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Microbleeds and Medial Temporal Atrophy Determine Cognitive Trajectories in Normal Aging: A Longitudinal PET-MRI Study

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Abstract.
Background: The cognitive trajectories in normal aging may be affected by medial temporal atrophy (MTA) and amyloid burden, as well as vascular pathologies such as cortical microbleeds (CMB) and white matter hyperintensities (WMH).
Objective: We addressed here the role of imaging markers in their prediction in a real-world situation.
Methods: We performed a 4.5-year longitudinal study in 90 older community-dwellers coupling two neuropsychological assessments, MTA estimated with the Schelten's scale, number of CMB, and WMH evaluated with the Fazekas score at inclusion and follow-up, visual rating of amyloid PET and glucose hypometabolism at follow-up, and *APOE* genotyping. Regression models were built to explore the association between the continuous cognitive score (CCS) and imaging parameters.
Results: The number of strictly lobar CMB at baseline (4 or more) was related to a 5.5-fold increase of the risk of cognitive decrement. This association persisted in multivariable models explaining 10.6% of the CCS decrease variance. MTA, and Fazekas score at baseline and amyloid positivity or abnormal FDG PET, were not related to the cognitive outcome. The increase of right MTA at follow-up was the only correlate of CCS decrease both in univariate and multivariable models explaining 9.2% of its variance.
Conclusion: The present data show that the accumulation of more than four CMB is associated with significant cognitive decrement over time in highly educated elderly persons. They also reveal that the progressive deterioration of cognitive performance within the age-adjusted norms is also related to the increase of visually assessed MTA.

Keywords: Atrophy, cognition, imaging markers, medial temporal lobe, microbleeds, normal aging

[1]These authors contributed equally to this work.

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INTRODUCTION

Cognitive decline affects a substantial proportion of elderly individuals as part of the normal aging process. It usually starts at mid-to-late life and concerns a wide range of cognitive domains such as information processing, executive functions, visuospatial abilities, and memory [1–4]. Cognitive trajectories in old age are, however, variable with some persons displaying stable performances, and others showing fluctuations with slow decrement over long time periods. In a limited number of cases, progressive worsening of neuropsychological performances corresponds to the pre-mild cognitive impairment (MCI) state that includes asymptomatic at risk and preclinical Alzheimer's disease (AD) cases [5–7]. Recent longitudinal studies in various cultural backgrounds suggested that almost 40% of elderly individuals showed stable and high memory and executive function performances (successful agers) whereas 20% displayed progressive decline (declining agers [8–10]).

Understanding the determinants of cognitive decrement at its very early phases is essential for improving the effectiveness of early interventions aiming to identify atypical trajectories and sustain brain resilience [11, 12]. Besides demographic, socioeconomic status, physical functioning, and health behaviors (body mass index, physical activity, alcohol and smoking) (for review, see [7]), AD signature-related brain changes such as medial temporal atrophy (MTA) and amyloid burden, as well as vascular lesions, mainly cortical microbleeds (CMB) and white matter hyperintensities (WMH), have all been thought to impact on cognitive performances at the pre-MCI state [13–22]. However, negative data were also frequently reported [23–28]. The absence of longitudinal design and short follow-up periods may partly explain these discrepancies. Three additional methodological problems should be taken into account. First, most of the longitudinal investigations in cognitively intact elderly individuals examined the evolution of a limited number of neuropsychological parameters (working and episodic memory as well as executive abilities [25, 29], or screening test (more frequently Mini-Mental State Examination, MMSE) scores over time. However, the temporal evolution of cognitive performances in normal aging is highly heterogeneous with some of them declining and others remaining stable or even improving (for review, see [1]).

An accurate approach of cognitive evolution in this population must consider both improvement and decline of task performances in a wide range of cognitive tests. Second, AD-signature and vascular brain changes are partly interdependent with nonlinear trajectories over time [30–36] so that concomitant consideration of imaging parameters along with well-known confounding factors (age, gender, socioeconomic status, *APOE* $\varepsilon 4$) in multivariable models are needed to define the relative weight of each of them in the prediction of cognitive decrement. Third, most observations were made in research settings using sophisticated quantification protocols that are rarely applicable in routine clinical environments. In order to address the role of imaging markers in the prediction of cognitive changes in a "real world" situation, we performed a longitudinal study of 90 community-dwelling elders coupling two neuropsychological assessments during a 4-5-year follow-up period, and visual rating of amyloid burden at inclusion as well as MTA, CMB, and WMH both at inclusion and last follow-up. Our main hypothesis is that cognitive decrement within the normal range is associated with significant changes in at least one AD-signature and vascular burden imaging markers. We also hypothesized that amyloid load per se would not affect cognition in this highly selected series of healthy elders.

MATERIALS AND METHODS

Participants

The study was approved by the local Ethics Committee and all participants gave written informed consent prior to inclusion. The selection of cases among participants of a still ongoing cohort study was described in detail elsewhere [37]. Briefly, the present cohort included only healthy controls with preserved cognition, no history of psychiatric, neurological, and major medical conditions, and no regular use of psychotropic medication [37–41]. Substantial vascular burden as evidenced by subtle cardiovascular symptoms, hypertension (non treated), and a history of stroke or transient ischemic episodes were exclusion criteria. All of these cases had three neuropsychological evaluations (baseline, 18 months, and 54 months), structural brain MRI at baseline and 54-months post-inclusion, *APOE* genotyping, and amyloid and FDG PET at last follow-up. Our sample included 90 individuals (55 (61%) female, age range 74–91 years).

Neurocognitive assessment

At baseline, all individuals were evaluated with a neuropsychological battery described in details previously [37–41]. All individuals were also evaluated with the Clinical Dementia Rating scale (CDR) [42]. According to the criteria of Petersen et al. [43], cases with focal or multifocal cognitive impairment with minimal impairment of instrumental activities of daily living (IADLs) were classified as MCI. All of these cases had CDR of 0.5 but no dementia and a score exceeding 1.5 standard deviations below the age-appropriate mean in any of the cognitive tests used. Participants with neither dementia nor MCI were classified as cognitively healthy controls and underwent two additional cognitive assessments after a mean period of 18 and 54 months.

In the absence of consensus, the definition of groups within the normal range on the basis of neuropsychological criteria should avoid to include *a priori* hypotheses on the cognitive fate of cases with unstable cognitive performances. Among them, some cases progress at the first follow-up and remain stable or even improve their performance at the second follow-up. Others are stable at the first follow-up and progress later on (but may improve or remain stable at later time points). To resolve this difficult question, we calculated the number of tests with improved minus the number of tests with decreased performances resulting in a final continuous cognitive score for each time point. Change in cognition between inclusion and last follow-up was defined as the sum of the continuous cognitive scores at two follow-ups. This new approach makes it possible to avoid *a priori* hypotheses regarding the longitudinal evolution of cognition in our cases. Cognitive trajectories were defined after summing the number of cognitive tests at follow-up with performances at least 0.5 standard deviation (SD) higher or lower compared with the first evaluation (Z-scores). Change in cognition between inclusion and last follow-up was defined as the sum of the continuous cognitive scores at two follow-ups as previously described [44]. This variable was used in all subsequent regression models. The assessment of cognitive changes over time was made using a continuous cognitive score taking into account both the increase and decrease of performances in a given test across the three assessments as described previously. Cognitive trajectories were defined after summing the number of cognitive tests at follow-up with performances at least 0.5 standard deviation higher or lower compared with the first evaluation (Z-scores). Changes in cognition between inclusion and last follow-up were defined as the sum of the continuous cognitive scores at two follow-ups as previously described [37, 44].

