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ORIGINAL ARTICLE

Effects of medial temporal lobe degeneration on brain perfusion in amnestic MCI of AD type: deafferentation and functional compensation?

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Abstract
Purpose Cortical atrophy is correlated with the progression of neuropathological lesions within the medial temporal lobes (MTL) in Alzheimer's disease (AD). Our aim was to determine which local and remote functional changes result from MTL volume loss at the predementia stage.

Methods We studied the relationship between entorhinal and hippocampal MR volumes and whole-brain SPECT perfusion via a voxel-based correlative analysis in 19 patients with amnestic mild cognitive impairment with a memory profile suggestive of early AD.

Results Right MTL volumes were positively correlated with remote posterior perfusion of the posterior cingulate cortex, and negatively correlated with remote anterior perfusion of the right medial and dorsolateral prefrontal cortex. There was no local correlation between volumes and perfusion within the MTL.

Conclusion These findings provide further insight into functional changes that result from MTL volume loss during the predementia stage of AD. The positive correlation between MTL volumes and posterior cingulate perfusion may reflect the deafferentation of a temporocingulate network due to mediotemporal degeneration. The paradoxical negative correlation between MTL volumes and prefrontal perfusion may result from recruitment of an alternative anterior temporofrontal network. It remains to be investigated how the "net sum" of this perfusion modulation affects memory and other cognitive domains through a possible compensatory perspective.

Keywords MCI · AD · Deafferentation · Functional compensation · Brain SPECT · SPM

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Introduction

Over recent years, neuroimaging has significantly advanced our knowledge about the functional and anatomical changes in early Alzheimer's disease (AD). However, these studies have also raised additional issues concerning the relationship

between structural and functional changes. Morphological studies suggest that entorhinal and hippocampal atrophy may be the earliest and most specific MRI predictors of future dementia [1]. These findings are consistent with post-mortem examinations showing that neurofibrillary tangles (NFT) initially appear in the medial temporal lobes (MTL), sequentially affecting the rhinal cortex, and the hippocampus, before spreading to the neocortex [2, 3]. Yet functional impairment of MTL is far from being the most severe effect, even at the stage of dementia, in spite of the MTL being the most structurally impaired region [4, 5]. In contrast, hypoperfusion and hypometabolism begin in the posterior cortices [6–8], particularly in the posterior cingulate cortex whereas no NFT are reported in these areas during early stages [2, 3]. Following this line of thought, functional impairment of the posterior cortices exceeds atrophy, even at the stage of dementia [5].

There appears to be a paradox during AD, especially during the early stages, between (1) neuronal loss in the MTL with less severe hypoperfusion and hypometabolism, and (2) hypoperfusion and hypometabolism in the posterior cingulate cortex with less severe atrophy. This paradox between cerebral atrophy and perfusion has been longitudinally demonstrated during AD [9]. More recently, Chetelat et al. have confirmed these findings by a direct voxel-based comparison between grey matter (GM) hypometabolism and atrophy in patients with AD of mild severity [5].

This MTL paradox may be explained, other than by methodological issues [5, 10], by compensatory phenomena related to synaptic proliferation [11]. Atrophy of MTL structures is likely to lead to functional reorganization. However, to our knowledge, the hypothesis of local and remote functional compensation, related to atrophic MTL, has not been investigated at basal rest state using SPECT or PET in patients at a predementia stage of AD. Yet it is at this stage that mechanisms of functional compensation are probably most active [12].

The second puzzling paradox concerns the hypometabolism and the hypoperfusion of posterior cortical areas. This could be explained by a mechanism of corticocortical deafferentation between the MTL and its cortical connections. The demonstration in vivo of a direct correlation between atrophy of the MTL and remote functional abnormalities could be a strong argument in favour of this hypothesis. Following this line of thought, Jobst et al. were the first to report a significant correlation between CT hippocampal thickness and corresponding scores in posterior cortex SPECT hypoperfusion [13]. Yamaguchi et al. and Meguro et al. confirmed this correlation using MRI and FDG PET [14, 15]. However, the different components of the MTL were not evaluated, and no relationship was found with the metabolism of the posterior cingulate cortex. More recently, Villain et al. have demonstrated such a relationship between hippocampal atrophy and posterior cingulate hypometabolism [16]. Nevertheless, these different studies included patients at a dementia stage of AD, when degenerative lesions and atrophy have spread to the posterior cortex. Also, confounding effects of overall disease severity could not be formally excluded. It is therefore difficult to establish if these correlations are related to the posterior spread of NFT with atrophy or to deafferentation.

