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Autobiographical memory retrieval in patients with Alzheimer's disease

Olga Meulenbroek [a,b,c,*], Mark Rijpkema [a], Roy P.C. Kessels [a,c,d], Marcel G.M. Olde Rikkert [a,c], Guillén Fernández [a,b]

[a] Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, P.O. Box 9101 6500 HB Nijmegen, The Netherlands
[b] Radboud University Nijmegen Medical Centre, Department of Neurology, P.O. Box 9101 6500, HB Nijmegen, The Netherlands
[c] Radboud University Nijmegen Medical Centre, Department of Geriatric Medicine, P.O. Box 9101 6500, HB Nijmegen, The Netherlands
[d] Radboud University Nijmegen Medical Centre, Department of Medical Psychology, P.O. Box 9101 6500, HB Nijmegen, The Netherlands

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ABSTRACT

With aging, the content of self-reported autobiographical memories shifts from episodic to semantic. Onset of Alzheimer's disease enhances this pattern, but the neural underpinnings of this change in Autobiographical Memory (AM), in particular the role of hippocampal degradation, are unknown. We employed fMRI contrasting autobiographical and semantic retrieval, in 22 healthy elderly and 21 Alzheimer's patients. The shift towards semantic characteristics in AM retrieval was indeed enhanced in patients. Both groups activated brain regions commonly involved in AM retrieval, including occipital association areas, medial temporal lobes, lateral temporal and midline prefrontal areas. When compared to controls, Alzheimer's patients showed enhanced activity in the left inferior frontal gyrus (LIFG), ventromedial prefrontal cortex (vmPFC), right precuneus and left lingual gyrus. Activation of LIFG and vmPFC was significantly negatively correlated with hippocampal volume in patients only. Thus, we speculate that the linking function of the degraded hippocampus is taken over by the vmPFC; a shift recently observed during normal consolidation. This potentially compensatory process may support early Alzheimer's detection or prognosis.

Introduction

Various studies have focused on autobiographical memory (AM), identifying brain regions involved in remembering personal past experiences, including the hippocampus, medial and ventrolateral prefrontal cortices (PFC), medial and lateral temporal cortices, temporoparietal junction, retrosplenial (RSC)/posterior cingulate cortex and cerebellum (Cabeza and St Jacques, 2007; Conway et al., 2002; Maguire, 2001; Svoboda et al., 2006).

The classical distinction of declarative memory into episodic and semantic elements (Tulving, 1972) closely approximates AM content: semantic elements represent facts about the world and our life, unrelated to specific events (lacking contextual details). Conversely, episodic elements are unique and have associated contextual details, allowing for subjective re-experiencing ("mental time travel", Tulving, 2002). Semantic elements can probably guide the search to episodic elements, making recall of AM an iterative, hierarchical process, with left-lateralized search processes (supported by PFC) followed by recollection (hippocampus, RSC), subjective re-experiencing (supported by occipital areas) and self-referential processing (medial PFC) (Cabeza and St Jacques, 2007; Conway et al., 2002; Daselaar et al., 2008).

With aging, more semantic elements are reported per probed autobiographical memory, while the amount of episodic elements decreases, but the total number of details remains unaffected (Levine et al., 2002). Therefore, AM seems to "semanticize" with age, which could be related to faster decline of episodic than semantic memories (Piolino et al., 2002). In other words, semantic retrieval might compensate for episodic retrieval failure. Thus, it is not surprising that the episodic-to-semantic shift of AM becomes amplified with memory impairment, like amnestic Mild Cognitive Impairment (aMCI) (Murphy et al., 2008) and is probably further pronounced in Alzheimer's disease, but studies are lacking. This putatively compensatory mechanism is potentially detectable by fMRI and clinically relevant for early diagnosis. However, little is known about the neural correlates of AM retrieval in Alzheimer's patients. A neuropsychological study by Gilboa et al. (2005), correlating scores from the Autobiographical Memory Interview (Kopelman et al., 1990) with structural MRI, indicates where differences may be observed. Specifically, episodic scores of AM retrieval correlated positively with medial temporal lobe (MTL) volume. This corroborates the central role of the MTL in episodic memory retrieval (e.g. Squire et al., 1992), AM retrieval (Svoboda et al., 2006) and Alzheimer's disease course (Chetelat et al., 2003; Killiany et al., 2000).

Indeed, the hippocampus is a core structure in AM retrieval, and its activation enhances with increasing vividness, independent of recency

* Corresponding author. Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands. Fax: +31 24 3610989.
E-mail address: o.meulenbroek@donders.ru.nl (O. Meulenbroek).

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(Addis et al., 2004a,b,c). This is consistent with the multiple trace theory of consolidation (MTT), stating that retrieval is accompanied by sustained hippocampal dependence of episodic elements like vividness (Moscovitch et al., 2006). Structural hippocampal degradation, a hallmark of Alzheimer's disease (Blennow et al., 2006; Braak et al., 1999), is therefore bound to have functional consequences on AM retrieval.

According to MTT, AM will be less dependent on the hippocampus when it contains fewer episodic elements, like with semantization. Consequently, AM putatively becomes protected from the hippocampal damage in Alzheimer's disease. We therefore aimed to find neural evidence for increased semantic processing during AM retrieval in Alzheimer's patients. We specifically hypothesize that hippocampal volume (as a measure of disease severity) will be negatively correlated to activation in areas of compensation in these patients. In other words, the smaller the hippocampus, the larger the activation in these areas will be.

To test our hypotheses, we contrasted processing of autobiographical statements (derived from individual interviews) with a control condition, involving processing of matched semantic statements. This control was chosen, because it is commonly used as control in AM tasks (Addis et al., 2004a,b,c; Levine et al., 2004; Maguire and Mummery, 1999). We expect that the episodic-to-semantic shift in Alzheimer's patients leads to increased semantic processing and therefore enhanced activation of the left inferior frontal gyrus (LIFG), an area commonly involved in processing of language and world knowledge (Hagoort et al., 2004), during AM retrieval.

Semantic elements of autobiographical memories are probably very stable and can be regarded as well-consolidated (for a review on consolidation, see Frankland and Bontempi, 2005). Retrieval of consolidated memories appears to involve the ventromedial PFC (vmPFC) (Takashima et al., 2006). Additionally in rodents, neural firing becomes selective for acquired memories (associations) during consolidation (Takehara-Nishiuchi and McNaughton, 2008), and lesions of vmPFC cause a selective retrieval deficit for remote but not recent memories (Takehara et al., 2003). Hence, we expect that the episodic-to-semantic shift results in enhanced vmPFC activation during AM retrieval in Alzheimer's patients.