MR imaging

At baseline, imaging data were acquired on a 3T MRI scanner (TRIO SIEMENS Medical Systems, Erlangen, Germany). The structural high-resolution T1-weighted anatomical scan was performed with the following fundamental parameters: 256×256 matrix, 176 slices, 1 mm isotropic, TR = 2300 ms, TE 2.27 ms; axial T2w sequences: 512×310 matrix, 30 slices, 4 mm thickness, TR 4000 ms, TE 105 ms; susceptibility weighted imaging (SWI): 256×208 matrix, 128 slices, TR 28 ms, TE 20 ms); pulsed ASL: 64×64 matrix, 20 slices, 6 mm thickness, TR 4000 ms, TE 12 ms, inversion time 1800 ms. At follow-up, data were acquired on a 3T MR750w scanner (GE Healthcare, Milwaukee, WI), including a high-resolution anatomical 3DT1 : 254×254 matrix, 178 slices, 1 mm isotropic, TR 7.2 ms; axial T2w sequences: 512×512 matrix, 30 slices, 4 mm thickness, TR 6900 ms, TE 105 ms,; susceptibility-weighted angiography (SWAN): 320×288 matrix, 176 slices, TR 28 ms, TE 20 ms; multi-delay (7) pseudo-continuous ASL (PCASL) 128×128 matrix, 32 slices, 4 mm thickness, TR 5936 ms, TE 10.5 ms, post label delays 1.00, 1.22, 1.48, 1.78, 2.15, 2.62, and 3.32 s.

Amyloid PET imaging

Fifty-nine ^{18}F-Florbetapir- (Amyvid) and thirty-one ^{18}F-Flutemetamol-PET (Vizamyl) data were acquired on two different tomographs (Siemens Biograph™ mCT and GE Healthcare Discovery PET/CT 710 scanners) of varying resolution and following different platform-specific acquisition protocols. The ^{18}F-Florbetapir images were acquired 50 to 70 min after injection and the ^{18}F-Flutemetamol images 90 to 120 min after injection. PET images were reconstructed using the parameters recommended by the ADNI protocol aimed at increasing data uniformity across the multicenter acquisitions. More information on the different imaging protocols for PET acquisition can be found on the ADNI web site (http://adni.loni.usc.edu/methods/).

FDG PET imaging

PET/CT data acquisition was performed on a Siemens Biograph™ mCT or Vision scanner according to the guidelines of the European Association of Nuclear Medicine (EANM) [45]. The PET acquisition was started approximately 30 min after injection of 200 MBq of ^{18}F-FDG. The PET emission study (20 min, one bed position) followed immediately the CT study used for attenuation correction. Ultra-law dose brain CT imaging was performed under standard conditions (120 kVp, 20 mAs, 128 × 0.6 collimation, a pitch of 1 and 1 s per rotation).

Visual MR assessment

The visual analysis of brain MRI images was conducted by an independent, board-certified specialist in neuroradiology (SH) blind to the neuropsychological data. MTA was assessed at baseline according to the established score [46], ranging from 0 (no atrophy) to 4 (significant atrophy). The MTA score is a simple and clinically established semi-quantitative scale. At follow-up MR imaging, each case was directly compared with the individual baseline exam and graded from 0 to 3 (0 = stable, 1 = slight increase, 2 = moderate increase, 3 = strong increase). A score of 1 indicates that the MTA score of this individual is still unchanged, yet there is a slight increase in the visual perception of MTA atrophy. Scores of 2 or 3 generally indicate progression from one MTA score to the next, for example MTA 1 to MTA2/MTA3 respectively.

WMH load at baseline was assessed according to the established Fazekas score [47] ranging from 0 (no white matter lesions) to 3 (confluent white matter lesions). Similar to the MTA score described above, the Fazekas score is simple and clinically established yet does not capture small intra-individual progression. At follow-up, the equivalent score of 0–3 was used (0 = stable, 1 = slight increase, 2 = moderate increase, 3 = strong increase). A score of 1 again indicated a slight increase in lesion load without passing from one Fazekas score to the next.

The number of CMB was assessed based on the SWI or SWAN sequences. Only lesions were considered which are probable CMB, and the corresponding phase images were also analyzed to discriminate probable CMB versus micro-calcifications [48]. At baseline, total number of CMB and number of CMB per location (supratentorial superficial, supratentorial deep, and infratentorial) were evaluated. At follow-up imaging, the number of additional CMB per region was assessed.

Amyloid PET analysis

The visual analysis of amyloid PET images was conducted by an independent, board-certified specialist in nuclear medicine (VG) blind to the neuropsychological data, following the tracer-specific standardized operating procedures approved by the European Medicinal Agency. Specifically, regional positivity was assessed for each scan, specifying if uptake was identified in the lateral frontal, parietal, posterior cingulate and precuneus, anterior cingulate, temporal lateral, and striatal regions in either of the two cerebral hemispheres [49].

In order to assess the global amyloid burden in the present series, we also calculated cortical SUVR values as provided by the centiloid project with pons as reference region [50]. Cortical uptake was calculated using the regions from the Harvard-Oxford atlas [51]. These data were not used in further statistical analysis that focused on visual amyloid rating.

Visual FDG PET analysis

FDG PET reading was performed by visual analysis of the output of an automated voxel-wise comparison with a reference database, as recommended in guidelines [45] and previously described in details [52]. Images were classified as normal when no significant deviations from the normal distribution were observed, and pathological when significant regional reductions of glucose metabolism were documented.

APOE ε4 status

APOE ε4 status was assessed as described earlier [41]. Subjects were divided according to whether they were a carrier of the *APOE* ε4 allele (4/3 versus 3/3, 3/2 carriers).

Statistical analysis

Gender-related differences in demographic, neuropsychological, and imaging data were assessed with χ^2, Mann-Whitney u test, and unpaired *t*-test depending on the variable distribution. Simple (Model 1) and multiple linear regression models (Model 2: adjusted for gender, age, education and *APOE* ε4 allele, Model 3: full model) were used

Table 1
Participants' baseline characteristics by gender (MTA: medial temporal atrophy).

