleotide polymorphisms: rs7412 and rs429358 (in 2 MZ pairs a co-twin had missing *APOE* information and we used their co-twins *APOE* status, in 2 MZ pairs both had missing *APOE* information but their zygosity was DNA based and we included these pairs in within-twin pair analyses as they were by design concordant for all genetic variants). *APOE* genotype was categorized into
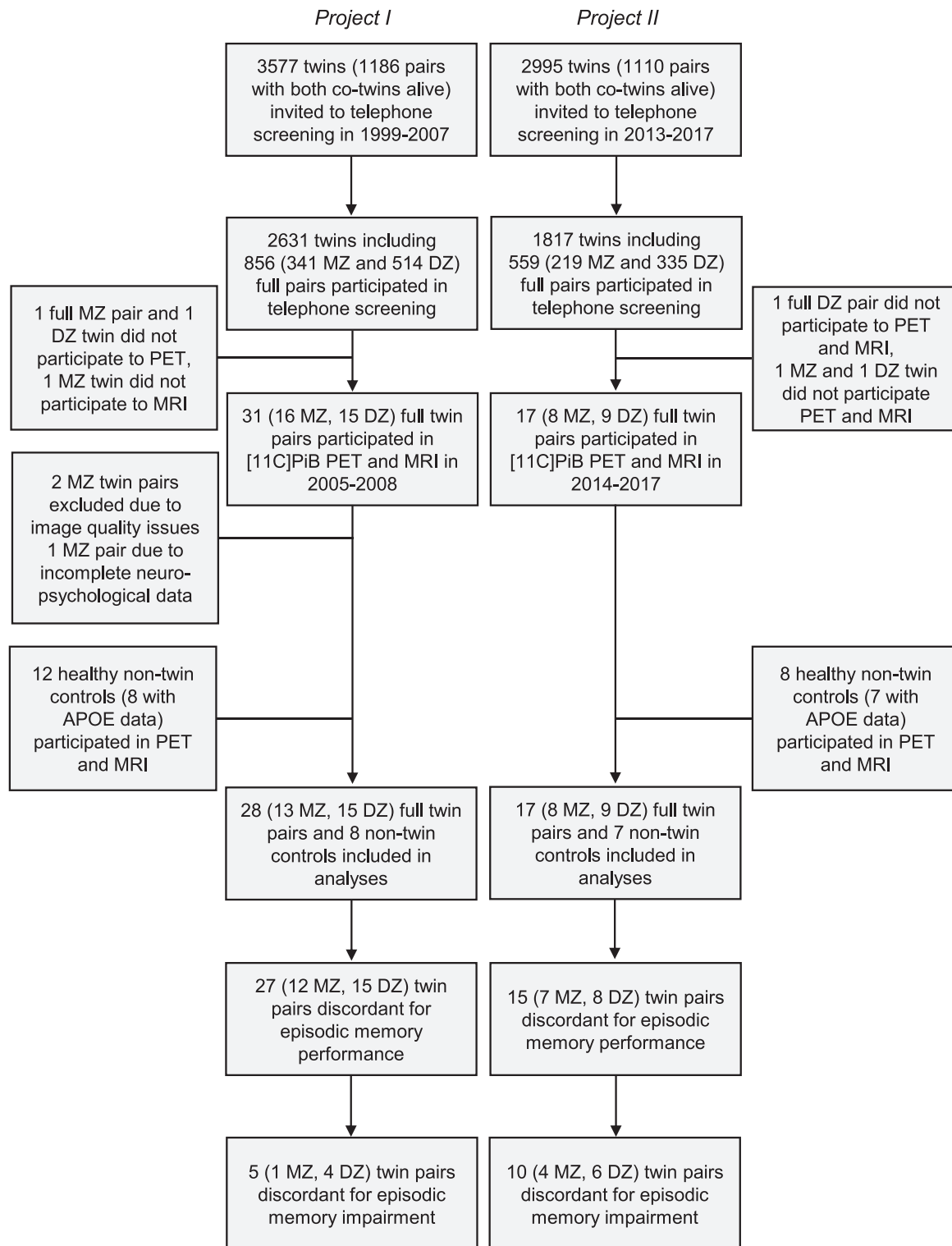
Project I   *Project II*

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┌─────────────────────┐        ┌─────────────────────┐
│ 3577 twins (1186    │        │ 2995 twins (1110    │
│ pairs with both     │        │ pairs with both     │
│ co-twins alive)     │        │ co-twins alive)     │
│ invited to telephone│        │ invited to telephone│
│ screening in        │        │ screening in        │
│ 1999-2007           │        │ 2013-2017           │
└─────────────────────┘        └─────────────────────┘
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┌─────────────────────┐        ┌─────────────────────┐
│ 2631 twins including│        │ 1817 twins including│
│ 856 (341 MZ and 514 │        │ 559 (219 MZ and 335 │
│ DZ) full pairs      │        │ DZ) full pairs      │
│ participated in     │        │ participated in     │
│ telephone screening │        │ telephone screening │
└─────────────────────┘        └─────────────────────┘
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┌──────────────────────┐   ┌──────────────────────┐
│ 1 full MZ pair and 1 │   │ 1 full DZ pair did not│
│ DZ twin did not   │   │ participate to PET   │
│ participate to PET, │   │ and MRI,   │
│ 1 MZ twin did not   │   │ 1 MZ and 1 DZ twin   │
│ participate to MRI   │   │ did not participate   │
└──────────────────────┘   │ PET and MRI   │
                                                                  └──────────────────────┘