The objective of the present study was to further investigate this paradox between anatomical and functional neuroimaging patterns at an early stage of AD. We aimed to determine which local and remote functional changes result from MTL volume loss at the predementia stage.

We used a voxel-by-voxel correlative approach in order to evaluate the relationship between volumes of two subregions of the MTL (entorhinal cortex and hippocampus) and local and remote cerebral SPECT perfusion in a population of patients with a memory profile of early AD. Patients with amnestic mild cognitive impairment (aMCI) have been shown to be at high risk of AD [17]. The present study included a subset of aMCI patients, who, according to neuropsychological criteria, are at high risk of AD [18, 19]. At this stage, neuropathological lesions and neuronal loss are mainly thought to be limited to the MTL, while the posterior cortices remain relatively unaffected by NFT [2, 3]. As mentioned, it is also at this stage that mechanisms of functional compensation are probably most active [12]. We examined the respective contribution of volume of each MTL substructure to the variation of local and remote perfusion, using positive and negative correlations. We therefore expected to find *positive* correlations (volume loss correlated with relatively diminished perfusion), that could be related to deafferentation, but also possible *negative* correlations (volume loss correlated with relatively increased perfusion), that could reflect functional compensation at basal state.

Materials and methods

Patients

A group of 19 patients at very high risk of prodromal AD were selected (10 men; 69.9±9.5 years of age). All patients met the criteria for MCI, as defined by Petersen et al. [17]. However, for the purposes of the present study, we selected a subset of MCI patients with a memory impairment indicating mesiotemporal dysfunction, as described below. These criteria included normal activities of daily living (assessed during a clinical interview, and requiring an IADL score of 0), MMSE ≥25, a memory complaint (assessed by clinical interview and the use of a rating scale) and objective memory impairment in neuropsychological tests. Whereas all patients had impaired memory, since this was the criterion

for inclusion, these 19 patients presented with a "genuine" memory impairment of the "medial temporal" type, thought to be highly suggestive of early AD [18–22]. This type of memory profile is characterized by impaired storage, i.e. poor recall despite controlled encoding and no significant benefit from categorical cues, suggestive of MTL dysfunction [23]. The memory test used to establish the profile of the memory dysfunction was the Free and Cued Selective Reminding (FCSR) test [20]. Each of these patients performed more than 1.5 standard deviation (SD) below the mean of control subjects on the total free and cued delayed recall of the FCSR. Patients with a clear deficit in one or more cognitive domains other than memory, as assessed through extensive neuropsychological testing, were excluded. Routine neuroimaging examination, laboratory screening and psychiatric interview excluded nondegenerative causes of memory impairment. Other exclusion criteria were a history of systemic and neurological disease and a modified Hachinski ischaemic score equal to or higher than 2.

All patients signed informed consent for this study, which was approved by the local Medical Ethics Committee.

Brain MRI

All MRI studies were performed on a 1.5-T system (Magnetom Vision Plus, Siemens, Erlangen, Germany). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using an MPRage sequence (repetition time 9.7 ms, echo time 4 ms, inversion time 250 ms, flip angle 12°, acquisition matrix 230×256). Images were reformatted to obtain an isotropic voxel of 1.5×1.5×1.5 mm, then magnified in order to improve the analysis of MTL substructures (Brain Voyager, Brain Innovation).

Volumes of interest (VOI) were manually outlined by the same skilled operator on a coronal MR section, perpendicular to the long axis of the hippocampus, individually for each patient and for both hemispheres. A second operator monitored the validity of the measures with an excellent reproducibility (mean difference 0.7±0.5%). We measured the entorhinal cortex and the hippocampus, since these structures are consistently atrophied in patients with early AD [1]. The VOI were anatomically defined according to the recommendations of Duvernoy [24] and Insausti et al. [25], as we have previously described [26], and normalized to the total brain volume [27].