Materials and methods

Participants

Twenty-two healthy older adults (mean age (SD) = 69.6 (8.6); years of education (SD) = 16.5 (3.2); 6 female) and 21 patients (mean age (SD) = 72.4 (7.1); years of education (SD) = 16.1 (3.9); 9 female) diagnosed with early stage, probable Alzheimer's disease according to the research criteria from Dubois et al. (2007), who had a Clinical Dementia Rating (CDR) ≤ 1, participated. Table 1 summarizes the demographics and neuropsychological scores of participants. Exclusion criteria comprised: cerebrovascular disease (modified Hachinski score > 4), depression (Geriatric Depression Scale; GDS > 11), severe presbyacusis, claustrophobia, psychopharmacological drugs, low vision or metal implants. The local medical-ethics committee approved this study.

None of the healthy elderly had a history of neurological/psychiatric disease or used psychopharmacological drugs, reported subjective memory impairment or showed cognitive decline on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) or the second story of the Wechsler Memory Scale-Revised (Wechsler, 1987). Six of 28 healthy elderly were excluded: two because of depression/low vision; one left the study before scanning; three were excluded from analysis (performance below chance level $N = 2$) or signal drop-out in the basal ganglia ($N = 1$). All elderly participants were autonomous community dwellers: while mostly retired, all were active in cultural pursuits, continuing education or with responsibilities in various associations. All were right-handed according to the Edinburgh handedness index (Oldfield, 1971).

Table 1
Demographic data and behavioral results of the Healthy elderly and Alzheimer's patients.

Demographic characteristics						
	Healthy elderly ($N = 22$)			Alzheimer's patients ($N = 21$)		
	Mean	*SD*		*Mean*	*SD*	
Age	69.6	8.6		72.4	7.1	
Sex (male/total)			16/22			12/21
Education (years)	16.5	3.2		16.1	3.9	
Neuropsychological test performance for diagnosis						
	Healthy elderly ($N = 22$)			Alzheimer's patients ($N = 21$)		
Test	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*
MMSE	*NA*			24.8	3.4	12
Digit span (WAIS-III)	*NA*					4
Forward				8.4	2.2	
Backward				5.2	1.9	
RAVLT	*NA*					
Immediate recall				25.0	7.0	15
Delayed recall				2.6	1.7	18
Delayed recognition				24.2	3.7	15
TMT	*NA*					
Part A				61.8	38.9	5
Part B				157.8	80.8	8
Neuropsychological test performance during intake						
	Healthy elderly ($N = 22$)			Alzheimer's patients ($N = 21$)		
Test	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*
MMSE	29.0	1.1	0	25.3***	3.2	12
WMS-R Logical Memory II Delayed	11.8	3.9	0	4.3***	5.0	15
GDS	2.6	3.1		3.8	2.4	
Performance during fMRI scan						
	Healthy elderly ($N = 22$)			Alzheimer's patients ($N = 21$)		
	Mean	*SD*		*Mean*	*SD*	
Condition AM	84.0	8.5		73.5***	8.8	
Hit rate	0.9	0.1		0.9	1.0	
False alarm rate	0.3.	0.2		0.5*	0.3	
Condition semantic	90.5	8.0		75.1***	13.0	
Hit rate	1.0	0.1		0.8***	0.1	
False alarm rate	0.2	0.2		0.3	0.3	
Mean memory rating	12.1	1.5		10.1***	2.1	

Note. MMSE = Mini-Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; WMS-R = Wechsler Memory Scale-Revised; GDS = Geriatric Depression Scale; ***$P < .0001$; *$P < .05$. Number of impaired were based on available normative data for the memory tests.

Alzheimer's patients were recruited within 3 months from diagnosis from the Memory Clinic of the Alzheimer Centre at the Radboud University Nijmegen Medical Centre ($N = 19$) and the Geriatrics department of the "Gelderse Vallei" hospital in Ede ($N = 2$). Diagnosis was supported by neuropsychological tests, assessing overall cognitive functioning with the MMSE (Folstein et al., 1975), working memory function using the Digit Span subtest of the Wechsler Adult Intelligence Test-Third Edition (WAIS-III) (Wechsler, 1997), psychomotor speed and mental flexibility (as part of executive functioning) with the Trail Making Test (TMT) (Bowie and Harvey, 2006), see Table 1. The Rey Auditory Verbal Learning Test (RAVLT) functioned as an index of word-list learning, assessing immediate and delayed free recall and delayed recognition (Van der Elst et al., 2005). Test scores were classified as 'impaired' if they were more than 1.5 SD below the normative mean, corrected for age, education and sex (Lezak et al., 2004). The biomarker

criterion for diagnosis of probable Alzheimer's disease (Dubois et al., 2007) in this study was MTL atrophy determined by visual scoring (Scheltens et al., 1992), and/or abnormal cerebrospinal fluid (Hulstaert et al., 1999).

Fourteen of 35 Alzheimer's patients were excluded: low vision ($N=1$), 3 left the study before scanning and 10 during analysis (performance below chance level: $N=7$, anxiety: $N=1$ or artifacts: $N=2$). All except one were right-handed according to the Edinburgh handedness index (Oldfield, 1971).

Intake and autobiographical interview

At intake, informed consent according to the Declaration of Helsinki (Lynoe et al., 1991), neuropsychological data, and an autobiographical interview (as basis for fMRI stimulus design) were obtained. Patients were accompanied by proxy. After administration of the WMS-R (Wechsler, 1987) second story, the MMSE (Folstein et al., 1975) and GDS (Yesavage et al., 1982), participants were comfortably seated in a living room-like setting (without proxy) for the interview.

Participants were instructed that the interview's purpose was to get a detailed account of memories (time/place specific) from their past. An overview of big life events (e.g., marriage, birth of children), made at the beginning, functioned as guideline. The interview (earliest memory to present) lasted until enough memories were gathered (approximately 3 h), while participants were encouraged to report as many details as possible. When no specific event could be remembered, the life-events list from the Autobiographical Interview Administration Manual (belonging to Levine et al., 2002) was given to the participant. The interview was semi-structured and corresponded to the "recall" and "general probe" condition from Levine et al. (2002) combined. Records of the interviews were transcribed subsequently.