	Female	Male	Total	*P*
	55	35	90	
Age at Amy PET	79.4 ± 4.0	78.8 ± 3.0	79.2 ± 3.7	0.436
Education [y]				0.002
<9	12 (21.8%)	1 (2.9%)	13 (14.4%)	
9–12	27 (49.1%)	14 (40.0%)	41 (45.6%)	
>12	16 (29.1%)	20 (57.1%)	36 (40.0%)	
MMSE at baseline	28.6 ± 1.0	28.5 ± 1.1	28.6 ± 1.0	0.600
APOE ε4	10 (18.2%)	5 (14.3%)	15 (16.7%)	0.775
Continuous cognitive score change	0.0 ± 3.6	–1.3 ± 3.7	–0.5 ± 3.7	0.093
Amy PET positive	15 (27.3%)	7 (20.0%)	22 (24.4%)	0.464
FDG PET abnormal	15 (27.3%)	7 (20.0%)	22 (24.4%)	0.464
Fazekas score				0.158
Absent	18 (32.7%)	17 (48.6%)	35 (38.9%)	
Mild	24 (43.6%)	12 (34.3%)	36 (40.0%)	
Moderate	10 (18.2%)	5 (14.3%)	15 (16.7%)	
Severe	3 (5.5%)	1 (2.9%)	4 (4.4%)	
MTA right				0.408
No atrophy	13 (23.6%)	10 (28.6%)	23 (25.6%)	
Only widening of choroid fissure	25 (45.5%)	17 (48.6%)	42 (46.7%)	
Also widening of temporal horn of lateral ventricle	15 (27.3%)	8 (22.9%)	23 (25.6%)	
Moderate loss of hippocampal volume	2 (3.6%)	0 (0.0%)	2 (2.2%)	
MTA left				0.674
No atrophy	13 (23.6%)	9 (25.7%)	22 (24.4%)	
Only widening of choroid fissure	31 (56.4%)	20 (57.1%)	51 (56.7%)	
Also widening of temporal horn of lateral ventricle	9 (16.4%)	6 (17.1%)	15 (16.7%)	
Moderate loss of hippocampal volume	2 (3.6%)	0 (0.0%)	2 (2.2%)	
Microbleeds presence	21 (38.2%)	11 (31.4%)	32 (35.6%)	0.652

explore the association between continuous cognitive score (CCS; dependent variable) and both binary (PET-amyloid, FGD-PET) and ordinal (MTA, CMB, Fazekas score at baseline and in separate models with their changes at follow-up) imaging data as well as potential confounders such as age, gender, education levels, and *APOE* genotyping. In the full model, we used 9 independent variables that is the maximum authorized given the number of participants according to Harrel's empirical rule [53]. The significance level was set at $p < 0.05$. All analyses were performed with Stata release 16.1 (College Station, TX, USA).

Power analysis

In a study involving 126 initially amyloid-negative and cognitively intact participants, Farrel et al. [54] examined the predictors of episodic memory decline. A sample size of 82 achieves 90% power to detect a partial ρ^2 of at least 0.200 attributed to one independent variable(s) when the significance level (alpha) is 0.050. These results are based on 5000 Monte Carlo samples from the bivariate normal distribution under the alternative hypothesis, computed with PASS v16.0.

RESULTS

Demographic data show no gender-related differences in age, *APOE* ε4 allele frequency, MMSE scores at baseline, and baseline imaging measures. Men were more educated than women in the present series (Table 1). The mean SUVR values were of 0.6 ± 0.1 in amyloid negative cases and 0.8 ± 0.1 in amyloid positive cases confirming the low rate of amyloid burden in this series. Of note, none of our cases evolved to MCI during the follow-up period pointing to the presence of cognitive resilience in these highly educated controls.

In univariate models, CCS decrement was not related to amyloid positivity, abnormal FDG PET, and MTA. This was also the case for the Fazekas score at baseline. In contrast, the number of CMB at baseline (4 or more) was associated with a 5.2 unit decrease of the CCS change; Table 2). When the location of CMB was considered, this association persisted only for supratentorial superficial (strictly lobar according to [55]) CMB. In multivariable models controlling for age, gender, MMSE score at baseline, education, and *APOE* ε4 allele, the negative association between the number of CMB (≥4) and CCS change was still significant explaining 10.6% of the

Table 2
Baseline variables associated with change in CCS assessed with linear regression (Model 1: univariate, Model 2: adjusted for gender, age, education, and *APOE* ε4 allele, Model 3: full model).

	Model 1		Model 2		Model 3	
	Coeff (95% CI)	*P*	Coeff (95% CI)	*P*	Coeff (95% CI)	*P*
Gender male	–1.35 (–2.91,0.21)	0.089			–1.77 (–3.53,–0.01)	0.049*
Age at Amy PET	–0.04 (–0.25,0.18)	0.742			–0.06 (–0.31,0.19)	0.649
Education [y]						
<9	–				–	
9–12	0.10 (–2.25,2.44)	0.936			0.09 (–2.57,2.75)	0.946
>12	–0.18 (–2.56,2.21)	0.883			0.01 (–2.83,2.85)	0.994
MMSE at baseline	–0.26 (–1.01,0.49)	0.488	–0.38 (–1.16,0.40)	0.339	–0.69 (–1.59,0.22)	0.133
APOE ε4	–1.41 (–3.47,0.64)	0.175	–1.50 (–3.57,0.57)	0.153	–1.09 (–3.35,1.17)	0.341
Fazekas score						
Absent	–		–		–	
Mild	–0.52 (–2.26,1.23)	0.559	–0.72 (–2.52,1.08)	0.426	–0.87 (–2.79,1.05)	0.368
Moderate	0.79 (–1.48,3.06)	0.491	0.86 (–1.50,3.22)	0.470	–0.03 (–2.63,2.57)	0.980
Severe	0.96 (–2.93,4.84)	0.625	1.18 (–2.91,5.27)	0.567	1.66 (–2.73,6.06)	0.453
MTA right						
No atrophy	–		–		–	
Only widening of choroid fissure	–1.00 (–2.90,0.90)	0.299	–1.15 (–3.11,0.81)	0.246	–1.57 (–3.66,0.51)	0.138
Alsowidening of temporal horn of lateral ventricle	0.09 (–2.08,2.25)	0.937	–0.13 (–2.36,2.10)	0.908	–0.79 (–3.08,1.50)	0.495
Moderate loss of hippocampal volume	–2.00 (–7.41,3.41)	0.464	–2.22 (–8.17,3.72)	0.459	–4.04 (–10.47,2.38)	0.214
Number of microbleeds						
0	–		–		–	
1	–0.93 (–3.00,1.15)	0.376	–0.90 (–3.02,1.22)	0.401	–0.96 (–3.19,1.27)	0.394
2–3	–0.15 (–2.28,1.99)	0.891	–0.44 (–2.61,1.73)	0.685	–0.53 (–2.80,1.73)	0.640
4–6	–5.20 (–9.44,–0.95)	0.017*	–5.49 (–9.96,–1.02)	0.017*	–5.36 (–10.07,–0.65)	0.026*
Amy PET positive	–0.50 (–2.29,1.30)	0.585	–0.70 (–2.55,1.15)	0.455	–0.01 (–2.06,2.05)	0.994
FDG PET abnormal	–0.80 (–2.59,1.00)	0.379	–0.96 (–2.78,0.87)	0.300	–0.58 (–2.48,1.33)	0.548

variance of this latter variable (Table 2). In multivariable models including the above-mentioned variables plus MTA at baseline, Fazekas score, amyloid positivity and abnormal FDG PET, a number of CMB higher than 4 remained associated with the cognitive outcome at follow-up (Table 2). A distinct pattern of clinic-radiologic associations emerged when the evolution of imaging markers was considered. Cognitive decrement was then related to the increase of right MTA at follow-up both in univariate and multivariable models. This imaging parameter explained 6.1% of CCS change variance. In multivariable models including Fazekas score and CMB change as well as amyloid positivity and abnormal FDG PET, the increase of right MTA was the only measure to be associated with CCS change (Table 3).