In order to establish the degree of atrophy, volumetric results were compared with those of 28 aged-matched healthy subjects with normal cognitive function and no history of systemic, mental or neurological disorder (14 women; 66.7±6.9 years of age; MMSE 28.8±1.0; total free and cued delayed recall on the FCSR 15.60±0.91; delayed recall on the DMS48 visual recognition memory test 0.98±0.03; and bilateral normalized volume of entorhinal cortex 2,370±293 mm^3, and of the hippocampus 6,338±710 mm^3).

Brain SPECT

Brain SPECT was carried out in all patients. ^{99m}Tc-ECD (740 MBq; Neurolite, BMS) was injected into the antecubital vein, at rest in quiet surroundings with the eyes closed. Acquisition was begun 1 h after injection with a double-head rotating gamma camera (ECAM; Siemens, Erlangen, Germany) equipped with a fan beam collimator. Data were collected in 64 projections of 40 s over 360° (matrix 128×128). Tomographic slices were reconstructed using a filtered back projection algorithm (Butterworth filter of order 4 with a cut-off frequency of 0.4 cm^{-1}) with a Chang attenuation correction. Individual brain SPECT abnormalities found in patients were visually described.

Voxel-based analysis

Voxel-based morphometry

Voxel-based morphometry (VBM) was performed in order to determine without an a priori hypothesis the site of GM loss. Volumetric T1-weighted images were spatially normalized into the Montreal Neurological Institute (MNI) space using the T1 anatomical template provided in the SPM2 program (Wellcome Department of Cognitive Neurology, University College, London; running on Matlab 6.0. Mathworks, Sherborn, MA). An isotropic voxel of 1.5×1.5×1.5 mm was used. The spatial normalization algorithm preserved voxel intensities (concentrations) even when region volumes were stretched by warping. Segmentation was performed onto the normalized T1-weighted images (SPM2). The resulting GM fraction maps were smoothed using a 6-mm Gaussian filter (fourfold the nominal spatial resolution of the T1 weighted MRI). The smoothed GM concentration maps of the aMCI patients were compared with those of the healthy subjects (ANCOVA with age as confounding covariate, $p<0.005$, adjusted for cluster volume and corrected for multiple comparisons with a threshold of $p<0.05$) to determine the location of clusters with significant differences in GM concentrations. Coordinates of significant clusters in the MNI space were transformed into Talairach coordinates using a nonlinear transformation to locate clusters and assign them as Brodmann areas.

Voxel-based morphofunctional correlations

We studied the voxel-by-voxel correlation between the normalized volume of each MTL substructure and whole-brain SPECT perfusion. SPECT images were converted from the DICOM to the Analyze format using MRIcro, and

then transferred to SPM2. The data were then standardized on the MNI atlas, using the MR images of each patient. We used a 12-parameter affine transformation, followed by a nonlinear transformation and a trilinear interpolation. The dimensions of the resulting voxel were 2×2×2 mm. Standardized data were subsequently smoothed by a Gaussian filter (FWHM 12 mm) to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. Global normalization was performed using proportional scaling to control for individual variation. The threshold was set at 80% of the whole-brain mean to minimize the edge effects. Proportional scaling and a threshold of 80% were both used as previously suggested [6], since little cortical atrophy was expected. We checked that the MTL region was included in the analysis. A second-line analysis was also performed in which the voxel-based analysis was limited to the GM MR mask of the patients derived from the VBM procedure, in order to specifically investigate the genuine GM involvement of our findings. SPM {T} maps were obtained at a height threshold of $p<0.005$, adjusted for cluster volume and corrected for multiple comparisons ($p<0.05$ corrected). At this threshold, no significant positive or negative correlation was observed with left and right precentral MR volumes, which are known to be preserved in AD. In the same way, evidence of local correlation between MTL volumes and GM density was checked using VBM, with this same statistical threshold. Correlations were performed using the "single subject, covariates only" statistical model. Contrasts were defined to examine both positive and negative correlations, i.e. MTL volume loss correlated, respectively, with relative perfusion decrease and relative perfusion increase. Perfusion values were extracted using a sphere VOI with a 24-mm radius (twice FWHM), centred on the most significant voxel of the cluster, in order to specifically identify subregions of the cluster. Correlation between MTL volumes and MTL perfusion was then performed using Spearman's rank coefficient.