Interview scoring procedure

Two researchers independently scored transcripts according to the Autobiographical Interview Scoring Manual (belonging to Levine et al., 2002) on place/time localization, perceptual richness, emotions/thoughts, time integration and episodic richness. The maximum score of a memory was 21 points (3 points each, except for 6 points for episodic richness), resulting in a mean memory rating, reflecting the amount of episodic re-experiencing per participant. For an example, see Fig. 1.

Additionally, memory details were divided into "internal" or "external", with internal details pertaining directly to the main event described. These reflect episodic re-experiencing, as they were time/place specific. Internal details contained five subcategories: (1) event (happenings, unfolding of the story), (2) place, (3) time, (4) perceptual (sensory information like sights or sounds) and (5) emotions/thoughts. External details pertained to extraneous information not uniquely specific to the main memory described. Sub-categorization included the previous five episodic categories, supplemented with: (6) semantic (general facts/knowledge related to the context of the event), (7) repetition and (8) other (e.g. metacognitive statements).

Details were tallied and summed: the internal-to-total ratio indicated the proportion of details per memory reflecting episodic re-experiencing unbiased by total verbal output.

Scores were entered in a multivariate ANOVA with Group as between-subjects factor (2 levels) and Detail-category as within-subjects factor (13 levels), testing for interaction, main effects and between-subject effects. Results were corrected for multiple comparisons using Bonferroni correction. Alpha was set at 0.05.

For each participant, the most salient (highest amount of details and place/time specific) autobiographical memories distributed evenly over the lifetime were chosen to create 24 subject-unique stimuli (statements) for fMRI. On average, one memory served as the basis for 1.5 ± 0.5 statements (Healthy participants: 1.2 ± 0.2 statements/memory; Patients: 1.7 ± 0.5; $t_{41}=-4.43$, $P<0.0001$), with a maximum of four distinct statements per memory.

fMRI: Stimulus material and experimental procedure

At least 6 weeks after the interview, participants returned for fMRI. All statements were randomized within condition (and therefore, there was no chronological order) and divided into eight blocks of three statements per condition. This means there was no chronological order

Event **Place** **Place** **Semantic**
I went on a business trip to Wolokda, Russia. I only knew Russia and Russian
Event
women from pictures of the cold war. I was going to meet my interpreter at the
Place **Event** **Time** **Emo/Th** **Percep** **Percep**
station. As I arrived that morning, I saw this beautiful young woman, around 20
Percep **Percep** **Percep**
years old, with pitch blond hair, a fur cap and an awesome figure. I had never
Emo/Th **Percep** **Percep**
expected that. She could speak English and German, and had a chauffeur. Who
Rep **Time**
could ever expect to arrive on a Sunday morning in Russia, encounter a beautiful
Percep **Time**
woman who addresses you in English and German? It was cold, January and I
Rep
only knew Russian women from pictures where you see them sweeping the snow
Rep **Time** **Event**
off the street. It must have been January '95, I was alone on a small business

trip.

Fig. 1. Scoring example of a healthy older participant. This memory was scored as follows: *Main event*: Meeting interpreter at the station. Internal details: event = 4, place = 3, time = 4, perception (Percep) = 8, thought/emotion (T/Em) = 2; external details: external (Ext.) event = 0, semantic = 1, repetitions = 3, other = 0; ratings: place = 2/3 (larger scale information, lacking specific context), time = 2/3 (four pieces of time information, lacking specific context), perception = 3/3 (eight perceptual details, richly described), thought/emotion = 2/3 (response partially captures cognitive/emotional state at the time of the event), episodic richness = 3/6 (response had moderate detail but fell short of a rich re-lived description), time integration = 2/3 (a few details were given about a larger time frame, but lacked a fuller description). The statement that was presented to the participant in the scanner: "You arrived in Wolokda and met a beautiful interpreter."

in the autobiographical statements being presented. Condition blocks alternated (A, S, A, etc.) and were separated by a 300 ms white fixation cross. Condition order was counterbalanced over participants. Each statement was presented in white against a black background for 8 s, followed by a 300 ms white fixation cross, resulting in a 24.6 s block length. Each statement was spread over three lines which were simultaneously presented in the centre of the screen, to minimize head movement. Above, "True/False?" was shown in yellow. We used Presentation software (www.neurobs.com) to present stimuli and record button presses. Stimuli were back-projected via an LCD-projector onto a translucent screen that participants viewed through a mirror on the head coil. The participant's head was immobilized to reduce motion.

Participants indicated by button press if each statement was true or false (true: false ratio = 3:1). For example: "All your colleagues watched as you arrived on a scooter on your first day at work" (true), "All your colleagues watched as you arrived on a bicycle on your first day at work" (false). Autobiographical statements (A) were matched for grammar, word frequency and number of syllables with 24 semantic statements (S), to prevent differences in semantic processing. For example: "Snoopy is a cartoon about a white dog" (true), "Snoopy is a cartoon about a white cat" (false).

Before going into the scanner, participants were extensively instructed and trained with two supplementary statements (i.e. statements that were not used in the actual experiment) for each condition. Participants had already visited the MRI suite during intake, familiarizing them with the experimental setup. For the autobiographical condition, participants were instructed to read and subsequently recollect, i.e. "subjectively re-experience", (part of) the episode described to judge truthfulness. For the semantic condition, participants were instructed to read the statement and judge without relying on autobiographical events.

Data acquisition

Whole head T2*-weighted EPI-BOLD fMRI data were acquired with Siemens Sonata (12 healthy elderly, 9 patients) and Avanto (10 healthy elderly, 12 patients) 1.5T MR scanners using an interleaved slice acquisition sequence (TR = 2.27 s, TE = 30 ms, 90° flip-angle, 33 axial slices, slice-matrix size = 64 × 64, slice thickness = 3.5 mm, no gap, FOV = 224 mm, isotropic voxel-size = 3.5 × 3.5 × 3.5 mm^3). High-resolution structural MR images were acquired with a T1-weighted MP-RAGE sequence (TR = 2.25 s, TE = 3.93 ms, 15° flip-angle, 176 sagittal slices, slice-matrix size = 256 × 256, slice thickness = 1 mm, voxel-size = 1 × 1 × 1mm^3).