DISCUSSION

In this community-based cohort of older adults, the careful exclusion of neurological and psychiatric disorders, regular use of psychotropic medication, and previous history of cerebrovascular pathologies makes it possible to isolate the relative contribution of neurodegenerative and vascular burden assessed by visual inspection of MRI and PET scans. The present data show that the accumulation of four CMB or more is associated with significant cognitive decrement over time in highly educated elderly persons. They also reveal that the progressive deterioration of cognitive performance within the age-adjusted norms is also related to the increase of visually assessed MTA, a well-known AD-signature marker. In contrast, amyloid burden, synaptic loss (as documented by FDG PET abnormalities), and WMH did not affect cognition in this early pre-MCI state.

The association between CMB and cognition in old age is still a highly disputed issue. Early after their first description, CMB have been suggested to increase the risk of incident dementia [55, 56]. Subsequent meta-analyses led to more ambiguous results. Lei et al. [57] reported a positive association between CMB and cognitive decline using the MMSE score or the Montreal cognitive assessment scale. Another meta-analysis in AD cases failed to identify significant differences in cognition depending on the presence of CMB [58]. Two memory clinic

Table 3
Effect of Fazekas score, MTA, and number of microbleeds change on the evolution of CCS assessed with linear regression (Model 1: univariate, Model 2: adjusted for gender, age, education, and *APOE* ε4 allele, Model 3: full model)

	Model 1		Model 2		Model 3	
	Coeff (95% CI)	*P*	Coeff (95% CI)	*P*	Coeff (95% CI)	*P*
Gender male					–1.33 (–3.07,0.41)	0.131
Age at Amy PET					0.01 (–0.21,0.24)	0.917
Education [y]						
<9					–	
9–12					1.62 (–1.04,4.28)	0.229
>12					1.42 (–1.34,4.17)	0.308
APOE ε4					–1.60 (–3.85,0.64)	0.159
Fazekas score change						
Stable	–		–		–	
Slight increase	–0.21 (–1.87,1.45)	0.805	–0.26 (–1.98,1.46)	0.761	0.20 (–1.66,2.07)	0.830
Moderate increase	2.85 (–1.47,7.18)	0.194	2.80 (–1.73,7.34)	0.222	3.79 (–0.99,8.57)	0.118
MTA change						
Stable	–		–		–	
Slight increase	–1.86 (–3.54,–0.17)	0.031*	–1.91 (–3.70,–0.12)	0.037*	–2.28 (–4.12,–0.45)	0.016*
Moderate increase	–0.09 (–2.44,2.27)	0.942	–0.31 (–2.74,2.11)	0.799	–0.71 (–3.20,1.77)	0.568
Strong increase	–0.73 (–5.07,3.61)	0.740	–1.03 (–5.50,3.45)	0.650	0.73 (–4.11,5.57)	0.765
Number of microbleeds change						
0	–		–		–	
1	1.36 (–1.03,3.75)	0.260	1.40 (–1.02,3.82)	0.252	1.83 (–0.58,4.24)	0.135
2–3	–0.79 (–3.40,1.82)	0.550	–0.41 (–3.13,2.31)	0.766	–0.06 (–2.85,2.73)	0.965
4+	–0.70 (–4.48,3.08)	0.712	–0.55 (–4.40,3.30)	0.776	–1.80 (–6.15,2.55)	0.412
Amy PET positive					–1.00 (–2.94,0.94)	0.308
FDG PET abnormal					–0.94 (–2.81,0.92)	0.317

studies including mostly MCI cases [59, 60] and two studies in elderly individuals with vascular risk factors [61, 62] led also to negative data. The most solid data supporting the deleterious effect of CMB on cognition comes from three population-based studies (Rotterdam [63], Framingham Heart [64]; and AGES-Reyjkavik [65]) including non-demented persons. Their meta-analysis yielded a statistically significant association between CMB presence and incident dementia (two-fold risk increase). However, another meta-analysis using the same data found no significant association between CMB presence and incidence of dementia [66]. Besides methodological reasons such as absence of adjustment for other small vessel disease biomarkers and variability in cognitive assessments, one main reason explaining these discrepancies is the absence of CMB quantification in most of these studies.

From a pathophysiological standpoint, it seems plausible that the total number of CMB is more relevant than their single presence. The present data reveal that a number of CMB equal or higher than four is associated with a 5.2 unit decrease of the CCS change at 4.5-year follow-up. This observation concerned only strictly lobar CMB that affect gray matter in neocortical areas and are usually but not exclusively associated with cerebral amyloid angiopathy [55, 67]. Importantly, the deleterious effect of CMB on cognition persisted when adjusting for WMH score, amyloid positivity, abnormal FDG PET, and MTA score. This finding contrasts with a recent meta-analysis that simultaneously examined four small vessel disease biomarkers and reported that only WMH burden was associated with high incidence of dementia in general population and at risk individuals [68]. One should, however, keep in mind that the cognitive outcome in the present study was the longitudinal decrement of global cognition in healthy elders and not the occurrence of clinically overt dementia. Taken together, these observations indicate that prior to the emergence of cognitive symptoms, the presence of four or more CMB should be considered as a risk factor for future decline of cognitive performances in healthy elderly persons. Once this cut-off is reached, other MRI biomarkers are better associated with the cognitive outcome. In fact, at the end of the follow-up period, the increase of MTA, and not the accumulation of CMB, was the better correlate of the cognitive outcome.