Results

Patient characteristics

Performances on the total free and cued delayed recall of the FCSR (mean Z-score −4.90, SD 4.30) and on the delayed recall of the DMS48 visual recognition memory test (mean Z-score −3.75, SD 3.48) were severely impaired ($p<0.001$, in comparison to healthy control subjects). The patients showed severe deficits in the realm of memory, whereas other cognitive functions were intact. The mean MMSE score at the time of this study was 27.1±1.1 ($p<0.001$, in comparison to healthy control subjects).The demographic characteristics and neuropsychological features of the 19 patients are presented in Table 1.

At the time of this report, longitudinal follow-up was underway and was available for 10 of the 19 patients at 36 months. Four of these ten patients had converted to dementia stage of the AD type during this period (40%).

Individual brain SPECT scans

Brain SPECT scans were visually interpreted. The severity of hypoperfusion was always moderate. Posterior associative hypoperfusion, including in particular the posterior cingulate cortex, was found in 13 out of the 19 patients. Nine of these 13 patients had more diffuse abnormalities, involving frontal areas, and also including the MTL in five patients. Two other patients showed moderate hypoperfusion in anterior regions, and including the MTL in one patient. Four patients had visually normal brain scans.

MTL MR volumes

Manually outlined VOI showed GM loss both in the entorhinal cortex ($p<0.0001$) and the hippocampus ($p=0.0053$) in aMCI patients, in comparison to healthy subjects.

Voxel-based morphometry

In comparison to healthy subjects, aMCI patients showed GM loss in the bilateral amygdale and hippocampus, in the right entorhinal cortex (BA27), and in the left striatum, using VBM (Fig. 1, Table 2)

Evidence of local correlation between MTL volumes and GM density was checked using VBM (Fig. 2). Left entorhinal MR volume was positively correlated with GM density of the bilateral amygdale, hippocampus and parahippocampus (BA28 and BA34). Right entorhinal MR volume was positively correlated with GM density of the right amygdala and parahippocampus (BA28 and BA34). Left hippocampal MR volume was positively correlated with GM density of the bilateral amygdala and right hippocampus and parahippocampus (BA34). Right hippocampal MR volume was positively correlated with GM density of the right amygdala, hippocampus and parahippocampus (BA28 and BA34).

Brain perfusion correlated to entorhinal MR volumes

No correlation was found between the left entorhinal MR volume and brain perfusion. A positive correlation was found between the entorhinal MR volume of the right hemisphere and the perfusion of the posterior cingulate cortex bilaterally (BA23, BA31 and BA24; corrRho=0.7840, $p=0.0009$; Talairach coordinates of the local maxima 0, −18,

Table 1 Characteristics of the aMCI patients. Values in parentheses are standard deviations

Characteristic	Amnestic MCI patients	Z-score
No. of patients	19	
Men	9	
Women	10	
Age (years)		
Mean	69.9	
SD	9.5	
MMSE	27.1 (1.1)	
Memory		
Total free and cued delayed recall on the FCSR (verbal memory test; maximum 16)	11.6 (3.2)	−4.90 (4.30)
Delayed recall on the DMS48 (visual recognition memory test)	85% (11%)	−3.75 (3.48)
Executive functions		
Digit span – forward and backward (WMS-III), scaled score (mean 10, SD 3)	9.3 (2.8)	−0.25 (0.94)
Matrices reasoning (WAIS-III), scaled score (mean 10, SD 3)	10.3 (2.1)	+0.11 (0.70)
Lexical fluency (letter P, in two minutes)	17.4 (6.5)	−0.43 (0.94)
Language		
Picture naming (DO80) (impaired <74)	79.32 (1.34)	
Visuoperceptual and visuospatial abilities		
Benton face recognition test (maximum 56, impaired <41)	48.40 (3.58)	
Benton line orientation test (maximum 30, impaired <18)	28.40 (2.71)	