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┌─────────────────────┐        ┌─────────────────────┐
│ 31 (16 MZ, 15 DZ)   │        │ 17 (8 MZ, 9 DZ) full│
│ full twin pairs     │        │ twin pairs          │
│ participated in      │       │ participated in     │
│ [11C]PiB PET and MRI│        │ [11C]PiB PET and MRI│
│ in 2005-2008        │        │ in 2014-2017        │
└─────────────────────┘        └─────────────────────┘
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┌──────────────────────┐
│ 2 MZ twin pairs   │
│ excluded due to   │
│ image quality issues │
│ 1 MZ pair due to   │
│ incomplete neuro-   │
│ psychological data   │
└──────────────────────┘

┌──────────────────────┐   ┌──────────────────────┐
│ 12 healthy non-twin │   │ 8 healthy non-twin   │
│ controls (8 with   │   │ controls (7 with   │
│ APOE data)   │   │ APOE data)   │
│ participated in PET │   │ participated in PET │
│ and MRI   │   │ and MRI   │
└──────────────────────┘   └──────────────────────┘

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┌─────────────────────┐        ┌─────────────────────┐
│ 28 (13 MZ, 15 DZ)   │        │ 17 (8 MZ, 9 DZ) full│
│ full twin pairs and │        │ twin pairs and 7    │
│ 8 non-twin controls │        │ non-twin controls   │
│ included in analyses│        │ included in analyses│
└─────────────────────┘        └─────────────────────┘
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┌─────────────────────┐        ┌─────────────────────┐
│ 27 (12 MZ, 15 DZ)   │        │ 15 (7 MZ, 8 DZ) twin│
│ twin pairs discordant│       │ pairs discordant for│
│ for episodic memory │        │ episodic memory     │
│ performance         │        │ performance         │
└─────────────────────┘        └─────────────────────┘
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┌─────────────────────┐        ┌─────────────────────┐
│ 5 (1 MZ, 4 DZ) twin │        │ 10 (4 MZ, 6 DZ) twin│
│ pairs discordant for│        │ pairs discordant for│
│ episodic memory     │        │ episodic memory     │
│ impairment          │        │ impairment          │
└─────────────────────┘        └─────────────────────┘
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Fig. 1. Study flow diagram. MZ, monozygotic; DZ, dizygotic.

$\varepsilon 3/\varepsilon 4$, $\varepsilon 4/\varepsilon 4$, and $\varepsilon 4$ non-carriers ($\varepsilon 3/\varepsilon 3$ and $\varepsilon 2/\varepsilon 3$). A total of 5 non-twin controls did not have available *APOE* genotype information and were excluded from the analyses.

2.3. [11C]PiB PET imaging

The syntheses of [11C]PiB have been described elsewhere (Kemppainen et al., 2006; Snellman et al., 2017). In 2005–2008, participants received a mean injection of 469 (SD = 63) MBq of [11C]PiB, corresponding to 3.77 (SD = 1.13) µg when the mean molar radioactivity was 34 (SD = 10) MBq/nmol. In 2014–2017, participants received a mean injection of 490 (SD = 39) MBq of [11C]PiB, corresponding to 0.29 (SD = 0.16) µg when the mean molar radioactivity was 615 (SD = 399) MBq/nmol. Mean radiochemical purity of [11C]PiB injection was 99% (SD = 1).

In 2005-2008, participants underwent a 90-minute dynamic [^{11}C]PiB PET scan with an ECAT EXACT HR+ scanner (CTI, Knoxville, TN, USA) and MRI scan with a 1.5 T Intera scanner (Philips, Best, the Netherlands). In 2014–2017, participants underwent a [^{11}C]PiB PET scan from 40 to 90 minutes after injection and a T1-weighted MRI scan with a 3T PET-MRI scanner (Philips Ingenuity TF PET/MR, Philips Medical Systems, Cleveland, OH, USA). The preprocessing and analysis of PET data was carried out using an automated analysis pipeline Magia (https://github.com/tkkarjal/magia) (Karjalainen et al., 2020). The T1-weighted single subject image was coregistered with the single subject [11C]PiB PET image and normalized to the Montreal Neurological Institute space. Automated region of interest (ROI) analysis was applied using the anatomic labelling (AAL) atlas Tzourio-Mazoyer et al., 2002) to generate cortical gray matter and cerebellar cortex ROIs. Region to cerebellar cortex standardized uptake value ratios (SUVRs) were generated over the 60 to 90-minute scan duration. A cortical composite PiB SUVR was formed as the average of prefrontal, parietal, lateral temporal, anterior cingulate, posterior cingulate and precuneus ROI SUVRs, based on brain regions where early amyloid accumulation is typically first detectable (Braak and Braak, 1997).

2.4. Neuropsychological measures

Neuropsychological test battery included 6 tests that were used to calculate continuous EM measures as described in Lindgren et al. (2019) The test scores were transformed into standard deviation (SD) units based on age-appropriate Finnish norms (Sotaniemi et al., 2012; Ylikoski, 2000). Each EM measure was the mean of SD units from 2 tests. Verbal delayed free recall (VerDFR) was measured with the delayed word list recall from the Consortium to Establish a Registry for Alzheimer's disease Neuropsychological Battery (CERAD-NB) and Logical Memory (LM) delayed recall from the Wechsler Memory Scale-Revised (WMS-R). Verbal immediate free recall (VerIFR) was measured with the world list from the CERAD-NB and LM immediate free recall. Visual delayed free recall (VisDFR) was measured with Visual Reproductions from the WMS-R and constructional praxis savings from the CERAD-NB). We also examined the association between global cognitive performance measured with the CERAD-NB total score (Chandler et al., 2005) and [^{11}C]PiB SUVR. In post hoc analysis, we used a composite EM score consisting of all EM measures ([VerIFR + VerDFR + VisDFR] / 3) including calculation of Cook's distance, a formal index of outlier influence, to identify potentially influential twin pairs. Composite EM score was also used to look at individual-level association of EM with [^{11}C]PiB SUVR.