The association between MTA assessed with the Schelten's scale and cognitive evolution in old age is also matter of debate. For MCI transition to AD, this single marker has a high specificity but very

low sensitivity independently of the cut-off used [69, 70]. Results are even more ambiguous in preclinical AD cases and asymptomatic at-risk cases. In cognitively intact elders, Glodzik et al. [71] found that memory decline at 2-year follow-up was related to longitudinal MTA but not medial temporal lobe volume at baseline. Using the stage classification of preclinical AD cases [72, 73] reported that the rate of change of the medial temporal lobe volume (2.4 years follow-up) in all stages was not related to cognitive decline, yet individuals who progressed to MCI had smaller medial temporal lobe volumes. Based on these observations, they postulate that MTA takes place prior to molecular AD-signature changes possibly reflecting genetic or developmental abnormalities. Our data differ from these observations by the use of visual rating rather than quantitative measures of MTA and longer MRI follow-up (4.5 years). Moreover, we used a CCS rather than memory assessment or MCI progression. Of interest, no case with MCI transition at follow-up was included in our analysis. In this selected sample, the increase of MTA but not its presence at baseline was associated with cognitive decrement. In a recent study focusing on the determinants of MTA, measured with voxel-based morphometry, we reported a weak but still significant association between the cognitive outcome and MTA increase over time when taking into account age, gender, *APOE* genotype, and amyloid burden [37]. Our observations parallel a recent report by Albert and collaborators [74] who postulated that the combination of six independent measures (hippocampal and entorhinal cortex volume, cognitive tests score, *APOE4* allele, amyloid load, and phosphorylated tau) predict cognitive decline in a cohort of cognitively intact elders. Among these parameters and as reported by Pontecorvo and coworkers [75], MTL lobe volumetric changes are mostly related to aging process whereas the development of tau pathology and subsequent loss of grey matter beyond the MTL may be dependent on amyloid accumulation. One intriguing finding is that only right MTA increase was related to the cognitive outcome. Previous reports pointed to the brain asymmetry in respect to MTA with a more frequent and severe involvement of the right hemisphere in AD cases [76, 77]. In another report, Shen and collaborators [78] found that right MTA was the best MRI marker for differentiating amnestic MCI from healthy controls. In line with these contributions, the present findings also suggest that right, but not left, MTA is a reliable correlate of cognitive decrement in normal aging.

Some of the negative data merit consideration. In line with recent findings, visual PET amyloid positivity was not related to subtle cognitive changes in the present cohort [25, 44]. Current evidence about the role of amyloid accumulation in cognitively preserved controls remains ambiguous. Although early data suggested that elevated amyloid levels at baseline ($SUVr > 1.5$) were associated with greater cognitive decline at follow-up [19], more recent contributions indicated that PIB PET amyloid-β's relationship to cognitive decline was nonlinear being more prominent at lower amyloid-β levels [26]. The INSIGHT-pre AD data published recently showed no association between this parameter and cognitive fate at 30-month follow-up in healthy controls [25]. Our observations agree with this latter viewpoint implying that the detrimental effect of amyloid burden in cognitively preserved elders is limited. More surprisingly and in contrast to the idea that WMH is more deleterious than CMB in old age [68], the Fazekas score did not correlate with cognitive decrement in our cohort. Previous longitudinal studies also documented an effect of WMH presence and progression on cognitive functions in old age (mainly general intelligence, attention, and executive functions [79–81]). The use of a global cognitive score that takes into account both improvements and declines and the exclusion of cases with clinically overt cerebrovascular pathologies at baseline may partly explain this discrepancy. However, and as suggested by Alber et al. [82], the effect size of WMH impact is small and possibly below the detection threshold in this selected cohort of healthy elders.

Conclusions

Our data indicate that the number of CMB and progression of MTA are the best proxies of cognitive decrement in normal aging. Strengths and limitations of the present study should also be discussed. Among the first, one can note the inclusion of several imaging modalities covering both upstream (amyloid deposition) and downstream biomarkers of brain aging (MTA, abnormal PET), WMH and CMB, careful neuropsychological assessment considering the evolution of all of the main cognitive functions, and use of multivariable models controlling for the known interdependence between the above mentioned markers. One should, however, consider that in the absence of widely accepted standards in the evolution of cognition at the pre-MCI state, the cutoff values used here (0.5 SD higher or lower compared with the first

evaluation (Z-scores)) remain arbitrary. We opted for the use of visual MRI and PET rating in order to be close to the reality of busy routine clinical settings where sophisticated quantification methods are frequently absent. Moreover, and in order to define the relative weight of each imaging marker on cognitive evolution, cases with substantial medical comorbidities (including cerebrovascular ones) were *a priori* excluded. Our observations should thus be interpreted within this framework and cannot be transposed in other clinical or research settings. Both FDG and amyloid-PET were performed at endpoint so that cannot be considered as strict predictors of cognitive decrement. However, our mean SUVR data document that the amyloid burden is unusually low in our series ranging from 0.6 in amyloid negative cases to 0.8 in amyloid positive cases. The rate of amyloid accumulation is known to be very slow in this particular context so that one cannot expect major changes in amyloid uptake and distribution in the relatively short follow-up period [83]. An additional limitation concerns the absence of tau imaging to complete the AD-signature characterization. The observed effects of CMB and MTA may be considered rather weak (9 to 11% of cognitive variability explained by these variables). When interpreting this modest percentage, one should take into account that, in contrast to MCI and AD cases, healthy controls display an impressive variability in MRI parameters [84, 85]. Finally, MRI imaging was performed twice during the 4.5-year period. In the absence of additional time points and with a single amyloid assessment, we cannot comment on the validity of longitudinal trajectories of imaging parameters in predicting the cognitive fate of asymptomatic elderly individuals. Future studies with multimodal imaging in larger cohorts and multiple time points are warranted to address this issue.

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REFERENCES

[1] Abbott RA, Skirrow C, Jokisch M, Timmers M, Streffer J, van Nueten L, Krams M, Winkler A, Pundt N, Nathan PJ, Rock P, Cormack FK, Weimar C (2019) Normative data from linear and nonlinear quantile regression in CANTAB: Cognition in mid-to-late life in an epidemiological sample. *Alzheimers Dement (Amst)* **11**, 36-44.

[2] Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, Penke L, Rafnsson SB, Starr JM (2009) Age-associated cognitive decline. *Br Med Bull* **92**, 135-152.

[3] Hedden T, Gabrieli JD (2004) Insights into the ageing mind: A view from cognitive neuroscience. *Nat Rev Neurosci* **5**, 87-96.

[4] Hoogendam YY, Hofman A, van der Geest JN, van der Lugt A, Ikram MA (2014) Patterns of cognitive function in aging: The Rotterdam Study. *Eur J Epidemiol* **29**, 133-140.

[5] Rabbitt P, Diggle P, Smith D, Holland F, Mc Innes L (2001) Identifying and separating the effects of practice and of cognitive ageing during a large longitudinal study of elderly community residents. *Neuropsychologia* **39**, 532-543.

[6] Salthouse TA (2010) Selective review of cognitive aging. *J Int Neuropsychol Soc* **16**, 754-760.

[7] Zaninotto P, Batty GD, Allerhand M, Deary IJ (2018) Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *J Epidemiol Community Health* **72**, 685-694.

[8] Downer B, Chen NW, Raji M, Markides KS (2017) A longitudinal study of cognitive trajectories in Mexican Americans age 75 and older. *Int J Geriatr Psychiatry* **32**, 1122-1130.

[9] Lin FV, Wang X, Wu R, Rebok GW, Chapman BP, Alzheimer's Disease Neuroimaging Initiative (2017) Identification of successful cognitive aging in the Alzheimer's disease neuroimaging initiative study. *J Alzheimers Dis* **59**, 101-111.