MR image preprocessing and statistical analysis

Image preprocessing and statistical analysis was done with SPM5 software (www.fil.ion.ucl.ac.uk). Functional EPI-BOLD images were realigned and subject-mean functional MR images were co-registered with the corresponding structural images using mutual information optimization. These were subsequently normalized (i.e., the normalization transformations from the structural were applied to the functional images) and transformed into standardized MNI space defined by the MNI T1 template, and finally smoothed with an 8 mm Gaussian filter kernel (Hayasaka and Nichols, 2003; Petersson et al., 1999). Preprocessing was inspected visually to verify if the co-registration and normalization procedure worked properly and check realignment parameters. The fMRI data were proportionally scaled to account for global effects and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al., 1994). The linear model included explanatory variables (box-car regressors), convolved with the canonical hemodynamic response function, modeling the experimental conditions in a blocked fMRI design. The realignment parameters were added as regressors of no-interest. A temporal high-pass filter of 128 s was applied to account for various low-frequency effects. Contrasts (each condition versus an implicit baseline) for each participant were subjected to a second-level, random effects 2 × 2 ANCOVA, with Group as between-subject factor and Condition (AM or semantic: semantic being the control) as within-subject factor. Task performance (percentage), scanner, age of participant, mean memory rating (episodic re-experiencing score) and gender were included as covariates. Results of the random effects analysis were thresholded initially at $P = 0.001$ (uncorrected) and then the cluster-size statistics were used as the test statistic at $P < 0.05$ (corrected). Parameter estimates of significant clusters were extracted using Marsbar software (0.41, http://marsbar.sourceforge.net).

To determine total hippocampal volume (in mm^3) per participant, the structural MRI underwent automatic segmentation of subcortical structures with FSL4.1 FIRST v1.1 (Analysis Group, FMRIB, Oxford, UK) (Smith et al., 2004; Woolrich et al., 2009). This method is based on Bayesian statistical models of shape and appearance for subcortical structures from 317 manually labeled T1-weighted MR images (including brains from older persons and Alzheimer patients). To fit the models, the probability of the shape given the observed intensities is used (Patenaude, 2007). After segmentation, volumes were calculated using a script in Matlab7.2 (MathWorks; Natick, MA, USA). Only boundary corrected data were used. Visual inspection of the segmented structures projected onto the T1-weighted MRI scans was done using MRIcroN Beta 7 (www.mricro.com/mricron), to check if the segmented structures align with the same structures on the T1. One dataset was removed (failed segmentation).

Absolute total hippocampal volumes were transferred to SPSS 15.0 for Windows (Lead Technologies Inc. SPSS Inc., Chicago, IL, USA) and subjected to a partial correlation analysis (one-tailed) with the extracted parameter estimates of significant clusters from the Patients > Healthy elderly (Autobiographical > Semantic) contrast from the fMRI analysis, while controlling for Brain Parenchymal Fraction (BPF: Juengling and Kassubek, 2003). BPF (gray matter + white matter)/intracranial volume) is a measure of global brain atrophy, and therefore, any effects found will be specific to hippocampal atrophy. To determine gray matter, white matter and csf volume for calculation of BPF, the structural MR images were segmented into gray matter, white matter, and cerebrospinal fluid with the VBM toolbox in SPM using priors (default settings).

Results

Behavioural results: autobiographical interview

Compared to healthy elderly, Alzheimer's patients showed a shift from episodic to semantic elements in their autobiographical narratives (see Fig. 2). Alzheimer's patients and healthy elderly produced autobiographical memories of similar length (Mean number of words per memory (SD): Healthy elderly 302 (59); Patients 262 (76); $F_{(1,41)} = 3.65$, ns), indicating no difference in fluency.

On average, healthy elderly reported 20.4 ± 3.9 internal details and 10.9 ± 2.9 external details (not including semantic/repetitions/other). Patients reported 14.9 ± 4.6 internal details and 11.3 ± 2.5 external details. There was a significant Group × Detail interaction ($F_{(12,30)} = 10.63$, $P < 0.001$) and a main effect of Group ($F_{(12,30)} = 7.33$, $P < 0.05$) and a main effect of Detail ($F_{(12,30)} = 148.42$, $P < 0.001$). Post-hoc tests revealed that Alzheimer's patients reported less internal (episodic) details per memory regarding event (Mean (SD): Healthy elderly: 11.9 (3.5); Patients: 8.5 (3.2); $F_{(1,41)} = 11.60$, $P < 0.005$), time (Mean (SD): Healthy elderly: 2.0 (0.5); Patients: 1.6 (0.7); $F_{(1,41)} = 4.22$, $P < 0.05$) and perceptual information (Mean (SD): Healthy elderly: 3.3 (1.0); Patients: 2.2 (0.9); $F_{(1,41)} = 14.67$, $P < 0.0005$) (see also Fig. 1A). There were no differences in amount of place (Mean (SD): Healthy elderly: 1.0 (0.3); Patients: 1.0 (0.4); $F_{(1,41)} < 0.01$ ns.) and emotional details (Mean (SD): Healthy elderly: 2.0 (1.0); Patients: 1.6 (0.8); $F_{(1,41)} = 3.27$, ns.). This