VerDFR was further used in the dichotomic classification of EM discordance (a co-twin with poorer VerDRF versus a co-twin with better VerDFR). For sensitivity analyses, stricter definition of EM discordance was based on the Jak/Bondi actuarial neuropsychological criteria whereby amnestic mild cognitive impairment (aMCI) was defined by -1 SD or poorer performance in both two tests (CERAD-NB delayed word list recall and LM delayed free recall) (Jak et al., 2009; Lindgren et al., 2019). Here discordant pairs included a co-twin with at least aMCI level of impairment and a co-twin with age-normative performance in these two EM measures. Non-twin controls were all non-aMCI by this definition.

2.5. Statistical analysis

In continuous cognitive scores, we reported the correlations between twin pair differences in cognition and twin pair differences in SUVR. We also used linear conditional fixed effects regression analysis with *APOE* ε4 status as a covariate in analyses including DZ pairs. According to case-control design, scanner, sex and age did not vary within twin pairs (also no variation in APOE status within MZ pairs). Two-tailed *p*-values <0.05 indicated statistical significance.

Paired t-test was used to compare the differences in [^{11}C]PiB SUVRs between pairs discordant for EM or aMCI status and mean intra-pair differences were reported as percentages and SUVR units with 95% confidence intervals (CI). We also included *APOE* ε4 carrier status as a covariate using linear conditional fixed effects regression (Twisk, 2013). Linear regression with sex, *APOE*, project (scanner) and age as covariates was used to compare the differences in SUVRs between cognitively normal twins and non-twin controls. Considering Cook's distance, we calculated Cook's SD and used threshold value > 0.09 (4/N, where N=45) to indicate potential influential outliers.

2.6. Data availability statement

Due to the consent given by study participants and the high degree of identifiability, data cannot be made publicly available. Data are available through the Institute for Molecular Medicine Finland (FIMM) Data Access Committee (DAC) for authorized researchers who have IRB/ethics approval and an institutionally approved study plan. For more details, please contact the FIMM DAC (fimm-dac@helsinki.fi).

3. Results

3.1. Demographics

Altogether, 45 pairs (mean [SD] age 72.9 [4.0] years; 21 MZ, 24 DZ, 18 women pairs) had available PET, MRI and neuropsychological data and 43 pairs (19 MZ, 24 DZ) had also available *APOE* genotype information. The mean age [SD] of 15 healthy non-twin controls (10 women) was 72.0 [3.1] years (Table 1). Most twins, 85 out of 90, reported that they were completely independent in four activities of daily living whereas only 5 twin individuals (1 MZ pair with both co-twins, 2 MZ pairs with one co-twin and 1 DZ pair with one co-twin) reported that they needed help from others in one or more activities of daily living.

3.2. Analyses with continuous cognitive scores

Using continuous cognitive measures in all 45 pairs, within-twin pair differences in EM measures were negatively associated with within-twin pair differences in SUVR, that is, a co-twin with higher amyloid pathology had poorer EM performance compared to a co-twin with lower amyloid pathology (Fig. 2). In all pairs, within-pair differences in EM scores were significantly related to within-pair differences in SUVR with correlations ranging from -0.41 to -0.46 (*p's* < 0.006) (Fig. 2). In DZ pairs, within-pair differences in EM scores were significantly related to within-pair differences in SUVR with correlations ranging from -0.42 to -0.51 (*p's* < 0.05, N = 24) whereas in MZ pairs, correlations were attenuated but still substantial ranging from -0.31 to -0.36 (*p's* = 0.11 to 0.16, N = 21) (Fig. 3). There were no significant zygosity-EM interactions (*p's* > 0.05) on SUVR indicating that within-pair EM differences were similarly related to within-pair SUVR difference in DZ and MZ pairs. Results were similar when looking at within-twin pair differences in total CERAD-NB score (Fig. 2 for all twin pairs and Fig. 3 for MZ and DZ pairs, Table 2).

Controlling for *APOE* status, linear conditional regression analyses indicated significant relationships of within-twin pair differences in SUVR with within-twin pair differences in VisDFR (B = -0.14, 95% CI -0.26 to -0.01, *p* = 0.03) and VerIFR (B = -0.10, 95% CI -0.20 to -0.01, *p* = 0.04), whereas the association with VerDFR

Table 1

Characteristics of twin pairs discordant for delayed verbal episodic memory (EM) performance