[10] Min JW (2018) A longitudinal study of cognitive trajectories and its factors for Koreans aged 60 and over: A latent growth mixture model. *Int J Geriatr Psychiatry* **33**, 755-762.

[11] Daffner KR (2010) Promoting successful cognitive aging: A comprehensive review. *J Alzheimers Dis* **19**, 1101-1122.

[12] Plassman BL, Williams JW, Jr., Burke JR, Holsinger T, Benjamin S (2010) Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med* **153**, 182-193.

[13] Aljondi R, Szoeke C, Steward C, Gorelik A, Desmond P (2020) The effect of midlife cardiovascular risk factors on white matter hyperintensity volume and cognition two decades later in normal ageing women. *Brain Imaging Behav* **14**, 51-61.

[14] Bauer CM, Cabral HJ, Killiany RJ (2018) Multimodal discrimination between normal aging, mild cognitive impairment and Alzheimer's disease and prediction of cognitive decline. *Diagnostics (Basel)* **8**, 14.

[15] Cavallin L, Bronge L, Zhang Y, Oksengard AR, Wahlund LO, Fratiglioni L, Axelsson R (2012) Comparison between visual assessment of MTA and hippocampal volumes in an elderly, non-demented population. *Acta Radiol* **53**, 573-579.

[16] Daugherty AM, Raz N (2017) Incident risk and progression of cerebral microbleeds in healthy adults: A multi-occasion longitudinal study. *Neurobiol Aging* **59**, 22-29.

[17] Hirsiger S, Koppelmans V, Merillat S, Erdin C, Narkhede A, Brickman AM, Jancke L (2017) Executive functions in healthy older adults are differentially related to macro- and microstructural white matter characteristics of the cerebral lobes. *Front Aging Neurosci* **9**, 373.

[18] Meier IB, Gu Y, Guzaman VA, Wiegman AF, Schupf N, Manly JJ, Luchsinger JA, Viswanathan A, Martinez-Ramirez S, Greenberg SM, Mayeux R, Brickman AM (2014) Lobar microbleeds are associated with a decline in

executive functioning in older adults. *Cerebrovasc Dis* **38**, 377-383.

[19] Petersen RC, Wiste HJ, Weigand SD, Rocca WA, Roberts RO, Mielke MM, Lowe VJ, Knopman DS, Pankratz VS, Machulda MM, Geda YE, Jack CR, Jr. (2016) Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. *JAMA Neurol* **73**, 85-92.

[20] Ten Kate M, Barkhof F, Boccardi M, Visser PJ, Jack CR, Jr., Lovblad KO, Frisoni GB, Scheltens P, Geneva Task Force for the Roadmap of Alzheimer's Biomarkers (2017) Clinical validity of medial temporal atrophy as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiol Aging* **52**, 167-182 e161.

[21] Vanhoenacker AS, Sneyers B, De Keyzer F, Heye S, Demaerel P (2017) Evaluation and clinical correlation of practical cut-offs for visual rating scales of atrophy: Normal aging versus mild cognitive impairment and Alzheimer's disease. *Acta Neurol Belg* **117**, 661-669.

[22] Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J (2002) Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *J Neurol Neurosurg Psychiatry* **72**, 491-497.

[23] Arvanitakis Z, Fleischman DA, Arfanakis K, Leurgans SE, Barnes LL, Bennett DA (2016) Association of white matter hyperintensities and gray matter volume with cognition in older individuals without cognitive impairment. *Brain Struct Funct* **221**, 2135-2146.

[24] De Reuck JL, Deramecourt V, Auger F, Durieux N, Cordonnier C, Devos D, Defebvre L, Moreau C, Capparos-Lefebvre D, Pasquier F, Leys D, Maurage CA, Bordet R (2015) The significance of cortical cerebellar microbleeds and microinfarcts in neurodegenerative and cerebrovascular diseases. A post-mortem 7.0-tesla magnetic resonance study with neuropathological correlates. *Cerebrovasc Dis* **39**, 138-143.

[25] Dubois B, Epelbaum S, Nyasse F, Bakardjian H, Gagliardi G, Uspenskaya O, Houot M, Lista S, Cacciamani F, Potier MC, Bertrand A, Lamari F, Benali H, Mangin JF, Colliot O, Genthon R, Habert MO, Hampel H, INSIGHT-preAD study group (2018) Cognitive and neuroimaging features and brain beta-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): A longitudinal observational study. *Lancet Neurol* **17**, 335-346.

[26] Knopman DS, Lundt ES, Therneau TM, Vemuri P, Lowe VJ, Kantarci K, Gunter JL, Senjem ML, Mielke MM, Machulda MM, Roberts RO, Boeve BF, Jones DT, Petersen RC, Jack CR, Jr. (2018) Joint associations of beta-amyloidosis and cortical thickness with cognition. *Neurobiol Aging* **65**, 121-131.

[27] Li L, Wu DH, Li HQ, Tan L, Xu W, Dong Q, Tan L, Yu JT, Alzheimer's Disease Neuroimaging Initiative (2020) Association of cerebral microbleeds with cognitive decline: A longitudinal study. *J Alzheimers Dis* **75**, 571-579.

[28] Son SJ, Lee KS, Lee Y, Baek JH, Choi SH, Na DL, Seo SW, Oh BH, Hong CH (2012) Association between white matter hyperintensity severity and cognitive impairment according to the presence of the apolipoprotein E (APOE) epsilon4 allele in the elderly: Retrospective analysis of data from the CREDOS study. *J Clin Psychiatry* **73**, 1555-1562.

[29] Rabin JS, Schultz AP, Hedden T, Viswanathan A, Marshall GA, Kilpatrick E, Klein H, Buckley RF, Yang HS, Properzi M, Rao V, Kirn DR, Papp KV, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP (2018) Interactive associations of vascular risk and beta-amyloid burden with cognitive decline in clinically normal elderly individuals: Findings from the Harvard aging brain study. *JAMA Neurol* **75**, 1124-1131.

[30] Al-Janabi OM, Panuganti P, Abner EL, Bahrani AA, Murphy R, Bardach SH, Caban-Holt A, Nelson PT, Gold BT, Smith CD, Wilcock DM, Jicha GA (2018) Global cerebral atrophy detected by routine imaging: Relationship with age, hippocampal atrophy, and white matter hyperintensities. *J Neuroimaging* **28**, 301-306.

[31] Graff-Radford J, Lesnick T, Rabinstein AA, Gunter J, Aakre J, Przybelski SA, Spychalla AJ, Huston J, 3rd, Brown RD, Jr., Mielke MM, Lowe VJ, Knopman DS, Petersen RC, Jack CR, Jr., Vemuri P, Kremers W, Kantarci K (2020) Cerebral microbleed incidence, relationship to amyloid burden: The Mayo Clinic Study of Aging. *Neurology* **94**, e190-e199.

[32] Lim EY, Ryu SY, Shim YS, Yang DW, Cho AH (2020) Coexistence of cerebral microbleeds and amyloid pathology in patients with cognitive complaints. *J Clin Neurol* **16**, 83-89.