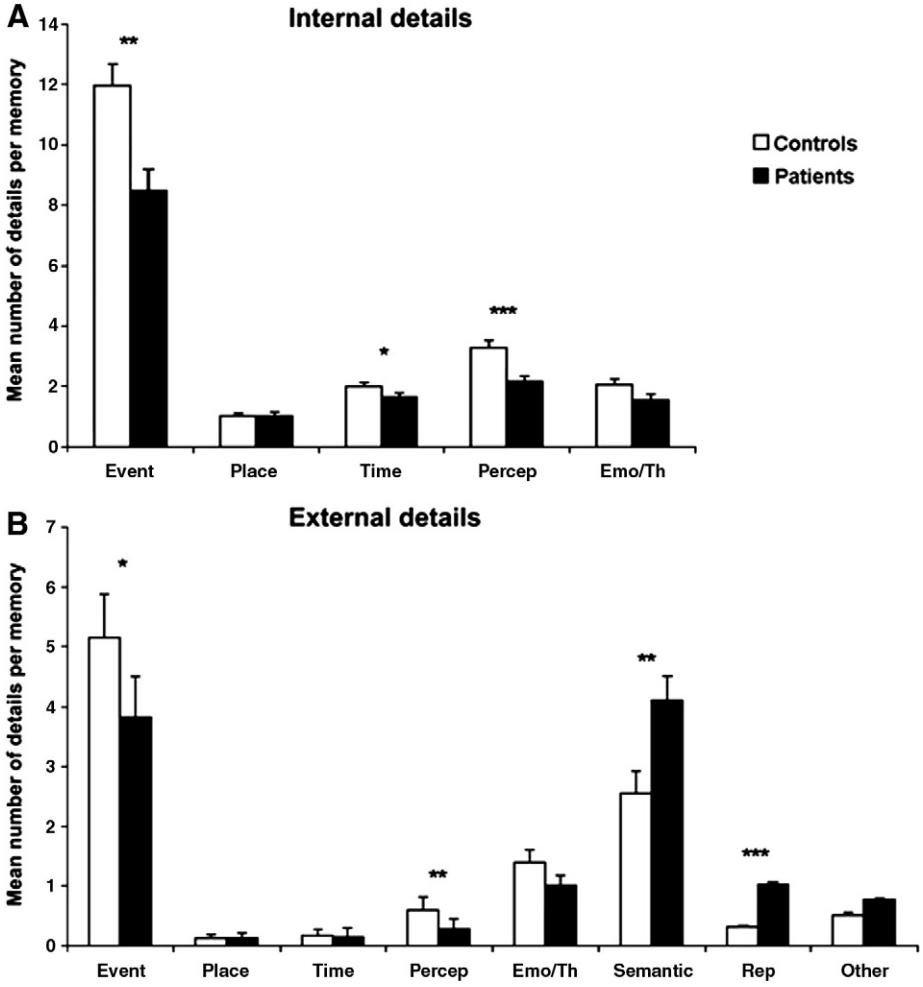

Fig. 2. Mean number of details per memory of Healthy elderly (Controls) and Alzheimer's patients, divided into Internal (A) and External (B) details. Percep = Perceptual, Emo/th = Emotional/thoughts, Rep = Repetitions. ***P<.001; **P<.01; *P<.05.

indicates the decrease in episodic re-experiencing in Alzheimer's patients is specifically pronounced in general event, time and perceptual elements.

Regarding external (episodic) details, Alzheimer's patients reported less event (Mean (SD): Healthy elderly: 5.2 (1.7); Patients 3.8 (1.9); $F_{(1,41)} = 5.90$, $P<0.05$) and perceptual (Mean (SD): Healthy elderly: 0.6 (0.4); Patients: 0.3 (0.2); $F_{(1,41)} = 11.53$, $P<0.01$) information per memory (see Fig. 1B). No differences were observed in the number of place (Mean (SD): Healthy elderly: 0.1 (0.1); Patients: 0.1 (0.2); $F_{(1,41)} = 0.06$, ns.), time (Mean (SD): Healthy elderly: 0.2 (0.2); Patients: 0.1 (0.2); $F_{(1,41)} = 0.55$, ns.), and emotional details (Mean (SD): Healthy elderly: 1.4 (0.7); Patients: 1.0 (0.7); $F_{(1,41)} = 3.62$, ns.). This indicates the decrease in episodic re-experiencing in Alzheimer's patients is also pronounced in their description of events and perceptions that were not uniquely pertaining to the main event described.

Alzheimer's patients report on average more semantic (Mean Semantic (SD): Healthy elderly: 2.6 (1.3); Patients: 4.1 (1.5); $F_{(1,41)} = 13.15$, $P<0.01$) and repetitive (Mean Rep (SD): Healthy elderly: 0.3 (0.3); Patients: 1.0 (0.7); $F_{(1,41)} = 17.91$, $P<0.001$) information (see also Fig. 1B). No differences were observed between the group regarding other statements (Mean Other (SD): Healthy elderly: 0.5 (0.3); Patients: 0.8 (0.7); $F_{(1,41)} = 2.27$, ns.).

The internal-to-total ratio in Alzheimer's patients was lower than in healthy elderly (Mean (SD) Healthy elderly 0.7 (0.1); Patients: 0.6 (0.1); $F_{(1,41)} = 27.85$, $P<0.0001$). Additionally, autobiographical memories from Alzheimer's patients received a lower mean memory rating than from healthy elderly (Mean (SD) Healthy elderly: 12.1 (1.5); Patients: 10.1 (2.1); $F_{(1,41)} = 18.37$, $P<0.001$). These results indicate that the autobiographical memories from healthy elderly were richer in episodic detail.

In conclusion, a whole set of behavioural measures confirms that autobiographical memories reported by Alzheimer's patients show an episodic-to-semantic content shift compared to healthy elderly.

Behavioural results: fMRI

Healthy elderly outperformed the Alzheimer's patients on both the autobiographical and the semantic condition (Mean Autobiographical (SD): Healthy elderly: 84.0 (8.5%); Patients: 73.5 (8.8%); $F_{(1,41)} = 15.89$, $P<0.001$; Semantic: Healthy elderly: 90.5 (8.0%); Patients: 75.1 (13.0%); $F_{(1,41)} = 21.88$, $P<0.001$). No main effect of condition or interaction was found (see Table 1). Upon asking, none of the participants reported thinking about the interview during scanning.

Hippocampal volume

Alzheimer's patients had smaller hippocampi than healthy elderly (Mean mm^3 (SD): Healthy elderly: 5.7 (0.82 mm^3); Patients: 5.2 (0.8 mm^3); $t_{40} = 2.02$, $P<0.05$). These values roughly correspond in healthy elderly to a medial temporal lobe atrophy (MTA) score (Scheltens et al., 1992) of 0–1 and in Alzheimer's patients to an MTA score of 1–2 (Knoops et al., 2009).

fMRI

AM retrieval (compared to semantic retrieval) activated a widespread set of brain regions, including occipital association areas, the medial temporal lobes, lateral temporal and prefrontal areas along the midline. These areas have previously been implicated as the core AM network (Cabeza and St Jacques, 2007; Svoboda et al., 2006). For an overview, see Fig. 3 and Table 2. The opposite contrast (Semantic versus Autobiographical retrieval) revealed no significant activations.

Turning to the analysis of main interest, Alzheimer's patients, compared to healthy elderly, displayed enhanced activation of the vmPFC, the LIFG, right precuneus and left lingual gyrus during autobiographical memory retrieval when compared to semantic retrieval. See Fig. 4.

A correlation analysis showed that across the Alzheimer's patients, the activity in the vmPFC and LIFG increased when hippocampal volume decreased (vmPFC: $r=-0.38$, $P<0.05$; LIFG: $r=-0.40$, $P<0.05$ (see Fig. 5).

The opposite contrast (healthy elderly versus patients) revealed no significant activations.

Table 2
Functional MRI results.