	All twins with poorer EM (n = 42)	All twins with better EM (n = 42)	MZ twins with poorer EM (n = 19)	MZ twins with better EM (n = 19)	DZ twins with poorer EM (n = 23)	DZ twins with better EM (n = 23)	Healthy non-twin controls (n = 15)
Project I/Project II	27/15	27/15	12/7	12/7	15/8	15/8	8/7
Men/women	25/17	25/17	15/4	15/4	10/13	10/13	5/10
Age, years (mean [SD], range)	72.8 (4.1), 57.3 to 83.0	72.8 (4.1), 57.3 to 83.0	74.2 (4.3), 68.9 to 83.0	74.1 (4.3), 68.9 to 83.0	71.7 (3.6), 57.3 to 76.0	71.7 (3.6), 57.3 to 76.0	72.0 (3.1), 66.8 to 76.6
Educational level							
≤6 y	22	23	15	15	7	8	1
7–12 y	20	16	4	3	16	13	12
≥13 y	0	3	0	1	0	2	2
APOE genotype							
APOE ε4 noncarriers	25	26	13	13	12	13	12
APOE ε4/ε3	13	12	3	3	10	9	3
APOE ε4/ε4	2	2	1	1	1	1	0
missing	2	2	2	2	0	0	0
CERAD-NB score (mean [SD], range)	66.7 (11.6), 34–83[c]	76.3 (11.3), 43–94	66.9 (11.1), 38–83[b]	72.4 (12.8), 43–90	66.6 (12.2), 34–83[c]	79.5 (9.1), 52–94	87.2 (6.9), 74–96
VerDFR score (mean [SD], range)	-1.1 (SD 1.1), -3.1 to 0.8[c]	0.1 (SD 1.2), -2.7 to 2.4	-1.0 (1.1), -2.8 to 0.8[c]	-0.2 (1.3), -2.7 to 2.2	-1.2 (1.1), -3.1 to 0.5[c]	0.4 (1.0), -1.9 to 2.4	1.0 (0.8), -0.4 to 2.4
VerIFR score (mean [SD], range)	-0.6 (1.2), -4.1 to 1.6[c]	0.2 (1.3), -2.2 to 2.6	-0.6 (1.1), -2.8 to 1.6	-0.1 (1.4), -1.8 to 2.6	-0.7 (1.3), -4.1 to 1.1[c]	0.5 (1.1), -2.2 to 2.5	1.3 (1.0), -0.5 to 3.1
VisDFR score (mean [SD], range)	-0.2 (0.8), -1.9 to 1.5[a]	0.2 (0.8), -2.2 to 1.5	-0.1 (0.8), -1.8 to 1.0	0.1 (0.9), -2.2 to 1.3	-0.2 (0.9), -1.9 to 1.5	0.3 (0.6), -0.7 to 1.5	0.8 (0.6), -2.2 to 1.5
PiB SUVR (mean [SD], range)	1.44 (0.47), 1.00–2.82	1.36 (0.34), 0.97–2.64	1.37 (0.36), 1.00–2.46	1.33 (0.25), 1.04–1.76	1.49 (0.54), 1.00–2.82	1.38 (0.40), 0.97–2.64	1.39 (0.43), 1.01–2.41

Project, I refer to brain scans conducted during 2005-2008 and project II to brain scans during 2014-2017. APOE ε4 noncarriers consists of APOE ε3/ε3 and ε2/ε3 genotypes.

Key: APOE, apolipoprotein E; CERAD-NB, the consortium to establish a registry for Alzheimer's disease neuropsychological battery; DZ, dizygotic; EM, episodic memory; MZ, monozygotic; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio; VerIFR, verbal immediate free recall; VerDFR, verbal delayed free recall; VisDFR, visual delayed free recall.

[a] refer to two-tailed *p*-values of <0.05,

[b] refer to two-tailed *p*-values of <0.01,

[c] refer to two-tailed *p*-values of <0.001 from a paired t-test comparison in respect to the better-performing co-twin.
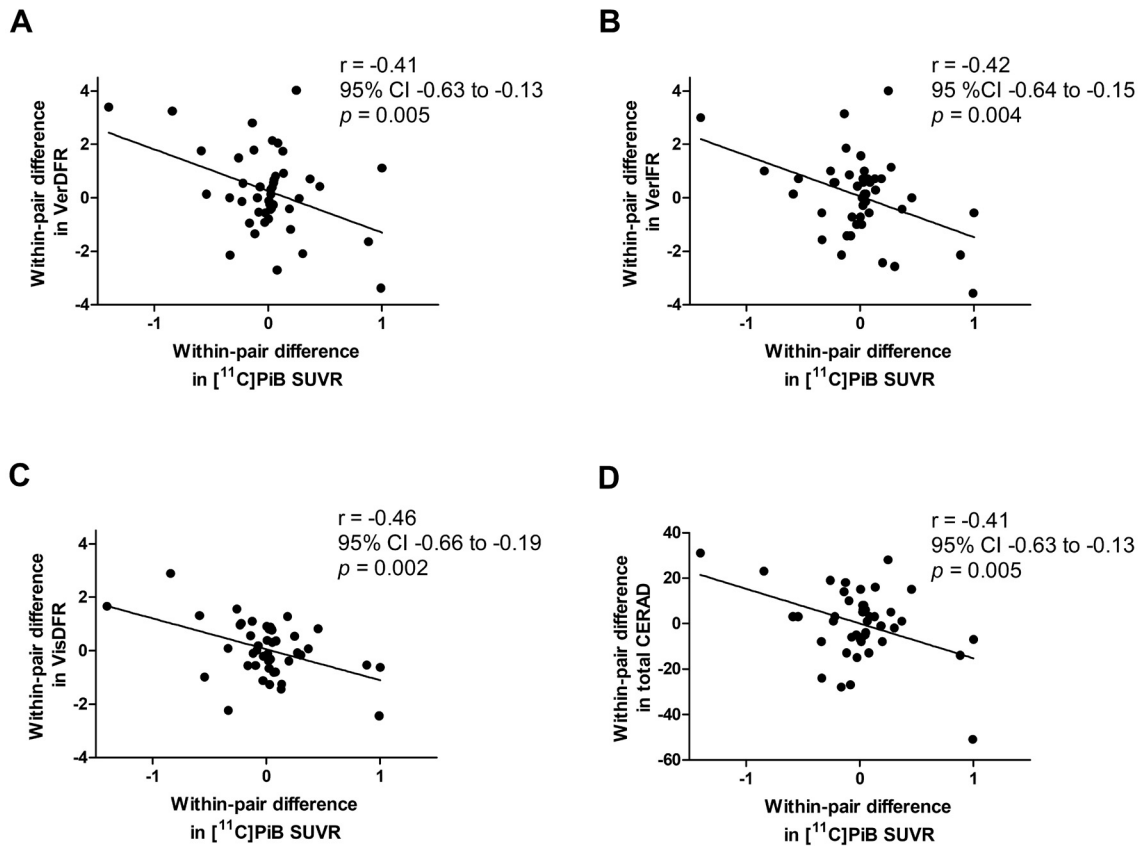
Fig. 2. Unadjusted within-pair differences in continuous cognitive scores in relation to within-pair differences in cortical [¹¹C]PiB standardized uptake value ratio (SUVR) in all 45 twin pairs. Pearson's correlation coefficients with 95% confidence intervals (CI)s and *p*-values are shown. Within-pair differences in verbal delayed free recall (VerDFR) score (A), verbal immediate free recall (VerIFR) score (B), visual delayed free recall (VisDFR) score (C), and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery total score (D) in relation to within-pair differences in [¹¹C]PiB SUVR.