DMS Delayed Matching-to-Sample, *DO* Oral Denomination, *FCSR* Free and Cued Selective Reminding, *MMSE* Mini-Mental State Examination, *WAIS* Wechler Adult Intelligence Scale, *WMS* Wechler Memory Scale

30) and thalami (Fig. 3a, Table 3). Besides this positive correlation, a negative correlation was also found between the right entorhinal MR volume and perfusion of the medial and dorsolateral prefrontal cortex of the right hemisphere (BA9 and BA10; corrRho=−0.8246, p=0.0005; Talairach coordinates of the local maxima 14, 55, 8; Fig. 3b, Table 3).

These clusters were also significant when limiting the voxel-based analysis to the GM MR mask of the patients (p<0.005 for the voxel, corrected for the cluster).

Brain perfusion correlated to hippocampal MR volumes

No positive correlation was found between the left hippocampal MR volume and brain perfusion. A positive correlation was found between the right hippocampal MR volume and the perfusion of the posterior cingulate cortex bilaterally (BA23, BA31 and BA24; corrRho=0.6456, p=0.0062; Talairach coordinates of the local maxima 16, −36, 26) and the perfusion of the right thalamus (Fig. 4a, Table 3). Besides this positive correlation, a negative correlation was also found between the right hippocampal MR volume and right perfusion of the medial and dorsolateral prefrontal cortices (BA9 and BA10; corrRho=-0.6213, p=0.0084; Talairach coordinates of the local maxima 10, 55, 8; Fig. 4b, Table 3).

These clusters were also significant when limiting the voxel-based analysis to the GM MR mask of the patients (p<0.005 for the voxel, adjusted for the cluster volume; correction for multiple comparison was obtained only for negative correlations).

Discussion

The aim of the present study was to examine the relationship between MTL volumes and regional cerebral blood flow on brain SPECT scans in aMCI patients with a memory profile indicating early AD [1, 18, 19]. A profile of early AD was also suggested by MTL volumes, VBM analysis and individual SPECT findings. By contrast, the outcome of patients with aMCI in general has been shown to be heterogeneous [17]. Further longitudinal follow-up is necessary to evaluate the genuine homogeneity of this subgroup of aMCI patients with a pattern of memory impairment of the “medial temporal type” [18].

Volume loss in the MTL did not correlate with changes of perfusion in these areas. Entorhinal and hippocampal MR volumes positively correlated with the perfusion of the posterior cingulate cortex, and negatively correlated with the perfusion of the right medial and dorsolateral prefrontal cortex. Since no control subjects were available for the SPECT study, we report variations in perfusion correlated with MTL volumes, and not significant hypo- or hyperperfusion. The