Healthy elderly (Autobiographical>Semantic)						
Region	Brodmann area	Size	*Z*	Local maxima MNI coordinates		
				x	*y*	*z*
Precuneus (l)/RSC	7/23/31	3480	6.97	−8	−58	32
Middle temporal gyrus (l)	21/22	2095	5.88	−62	−36	−6
Angular gyrus (l)	39/19	1903	5.83	−46	−68	24
Frontal midline	9/10/11/12/32	2043	5.56	−6	60	−10
Angular gyrus (r)	39	694	4.90	46	−76	30
Middle temporal gyrus (r)	21/22	371	4.43	58	−12	−18
Caudate nucleus (l)		630	4.42	−10	−6	14
Hippocampus (l)		213	4.18	−24	−10	−14
Patients (Autobiographical>Semantic)						
Region	Brodmann area	Size	*Z*	Local maxima MNI coordinates		
				x	*y*	*z*
Precuneus (l)/RSC	7/23/31/29/32	15230	7.84	−4	−58	32
Frontal midline	9/10/11/12/25					
Hippocampus (l+r)						
Caudate (l)						
Middle temporal gyrus (r)	21/22/38	2044	6.01	64	−8	−18
Middle temporal gyrus (l)	21/22/38	3052	6.00	−62	−8	−16
Angular gyrus (l)	39/19	2213	5.98	−48	−68	24
Angular gyrus (r)	39	1372	5.51	50	−56	22
DLPFC (r)	9	383	4.95	28	22	46
IFG (r)	44/45	386	4.12	54	36	−8
Patients>Healthy elderly (Autobiographical>Semantic)						
Region	Brodmann area	Size	*Z*	Local maxima MNI coordinates		
				x	*y*	*z*
IFG (l)	44/45	531	4.58	−44	20	20
Precuneus (r)	7	164	4.44	16	−54	42
Lingual gyrus (l)	18	259	4.32	−30	−74	−6
vmPFC	12	115	4.16	0	26	−18

Note. RSC = Retrosplenial Cortex; DLPFC = Dorsolateral Prefrontal Cortex; IFG = Inferior Frontal Gyrus; vmPFC = ventromedial Prefrontal Cortex; (l) = left; (r) = right.

Discussion

Our study shows that AM in Alzheimer's patients has undergone an episodic-to-semantic content shift compared to healthy elderly. When probed with semantic or autobiographical statements during fMRI, healthy elderly outperformed the patients, corroborating the decline of autobiographical and semantic memory in Alzheimer's disease. Independent of performance, Alzheimer's patients displayed enhanced activation of vmPFC, LIFG, right precuneus and left lingual gyrus during retrieval of episodic elements of AM compared to healthy elderly. Moreover, increased activation of vmPFC and LIFG was correlated with structural hippocampal decline observed in the patients, indicating a potential compensatory mechanism.

The data from the autobiographical interview extend the data of Murphy et al. (2008) and Levine et al. (2002) in that the episodic-to-semantic shift of AM observed in aging becomes exaggerated with Alzheimer-type dementia. Additionally, our study reveals specific differences in neural correlates of AM between Alzheimer's disease and healthy aging.

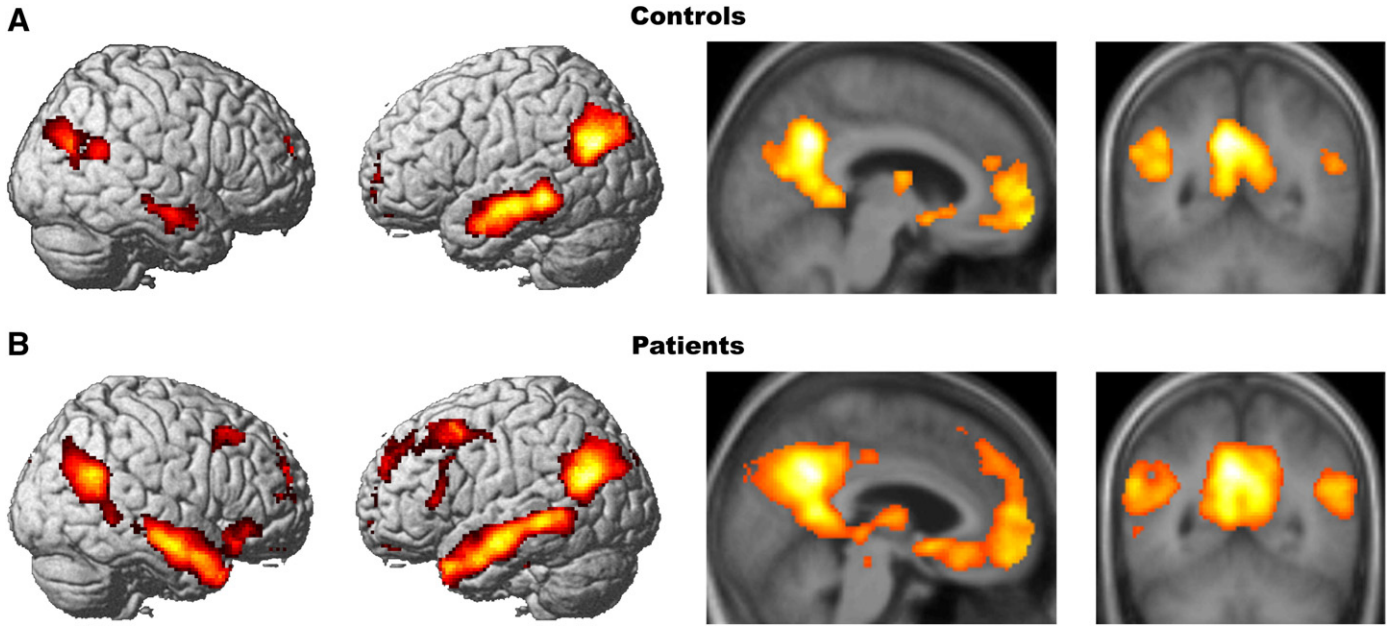

Fig. 3. Brain regions activated during autobiographical retrieval compared to semantic retrieval in (A) Healthy elderly (Controls) and (B) Alzheimer's patients. Activations are shown on an individual brain rendered in 3D; only significant clusters are shown ($P<.05$ FWE corr.).