Table 2
Associations between continuous cognitive scores and cortical composite [¹¹C]PiB SUVR (r = within pair differences in cognition - within twin pair differences in SUVR)

	All twins (n = 45 pairs)		MZs (n = 21 pairs)		DZs (n = 24 pairs)	
	r	95% CI	r	95% CI	r	95% CI
Composite EM	-0.48	-0.68 to -0.22	-0.42	-0.72 to 0.02	-0.49	-0.75 to -0.11
VerDFR	-0.41	-0.63 to -0.13	-0.32	-0.66 to 0.13	-0.42	-0.70 to -0.02
VerIFR	-0.42	-0.64 to -0.15	-0.36	-0.69 to 0.09	-0.43	-0.71 to -0.03
VisDFR	-0.46	-0.66 to -0.19	-0.31	-0.66 to 0.14	-0.51	-0.76 to -0.14
CERAD-NB score	-0.41	-0.63 to -0.13	-0.25	-0.61 to 0.21	-0.44	-0.71 to -0.04

Key: CERAD-NB, the consortium to establish a registry for Alzheimer's disease neuropsychological battery; DZ, dizygotic; EM, episodic memory; MZ, monozygotic; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio; VerIFR, verbal immediate free recall; VerDFR, verbal delayed free recall; VisDFR, visual delayed free recall.

was weaker and non-significant (B = -0.08, 95% CI -0.17 to 0.02, *p* = 0.10). Controlling for *APOE* status, there was also a significant negative association of within-twin pair differences in total CERAD scores and within-twin pair differences in SUVR (B = -0.010, 95% CI -0.018 to -0.002, *p* = 0.02). Though statistical significance was not reached when MZ or DZ twins were examined separately the effect sizes were very similar in both zygosity groups (Table 3).

3.3. Post hoc analyses with composite EM score

Within-twin pair differences in composite EM score (mean of all 6 measures) were significantly related to within-twin pair differences in SUVR (r = -0.48, 95% CI -0.68 to -0.22, *p* < 0.001). Correlations were -0.49 (95% CI -0.75 to -0.11, *p* = 0.01) and -0.42

(95% CI -0.72 to 0.02, *p* = 0.06) in DZ and MZ pairs, respectively (Fig. 4). There was no significant zygosity-EM interaction (*p* > 0.05) on SUVR indicating that within-pair EM differences were similarly related to within-pair SUVR difference in DZ and MZ pairs. There were six twin (1 MZ/5 DZ) pairs with Cook's distance value >0.09. Excluding these twin pairs, negative within-twin pair correlation (r = -0.19, 95% CI -0.48 to 0.13, *p* = 0.24) of composite EM score with SUVR was not significant in the remaining 39 twin pairs.

At individual level (n = 90, including all twin individuals), there was no significant correlation of [¹¹C]PiB SUVR with composite EM score r = -0.14 (95% CI -0.34 to 0.07, *p* = 0.18). Similarly, in linear regression analyses with age, sex, APOE genotype, and scanner (project) as covariates, association of [¹¹C]PiB SUVR with EM com-