[33] Park JH, Seo SW, Kim C, Kim GH, Noh HJ, Kim ST, Kwak KC, Yoon U, Lee JM, Lee JW, Shin JS, Kim CH, Noh Y, Cho H, Kim HJ, Yoon CW, Oh SJ, Kim JS, Choe YS, Lee KH, Lee JH, Ewers M, Weiner MW, Werring DJ, Na DL (2013) Pathogenesis of cerebral microbleeds: *In vivo* imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment. *Ann Neurol* **73**, 584-593.

[34] Roseborough A, Ramirez J, Black SE, Edwards JD (2017) Associations between amyloid beta and white matter hyperintensities: A systematic review. *Alzheimers Dement* **13**, 1154-1167.

[35] Scott JA, Braskie MN, Tosun D, Maillard P, Thompson PM, Weiner M, DeCarli C, Carmichael OT, ADNI (2016) Cerebral amyloid is associated with greater white-matter hyperintensity accrual in cognitively normal older adults. *Neurobiol Aging* **48**, 48-52.

[36] Vinke EJ, de Groot M, Venkatraghavan V, Klein S, Niessen WJ, Ikram MA, Vernooij MW (2018) Trajectories of imaging markers in brain aging: The Rotterdam Study. *Neurobiol Aging* **71**, 32-40.

[37] Montandon ML, Herrmann FR, Garibotto V, Rodriguez C, Haller S, Giannakopoulos P (2020) Determinants of mesial temporal lobe volume loss in older individuals with preserved cognition: A longitudinal PET amyloid study. *Neurobiol Aging* **87**, 108-114.

[38] Giannakopoulos P, Rodriguez C, Montandon ML, Garibotto V, Haller S, Herrmann FR (2020) Less agreeable, better preserved? A PET amyloid and MRI study in a community-based cohort. *Neurobiol Aging* **89**, 24-31.

[39] van der Thiel M, Rodriguez C, Giannakopoulos P, Burke MX, Lebel RM, Gninenko N, Van De Ville D, Haller S (2018) Brain perfusion measurements using multidelay arterial spin-labeling are systematically biased by the number of delays. *AJNR Am J Neuroradiol* **39**, 1432-1438.

[40] Xekardaki A, Rodriguez C, Montandon ML, Toma S, Tombeur E, Herrmann FR, Zekry D, Lovblad KO, Barkhof F, Giannakopoulos P, Haller S (2015) Arterial spin labeling may contribute to the prediction of cognitive deterioration in healthy elderly individuals. *Radiology* **274**, 490-499.

[41] Zanchi D, Montandon ML, Sinanaj I, Rodriguez C, Depoorter A, Herrmann FR, Borgwardt S, Giannakopoulos P, Haller S (2017) Decreased fronto-parietal and increased default mode network activation is associated with subtle cognitive deficits in elderly controls. *Neurosignals* **25**, 127-138.

[42] Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. *Br J Psychiatry* **140**, 566-572.

[43] Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A (2018) Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* **90**, 126-135.

[44] Herrmann FR, Rodriguez C, Haller S, Garibotto V, Montandon ML, Giannakopoulos P (2019) Gray matter densities in limbic areas and APOE4 independently predict cognitive decline in normal brain aging. *Front Aging Neurosci* **11**, 157.

[45] Varrone A, Asenbaum S, Vander Borght T, Booij J, Nobili F, Nagren K, Darcourt J, Kapucu OL, Tatsch K, Bartenstein P, Van Laere K, European Association of Nuclear Medicine Neuroimaging Committee (2009) EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur J Nucl Med Mol Imaging* **36**, 2103-2110.

[46] Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA (1995) Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: Interobserver reliability. *J Neurol* **242**, 557-560.

[47] Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* **149**, 351-356.

[48] Haller S, Vernooij MW, Kuijer JPA, Larsson EM, Jager HR, Barkhof F (2018) Cerebral microbleeds: Imaging and clinical significance. *Radiology* **287**, 11-28.

[49] Buckley CJ, Sherwin PF, Smith AP, Wolber J, Weick SM, Brooks DJ (2017) Validation of an electronic image reader training programme for interpretation of [18F]flutemetamol beta-amyloid PET brain images. *Nucl Med Commun* **38**, 234-241.

[50] Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD, Sr., Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, Rowe CC, Skovronsky DM, Mintun MA (2015) The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement* **11**, 1-15 e11-14.

[51] Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980.

[52] Garibotto V, Montandon ML, Viaud CT, Allaoua M, Assal F, Burkhard PR, Ratib O, Zaidi H (2013) Regions of interest-based discriminant analysis of DaTSCAN SPECT and FDG-PET for the classification of dementia. *Clin Nucl Med* **38**, e112-117.

[53] Harrell FE, Jr., Lee KL, Califf RM, Pryor DB, Rosati RA (1984) Regression modelling strategies for improved prognostic prediction. *Stat Med* **3**, 143-152.

[54] Farrell ME, Chen X, Rundle MM, Chan MY, Wig GS, Park DC (2018) Regional amyloid accumulation and cognitive decline in initially amyloid-negative adults. *Neurology* **91**, e1809-e1821.

[55] Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM, Microbleed Study Group (2009) Cerebral microbleeds: A guide to detection and interpretation. *Lancet Neurol* **8**, 165-174.

[56] Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, Krestin GP, Breteler MM (2008) Prevalence and risk factors of cerebral microbleeds: The Rotterdam Scan Study. *Neurology* **70**, 1208-1214.

[57] Lei C, Lin S, Tao W, Hao Z, Liu M, Wu B (2013) Association between cerebral microbleeds and cognitive function: A systematic review. *J Neurol Neurosurg Psychiatry* **84**, 693-697.

[58] Sepehry AA, Rauscher A, Hsiung GY, Lang DJ (2016) Microbleeds in Alzheimer's disease: A neuropsychological overview and meta-analysis. *Can J Neurol Sci* **43**, 753-759.

[59] Benedictus MR, van Harten AC, Leeuwis AE, Koene T, Scheltens P, Barkhof F, Prins ND, van der Flier WM (2015) White matter hyperintensities relate to clinical progression in subjective cognitive decline. *Stroke* **46**, 2661-2664.

[60] Staekenborg SS, Koedam EL, Henneman WJ, Stokman P, Barkhof F, Scheltens P, van der Flier WM (2009) Progression of mild cognitive impairment to dementia: Contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke* **40**, 1269-1274.

[61] Miwa K, Tanaka M, Okazaki S, Yagita Y, Sakaguchi M, Mochizuki H, Kitagawa K (2014) Multiple or mixed cerebral microbleeds and dementia in patients with vascular risk factors. *Neurology* **83**, 646-653.

[62] van Uden IW, van der Holst HM, Tuladhar AM, van Norden AG, de Laat KF, Rutten-Jacobs LC, Norris DG, Claassen JA, van Dijk EJ, Kessels RP, de Leeuw FE (2016) White matter and hippocampal volume predict the risk of dementia in patients with cerebral small vessel disease: The RUN DMC study. *J Alzheimers Dis* **49**, 863-873.