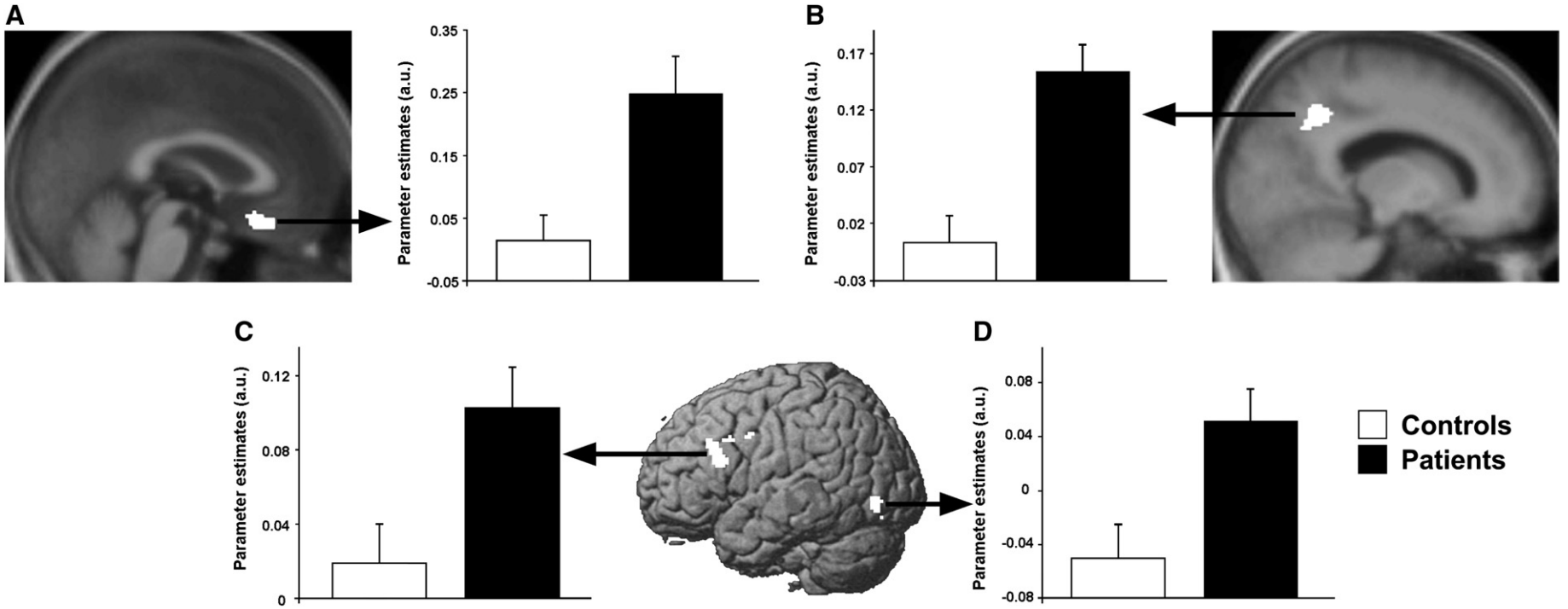

Fig. 4. Brain regions showing enhanced activation in Alzheimer's patients versus Healthy elderly (Controls), in the Autobiographical>Semantic contrast. (A) vmPFC: $x = 0$, (B) right precuneus: $x = 16$, (C) LIFG and (D) left lingual gyrus. Extracted parameter estimates (in arbitrary units; A.U.) of the clusters are shown alongside the images. Error bars represent standard errors of the mean. (A) and (B) are projected on the sagittal view of the mean normalized T1-image of all participants. (C) and (D) are shown on an individual brain rendered in 3D. Only significant clusters are shown ($P<.05$ FWE corr.).

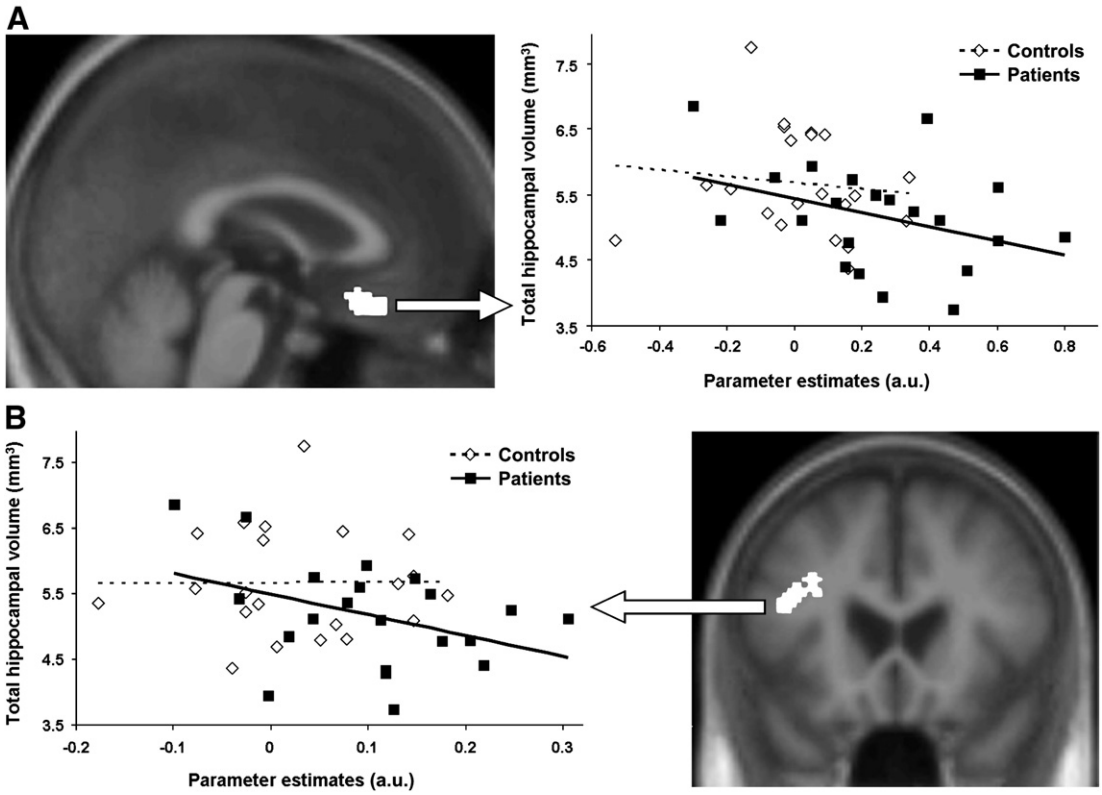

Fig. 5. Scatter plots of extracted cluster parameter estimates (in arbitrary units; A.U.) of (A) vmPFC: $x = 0$, and (B) LIFG: $y = 20$, related to total hippocampal volume (mm^3). Only in Alzheimer's patients, there is a significant negative correlation between activation in vmPFC ($r = -0.37$) or LIFG ($r = -0.40$) and total hippocampal volume, indicating enhanced activation of these areas during autobiographical retrieval with structural degradation of the hippocampus.