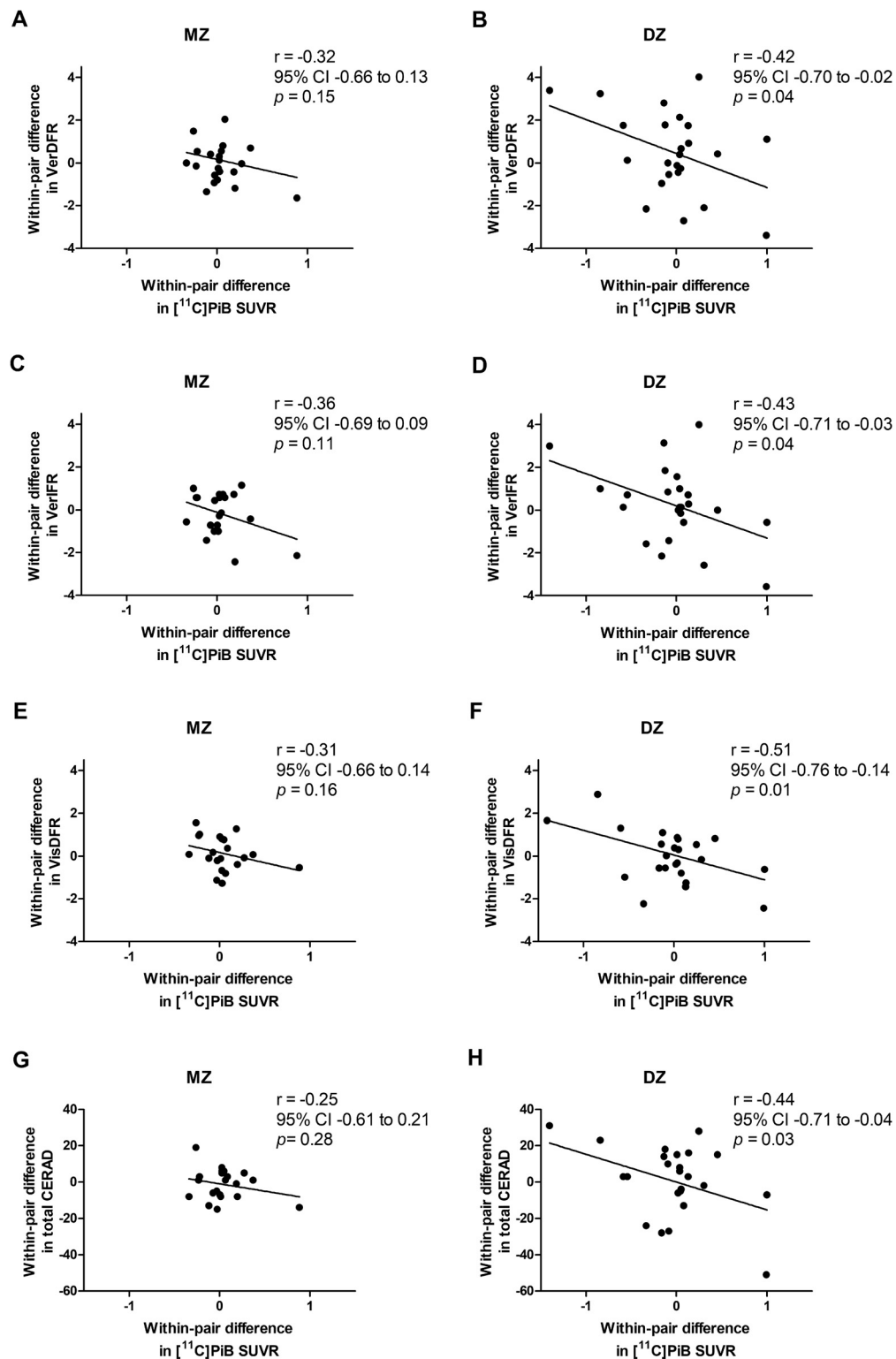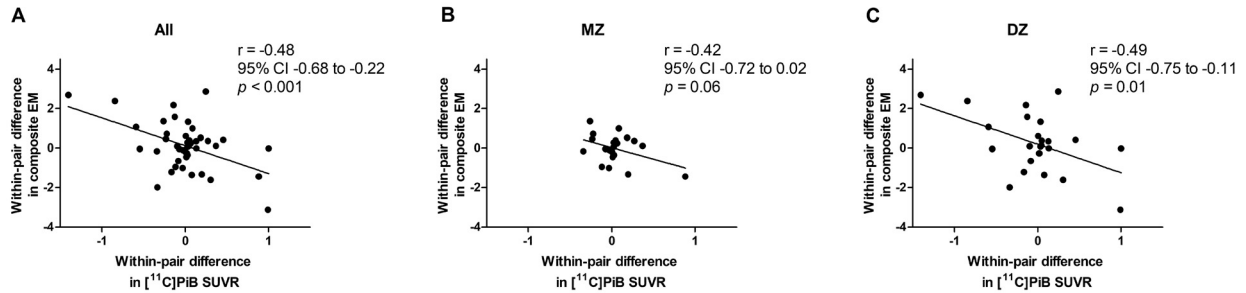**Fig. 3.** Unadjusted within-pair differences in continuous cognitive scores in relation to within-pair differences in cortical [¹¹C]PiB standardized uptake value ratio (SUVR) in all participated 21 monozygotic (MZ) and 24 dizygotic (DZ) twin pairs. Pearson's correlation coefficients with 95% confidence intervals (CI) and *p*-values are shown. Within-pair differences in verbal delayed free recall (VerDFR) score versus within-pair differences in [¹¹C]PiB SUVR in MZ (A) and DZ (B) twins. Within-pair differences in verbal immediate free recall (VerIFR) score versus within-pair differences in [¹¹C]PiB SUVR in MZ (C) and DZ (D) twins. Within-pair differences in visual delayed free recall (VisDFR) score versus within-pair differences in [¹¹C]PiB SUVR in MZ (E) and DZ (F) twins. Within-pair differences in in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery total score vs within-pair differences in [¹¹C]PiB SUVR in MZ (G) and DZ (H) twins.

Table 3
Conditional fixed effect regression analyses on the within-twin pair associations of [^{11}C]PiB SUVR with cognitive measures controlling for APOE genotype

	All twins (N = 45 pairs)			MZs (N = 21 pairs)			DZs (N = 24 pairs)		
	B	95% CIs	*p*-value	B	95% CIs	*p*-value	B	95% CIs	*p*-value
VerDFR	-0.08	-0.17 to 0.02	0.10	-0.09	-0.36 to 0.17	0.47	-0.07	-0.23 to 0.09	0.35
VisDFR	-0.14	-0.26 to -0.01	0.03	-0.09	-0.26 to 0.08	0.27	-0.16	-0.42 to 0.10	0.22
VerIFR	-0.10	-0.20 to -0.01	0.04	-0.10	-0.33 to 0.13	0.39	-0.10	-0.29 to 0.08	0.24
CERAD-NB	-0.01	-0.018 to -0.002	0.02	-0.01	-0.03 to 0.02	0.51	-0.01	-0.02to 0.004	0.15

Abbreviations: APOE, apolipoprotein E; CERAD-NB, the consortium to establish a registry for Alzheimer's disease neuropsychological battery; DZ, dizygotic; MZ, monozygotic; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio; VerIFR, verbal immediate free recall; VerDFR, verbal delayed free recall; VisDFR, visual delayed free recall.