[63] Akoudad S, Wolters FJ, Viswanathan A, de Bruijn RF, van der Lugt A, Hofman A, Koudstaal PJ, Ikram MA, Vernooij MW (2016) Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol* **73**, 934-943.

[64] Romero JR, Preis SR, Beiser A, Himali JJ, Shoamanesh A, Wolf PA, Kase CS, Vasan RS, DeCarli C, Seshadri S (2017) Cerebral microbleeds as predictors of mortality: The Framingham Heart study. *Stroke* **48**, 781-783.

[65] Ding J, Sigurethsson S, Jonsson PV, Eiriksdottir G, Meirelles O, Kjartansson O, Lopez OL, van Buchem MA, Gudnason V, Launer LJ (2017) Space and location of cerebral microbleeds, cognitive decline, and dementia in the community. *Neurology* **88**, 2089-2097.

[66] Bos D, Wolters FJ, Darweesh SKL, Vernooij MW, de Wolf F, Ikram MA, Hofman A (2018) Cerebral small vessel disease and the risk of dementia: A systematic review and meta-analysis of population-based evidence. *Alzheimers Dement* **14**, 1482-1492.

[67] Pasi M, Charidimou A, Boulouis G, Auriel E, Ayres A, Schwab KM, Goldstein JN, Rosand J, Viswanathan A, Pantoni L, Greenberg SM, Gurol ME (2018) Mixed-location cerebral hemorrhage/microbleeds: Underlying microangiopathy and recurrence risk. *Neurology* **90**, e119-e126.

[68] Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS (2019) Clinical significance of magnetic resonance imaging markers of vascular brain injury: A systematic review and meta-analysis. *JAMA Neurol* **76**, 81-94.

[69] DeCarli C, Frisoni GB, Clark CM, Harvey D, Grundman M, Petersen RC, Thal LJ, Jin S, Jack CR, Jr., Scheltens P, Alzheimer's Disease Cooperative Study Group (2007) Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol* **64**, 108-115.

[70] Liu Y, Mattila J, Ruiz MA, Paajanen T, Koikkalainen J, van Gils M, Herukka SK, Waldemar G, Lotjonen J, Soininen H, Alzheimer's Disease Neuroimaging Initiative (2013) Predicting AD conversion: Comparison between prodromal AD guidelines and computer assisted PredictAD tool. *PLoS One* **8**, e55246.

[71] Glodzik L, de Santi S, Tsui WH, Mosconi L, Zinkowski R, Pirraglia E, Wang HY, Li Y, Rich KE, Zetterberg H, Blennow K, Mehta P, de Leon MJ (2011) Phosphorylated tau 231, memory decline and medial temporal atrophy in normal elders. *Neurobiol Aging* **32**, 2131-2141.

[72] Pettigrew C, Soldan A, Sloane K, Cai Q, Wang J, Wang MC, Moghekar A, Miller MI, Albert M, BIOCARD Research Team (2017) Progressive medial temporal lobe atrophy during preclinical Alzheimer's disease. *Neuroimage Clin* **16**, 439-446.

[73] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Jr., Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.

[74] Albert M, Zhu Y, Moghekar A, Mori S, Miller MI, Soldan A, Pettigrew C, Selnes O, Li S, Wang MC (2018) Predicting progression from normal cognition to mild cognitive impairment for individuals at 5 years. *Brain* **141**, 877-887.

[75] Pontecorvo MJ, Devous MD, Sr., Navitsky M, Lu M, Salloway S, Schaerf FW, Jennings D, Arora AK, McGeehan A, Lim NC, Xiong H, Joshi AD, Siderowf A, Mintun MA, 18F-AV-1451-A05 investigators (2017) Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. *Brain* **140**, 748-763.

[76] Cavedo E, Pievani M, Boccardi M, Galluzzi S, Bocchetta M, Bonetti M, Thompson PM, Frisoni GB (2014) Medial temporal atrophy in early and late-onset Alzheimer's disease. *Neurobiol Aging* **35**, 2004-2012.

[77] Frisoni GB, Pievani M, Testa C, Sabattoli F, Bresciani L, Bonetti M, Beltramello A, Hayashi KM, Toga AW, Thompson PM (2007) The topography of grey matter involvement in early and late onset Alzheimer's disease. *Brain* **130**, 720-730.

[78] Shen Q, Loewenstein DA, Potter E, Zhao W, Appel J, Greig MT, Raj A, Acevedo A, Schofield E, Barker W, Wu Y, Potter H, Duara R (2011) Volumetric and visual rating of magnetic resonance imaging scans in the diagnosis of amnestic mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement* **7**, e101-108.

[79] Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E (2014) Presence and progression of white matter hyperintensities and cognition: A meta-analysis. *Neurology* **82**, 2127-2138.

[80] Prins ND, Scheltens P (2015) White matter hyperintensities, cognitive impairment and dementia: An update. *Nat Rev Neurol* **11**, 157-165.

[81] Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, Pantoni L, Fazekas F, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D, LADIS Study (2010) White matter changes and diabetes predict cognitive decline in the elderly: The LADIS study. *Neurology* **75**, 160-167.

[82] Alber J, Alladi S, Bae HJ, Barton DA, Beckett LA, Bell JM, Berman SE, Biessels GJ, Black SE, Bos I, Bowman GL, Brai E, Brickman AM, Callahan BL, Corriveau RA, Fossati S, Gottesman RF, Gustafson DR, Hachinski V, Hayden KM, Helman AM, Hughes TM, Isaacs JD, Jefferson AL, Johnson SC, Kapasi A, Kern S, Kwon JC, Kukolja J, Lee A, Lockhart SN, Murray A, Osborn KE, Power MC, Price BR, Rhodius-Meester HFM, Rondeau JA, Rosen AC, Rosene DL, Schneider JA, Scholtzova H, Shaaban CE, Silva N, Snyder HM, Swardfager W, Troen AM, van Veluw SJ, Vemuri P, Wallin A, Wellington C, Wilcock DM, Xie SX, Hainsworth AH (2019) White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. *Alzheimers Dement (N Y)* **5**, 107-117.

[83] Jack CR, Jr., Wiste HJ, Lesnick TG, Weigand SD, Knopman DS, Vemuri P, Pankratz VS, Senjem ML, Gunter JL, Mielke MM, Lowe VJ, Boeve BF, Petersen RC (2013) Brain beta-amyloid load approaches a plateau. *Neurology* **80**, 890-896.

[84] Lauriola M, Esposito R, Delli Pizzi S, de Zambotti M, Londrillo F, Kramer JH, Rabinovici GD, Tartaro A (2017) Sleep changes without medial temporal lobe or brain cortical changes in community-dwelling individuals with subjective cognitive decline. *Alzheimers Dement* **13**, 783-791.

[85] Perrotin A, La Joie R, de La Sayette V, Barre L, Mezenge F, Mutlu J, Guilloteau D, Egret S, Eustache F, Chetelat G (2017) Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimers Dement* **13**, 550-560.