Firstly, Alzheimer's patients displayed enhanced activation of the LIFG, which is consistent with our hypothesis that patients would show enhanced semantic processing as a consequence of semantization (for reviews on the role of LIFG in semantic processing, see Cabeza and Nyberg, 2000; Thompson-Schill, 2003). In the memory domain, LIFG has been implicated in post-retrieval selection (Badre and Wagner, 2007), since its activity increases with increasing number or strength of retrieved competitors (Badre and Wagner, 2005). This denotes a selection process that focuses attention on the essential details to reach task goal (true/false judgement) and indicates this selection process might be enhanced in Alzheimer's patients, reflecting compensation. Indeed, activation of LIFG correlates positively with memory performance of Alzheimer's patients (Grady et al., 2003) and moreover, a recent meta-analysis showed Alzheimer's patients displayed increased activation of bilateral IFG during retrieval in various memory tasks when compared to healthy elderly (Schwindt and Black, 2009). For the right IFG, an inverse relationship with MTL activity was observed at successful recognition in young subjects and healthy elderly (Grady et al., 2005). The enhanced activation in Alzheimer's patients in our study is therefore likely compensatory for the reduction in episodic richness. This conclusion is strengthened by the correlation we observed with the hippocampal degradation, because hippocampal volume is related to episodic content of AM (Gilboa et al., 2005), which is reduced in our Alzheimer's patients.

Secondly, Alzheimer's patients showed enhanced activation of the vmPFC compared to healthy elderly. In AM studies (Cabeza and St Jacques, 2007; Gilboa, 2004; Piefke et al., 2003; Summerfield et al., 2009; Svoboda et al., 2006), its activation is mostly attributed to monitoring or "feeling of rightness" (Moscovitch and Winocur, 2002), since lesions cause confabulation (Curran et al., 1997; Gilboa et al., 2006; Johnson and Raye, 1998; Parkin et al., 1996; Schacter et al., 1996; Verfaellie et al., 2004). Importantly, retrieval activation in vmPFC increases while activation of the hippocampus decreases with consolidation in humans (Takashima et al., 2006) and rodents (Bontempi et al., 1999; Takehara-Nishiuchi and McNaughton, 2008). Also, lesions in rodents cause a selective memory deficit for remote but not recent memories (Akirav and Maroun, 2006; Takehara et al., 2003). These studies indicate that the initial linking of neocortical representations by the hippocampus is passed to the vmPFC, suggesting close interaction with the hippocampus during consolidation (for a review on transformation of memories to cortical networks, see Frankland and Bontempi, 2005, but see also van Kesteren et al., 2010). The intricate connections between the vmPFC and MTL support this view (Petrides and Pandya, 2002). One might consider that the linking function of the hippocampus is related to vivid, episodic retrieval and the linking function of the vmPFC is related to semantic retrieval. Following that line of thought, semantization of autobiographical memories will be reflected by a shift in the balance between hippocampus and vmPFC towards the vmPFC. This shift is especially pronounced in Alzheimer's patients, since their episodic retrieval deficit (caused by hippocampal damage) probably causes semantic retrieval to come into the limelight. But, since no decrease in hippocampal activation was observed in the Alzheimer's patients in this study, this parsimonious explanation is indirect.

We are intended to speculate that the correlations found between the hippocampal degradation and activation of LIFG and vmPFC point to compensatory processes in Alzheimer's patients (Reuter-Lorenz and Lustig, 2005). However, we can only speak of a possible attempt to compensate, since performance of the patients is lower than that of the healthy elderly. Perhaps these processes can already be observed at an earlier stage when performance is not (yet) reduced and the hippocampus is still macroscopically intact, making them ideally suited as early markers. Future studies need to support these speculations.

The results on the enhanced activation of the right precuneus and left lingual gyrus in Alzheimer's patients are harder to interpret.

The precuneus shows the highest resting metabolic rate of the human cerebral cortex (Gusnard and Raichle, 2001), which reduces as Alzheimer's disease progresses (Buckner et al., 2005), possibly resulting in reduced modulation. Enhanced activation of the precuneus in our study could therefore be a consequence of disrupted metabolism. Studies in healthy participants have implicated the precuneus in (visuo-spatial) imagery (for review, see Cavanna and Trimble, 2006) and propose an important role for the lingual gyrus in visual processing, since lesions of the lingual gyrus reduce dreaming and disable recognition of illusionary contours or faces (e.g., Girkin and Miller, 2001). The enhanced activation of the precuneus and lingual gyrus observed in the Alzheimer's patients could be related to an attempted compensation for decreased vividness, as patients reported fewer event and perceptual details than healthy elderly during the autobiographical interview. This is, however, speculative. Recently, Kinkingnehun et al. (2008) found that the precuneus and lingual gyrus of "fast decliners" (mild Alzheimer's patients with a drop of nine MMSE points in three years) contained less gray matter at baseline compared to "slow decliners" (decrease of two MMSE points), ascribing a predictive value to this measure, since no clinical or neuropsychological differences were observed at baseline. Future studies can elucidate if enhanced activation is indicative of faster decline.

Since semantic memory is known to involve the temporal poles (Mummery et al., 2000), one might expect that a change in semantic processing, as expected in this study, would lead to activation differences in this area. In this study, both groups did activate the temporal poles when autobiographical and semantic statements were contrasted (Fig. 3), which is in accordance with sensitivity of the temporal poles to narrative stimuli and personal knowledge (Olson et al., 2007). We however, did not observe any differences between the healthy elderly and Alzheimer's patients in the temporal poles. This lack of activation difference between the groups is difficult to interpret. Probably, the demand on the temporal poles is equal to both groups.

One thing that remains unclear is the mechanism behind semantization. This is especially interesting in the light of Alzheimer's disease, since it seems to work as a protective mechanism. If semantization of AM is the result of rehearsal (because of telling the story repeatedly), than semantization is more a by-product, leaving only the most salient memories available for remembering (see also Meeter and Murre, 2004). This does not readily explain increased semantization in Alzheimer's patients, since yet there are no indications that Alzheimer's patients are more reminiscent than healthy elderly.

In conclusion, the findings reported here show that Alzheimer's disease related MTL pathology is probably associated with semantization of autobiographical memories in Alzheimer's patients, leading to increased semantic processing and presumably an increased dependence on the linking function of the vmPFC. These findings provide important insights in the consequences Alzheimer's disease has on the functionality of brain regions during AM retrieval and point at potential routes for early diagnosis.

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