Fig. 4. Unadjusted within-pair differences in in composite episodic memory (EM) score in relation to within-pair differences in cortical [11C]PiB SUVR in all 45 twin pairs (A), in 21 monozygotic (MZ) twin pairs (B), and in 24 dizygotic (DZ) twin pairs. Pearson's correlation coefficients with 95% CIs and *p*-values are shown.

posite score was non-significant: (B = -0.02, 95% CI -0.11 to 0.08, *p* = 0.70).

Controlling for *APOE* status (n = 45 pairs), one SD lower composite EM score was associated with 0.13 higher SUVR within twin pairs (B = -0.13, 95% CI -0.25 to -0.01, *p* = 0.03). Regression coefficients were similar in magnitude, but statistical significance was not reached when MZ or DZ twins were examined separately (DZs: B = -0.13, 95% CI -0.34 to 0.08, *p* = 0.22; MZs: B = -0.15, 95% CI -0.46 to 0.16, *p* = 0.32).

3.4. Analyses with dichotomic discordance

There were 42 twin pairs (mean [SD] age 72.8 [4.1] years; 19 MZ, 23 DZ) with difference in VerDFR and 40 of these pairs had available *APOE* information (Table 1). The mean VerDFR score of twins with poorer performance was -1.1 (SD 1.1) compared to their better performing co-twins with a mean score of 0.1 (SD 1.2) (*p*-value for the difference <0.001). There was a significant difference (*p* < 0.001) in CERAD total score between twins with poorer performance (M = 66.7; SD = 11.6) compared to their better-performing co-twins (M = 76.3; SD = 11.3).

3.4.1. Pairs discordant for EM

Among 42 pairs, twins with poorer EM had higher, but not statistically significant, cortical SUVR compared to their co-twins (1.44 vs. 1.36), with a mean intra-pair difference of 6% / 0.08 SUVR units [95% CI: -0.05 to 0.20, *p* = 0.23], (Fig. 5, Table 1). Non-significant mean intra-pair differences were 7% (0.10 SUVR units, 95% CI: -0.11 to 0.32; SUVR M = 1.49 vs. 1.38, *p* = 0.33) and 3% (0.04 SUVR units, 95% CI: -0.08 to 0.17; SUVR M = 1.37 vs. 1.33, *p* = 0.46) in 23 DZ and 19 MZ pairs, respectively (Fig. 5, Table 1). Results were similar when controlling for *APOE* ε4 carrier status in 40 twin pairs (results not shown).

3.4.2. Pairs discordant for at least aMCI-level impairment

There were 15 pairs discordant for aMCI. With a mean intra-pair difference of 12% (0.17 SUVR units, 95% CI: -0.13 to 0.47), co-
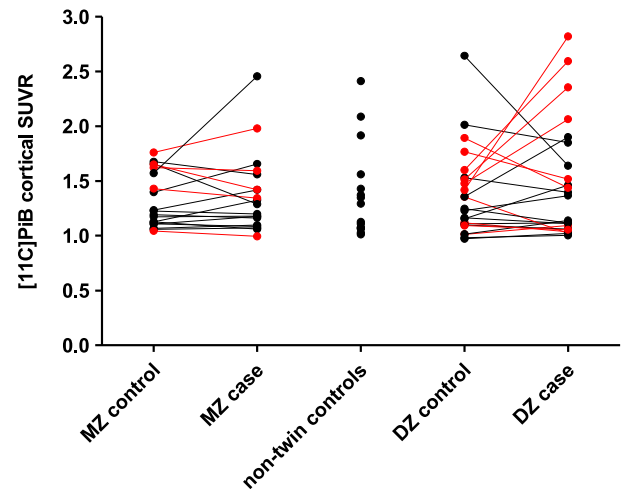

Fig. 5. Unadjusted [^{11}C]PiB cortical standardized uptake value ratios (SUVR) of 42 (19 monozygotic [MZ], 23 dizygotic [DZ]) twin pairs discordant for delayed verbal episodic memory performance and 15 cognitively normal non-twin controls. Control refers to the better-performing twin and case to the poorer-performing co-twin. Discordant twin pairs who are also discordant for amnestic mild cognitive impairment are presented with red colour. (For interpretation of the references to colour in their figure legend, the reader is referred to the web version of this article.)

twins with aMCI-level impairment had higher SUVR (M = 1.62) compared to their cognitively normal co-twins (SUVR M = 1.45), but this difference was not statistically significant (*p* = 0.24) (Fig. 5). Results were similar when controlling for *APOE* ε4 carrier status (results not shown). No significant differences were seen among DZ or MZ pairs (Fig. 5).

3.4.3. Comparison of cognitively normal twins and non-twin controls

There was no significant difference in SUVR between 14 cognitively normal co-twins from aMCI discordant pairs (SUVR

M = 1.39) and 15 cognitively normal non-twin controls (SUVR M = 1.48) with a mean difference of 0.08 SUVR units (95% CI: - 0.14 to 0.31, p = 0.44) (Fig. 5).