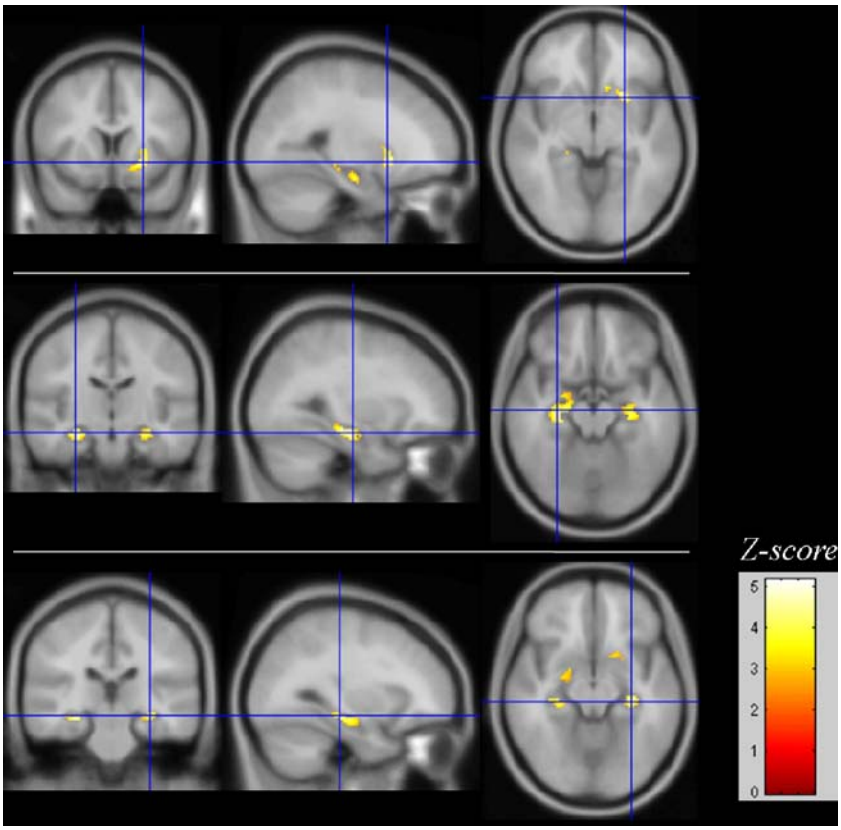

Fig. 1 Anatomical localization of the peaks of significant atrophy between aMCI patients and healthy subjects projected onto sections of a normal MRI set, spatially normalized into the standard SPM2 template. The left hemisphere is on the right side. aMCI patients showed GM loss in the bilateral amygdale and hippocampus, in the right entorhinal cortex, and in the left striatum, in comparison to healthy subjects

direct comparison of functional imaging data between MCI patients and healthy subjects, however, has been largely reported at the group level in the literature [6, 8]. Individual brain SPECT scans, were described visually. Similar patterns of correlation with perfusion were observed for both the entorhinal cortex and the hippocampus. These allocortical structures anatomically belong to the same system, the hippocampal formation. That atrophy of these areas results in the same pattern of remote cortical change could therefore be expected. However, NFT invade these mediotemporal structures in a sequential manner. As NFT first appear in the entorhinal cortex [2, 3], it would be expected that lesions of this area early in the course of the disease would be sufficient to lead to the pattern of posterior positive and anterior negative correlations found in the present study. This cannot be confirmed with the available data because of a cross-correlation with the hippocampus, but raises the more general and important question of when remote functional changes appear.

As previously reported at the stage of dementia [15], correlations were only found for right MTL volumes. Although AD lesions are generally thought to affect brain

Table 2 Talairach coordinates of significant atrophy in aMCI patients, in comparison to healthy subjects ($p<0.005$ for the voxel, uncorrected; correction was obtained for the cluster). Results from SPM2 are listed in decreasing order of peak *T*-score value; *k* values represent the number of significant voxels in the particular cluster

Cluster *p*(cor)	*k*	Voxel *T*-score	Coordinates (mm)			Localization
			x	*y*	*z*	
0.011	140	5.17	−24	11	−6	Left putamen
		3.60	−12	19	−4	Left caudate
0.011	140	4.79	−30	−26	−9	Left hippocampus
		2.74	−26	−8	−11	Left amygdala
<0.001	225	4.73	28	−24	−11	Right hippocampus
		3.79	26	−29	−7	Right entorhinal cortex (BA27)
		3.76	24	−4	−12	Right amygdala

BA Brodmann area, *cor* corrected.