4. Discussion

We found a negative association between cortical fibrillar Aβ pathology measured with [11C]PiB PET and EM performance measured with multiple neuropsychological tests within older twin pairs. As hypothesized, co-twins with poorer EM performance had higher cortical [11C]PiB uptake than their better-performing co-twins. The negative Aβ-EM relationship was supported by within-twin pair analyses of continuous EM measures and [11C]PiB uptake. Within-twin pair correlations were statistically significant in 24 DZ pairs but not in 21 MZ pairs. However, we found no significant difference between DZ and MZ pair correlations. These results suggest that Aβ-EM association is not confounded by genetic effects, but we note that the number of MZ pairs was smaller compared to DZ pairs and although not significantly different from DZ within-pair correlations, the within twin-pair difference correlations ranging from -0.31 to -0.36 in MZ pairs were smaller than DZ within-pair difference correlations ranging from -0.42 to -0.51. When examining the composite EM score, correlations of -0.49 and -0.42 in DZ's and MZ's were very similar in magnitude. However, larger samples of DZ and MZ twins would be needed to draw more definite conclusions.

We also used the composite EM score to investigate individual-level Aβ-EM association, but did not detect a significant association. This was not unexpected as there is only a small effect size on the relationship between amyloid and memory in cognitive healthy older adults (Baker et al., 2017). In line with that, an earlier study of cognitively healthy MZ twins found no significant differences in episodic memory between amyloid-PET positive and negative co-twins (Konijnenberg et al., 2019).

A meta-analysis by Baker et al. (2017) further indicated that Aβ-related cognitive impairment was moderated by age, amyloid measure, type of analysis, and inclusion of control variables. Heterogeneity in samples may account for some of the discrepancy in findings and by focusing on a more homogenous memory clinic sample of cognitively healthy individuals with subjective memory complaint, Timmers et al. (2019) found that amyloid PET was associated with baseline cognition and with cognitive decline including memory domain. In our co-twin analyses, cases and controls were – by design – perfectly matched for age but also for all unmeasured environmental effects that make co-twins similar. Our design also purposefully selected twin pairs with the greatest difference in cognition. This design may explain why we detected a significant association between PET amyloid and cognition. Moreover, by including both DZ and MZ twin pairs, who differ in their level of genetic relatedness, we were able to investigate the contribution of genetic effects in this relationship. *APOE* genotype is related to both amyloid accumulation and EM and may also modify the Aβ-EM relationship (Kantarci et al., 2012; Mormino et al., 2014). Our results were generally similar when controlling for *APOE* genotype implicating also the importance of other genes in individual differences in cortical Aβ and EM.

Using dichotomic discordance classification, the average intra-pair [11C]PiB uptake differences of 6% (Cohen's d = 0.2) for any discordance and 12% (Cohen's d = 0.3) for aMCI vs. normal EM classification did not reach statistical significance. With both classifications, intra-pair differences were larger in DZ pairs (7% and 19%) compared to MZ pairs (3% and -2%), but none of these within-pair differences were statistically significant. This may be in part due to the loss in power when using a binary classification rather than a continuous within-pair difference. These numbers

suggest possible genetic confounding but also larger differences when using more stringent criteria of EM discordance.

We also hypothesized that cognitively normal twins with EM impaired co-twins would have greater [11C]PiB uptake compared to cognitively healthy non-twin controls. Using this approach, we have earlier reported that 9 cognitively preserved monozygotic – but not dizygotic – co-twins of cognitively impaired probands had increased [11C]PiB uptake compared to 9 cognitively healthy non-twin controls (Scheinin et al., 2011). We were not able to replicate our earlier finding of higher cortical [11C]PiB uptake in unaffected MZ twins from cognitively discordant twin pairs compared to cognitively normal non-twin controls (Scheinin et al., 2011). The participated twins were representative of the general Finnish population, but it was more difficult to recruit a volunteer sample of non-twin controls who would be representative of the general population through open invitation. In the current study, twins and non-twin controls were better matched for age, which is known to have a positive association with Aβ accumulation, (Roberts et al., 2018) than in the previous study. We also applied different criteria for normal cognition. Finally, non-twin controls had more years of education than twins which may have enabled them to better maintain EM in the presence of pathological Aβ accumulation (Joannette et al., 2019; Kemppainen et al., 2008). These factors could explain the contradictory findings.

A limitation was that despite having a large cognitive screening sample for selection of twin pairs with the greatest difference in cognitive performance, we identified only few cognitively discordant MZ twin pairs. Moreover, 13% (6/45) among all the discordant pairs were driving the EM-Aβ correlation. Screening with more specific EM measures could improve the detection of discordant pairs. Another limitation was the cross-sectional setting; only a longitudinal setting could verify the causal Aβ-EM relationship. Due to the long time-course of the study, two different scanners and [11C]PiB synthesis methods were used. However, imaging of both co-twins in a pair was always done with the same scanner, and because the statistical inference relies on within-pair comparisons, differences between the scanners should not influence the results.

In conclusion, our results suggest that Aβ is negatively related to EM and this association is evident even when controlling for shared genetic effects. Because it is not possible to randomly assign individuals to high versus low Aβ pathology, the case-control twin design is closest to an experimental design in humans. Clinical Aβ trials may have failed in part due to the selection of participants. Other studies suggest that participant selection could be improved with more specific measurement of EM (Edmonds et al., 2018; Vuoksimaa et al., 2018), and also using more specific focal measures of Aβ accumulation (Insel et al., 2020). Our results provided evidence for the relationship between cortical amyloid and cognitive function and indicate that this association is not confounded by genetic effects.

Disclosure statement

Author contributions

the manuscript for important intellectual content: All authors; Statistical analysis: Lindgren, Rinne, Vuoksimaa; Obtained funding: Kaprio, Rinne, Vuoksimaa; Administrative, technical, or material support: Kaprio, Karjalainen, Helin, Teuho, Rinne; Study supervision: Rinne, Vuoksimaa

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