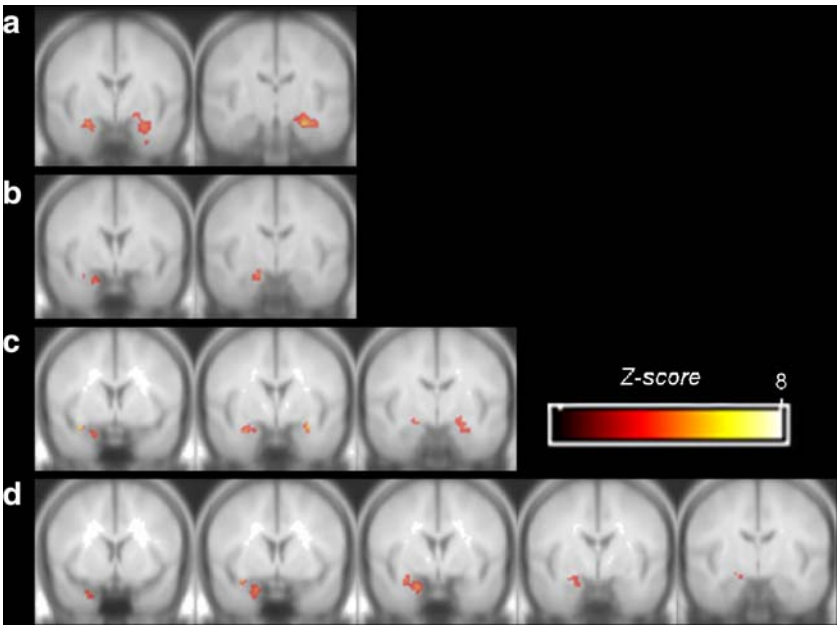

Fig. 2 Anatomical localization of the peaks of significant correlations between MTL volumes evaluated by VOI and GM density using VBM projected onto sections of a normal MRI set, spatially normalized into the standard SPM2 template. The left hemisphere is on the right side. *a* Left entorhinal MR volume is positively correlated with GM density of the bilateral amygdale, hippocampus and parahippocampus (BA28 and BA34). *b* Right entorhinal MR volume is positively correlated with GM density of the right amygdala and parahippocampus (BA28 and BA34). *c* Left hippocampal MR volume is positively correlated with GM density of the bilateral amygdala and right hippocampus and parahippocampus (BA34). *d* Right hippocampal MR volume is positively correlated with GM density of the right amygdala, hippocampus and parahippocampus (BA28 and BA34)

structures to a similar extent bilaterally, lateralized effects are often found in neuroimaging studies for reasons that remain unclear [28, 29]. It has been suggested that in patients with atrophy predominating on the left, the impact on daily life may be more severe, leading to lower scores on global scale assessments (e.g. MMSE) than in patients with predominant right atrophy at the same neuropathological stage. Therefore, patients with predominant atrophy on the left may be classified as probable AD, and those with predominant right atrophy as MCI [30].

In addition to bilateral MTL involvement, VBM analysis showed atrophy of the left striatum. Significant subcortical atrophy has been reported in the caudate, putamen, thalamus and pallidum [5, 31]. These findings are, however, debatable since these nuclei are particularly prone to artefacts due to their boundary position between white matter and ventricles, potentially leading to misclassification of voxels as false-negative, or deformations due to ventricular size enlargement [5, 32].

MTL volumes and perfusion

There was no local correlation between MTL volumes and perfusion. Our finding is methodologically reinforced by the demonstration of a direct correlation between MTL volumes and local GM using VBM.

MTL hypoperfusion/hypometabolism has been inconsistently reported in aMCI or AD. Since cerebral global mean metabolism has recently been shown to be already reduced at the stage of aMCI [33], the proportional scaling used to adjust for variability between individuals could lead to a significant underestimation of the extent of metabolic/perfusion reductions, especially in regions of atrophy in the absence of partial-volume correction, and could thus explain this discrepancy. In studies using regions of interests, the absence of a coregistered MRI or anatomical atlas may also contribute to this incongruity. Moreover, this discrepancy may be related to the anatomical complexity of this region which may interfere with spatial normalization processes [10]. However, when the same voxel-based method was performed for MR and SPECT comparisons, the MTL was found to have more atrophy than hypoperfusion [9].

Recently MTL hypometabolism has been demonstrated using stringent methodology in AD of mild severity, involving both partial-volume correction and normalization by individual vermis uptake value to control for individual variations in global measures [5]. However, MTL was far from being the most severely affected of all brain regions in spite of it being the most structurally impaired. An alternative explanation could be a functional MTL plastic upregulation related to synaptic proliferation. Following this line of thought, enhanced hippocampal activity in patients at risk of

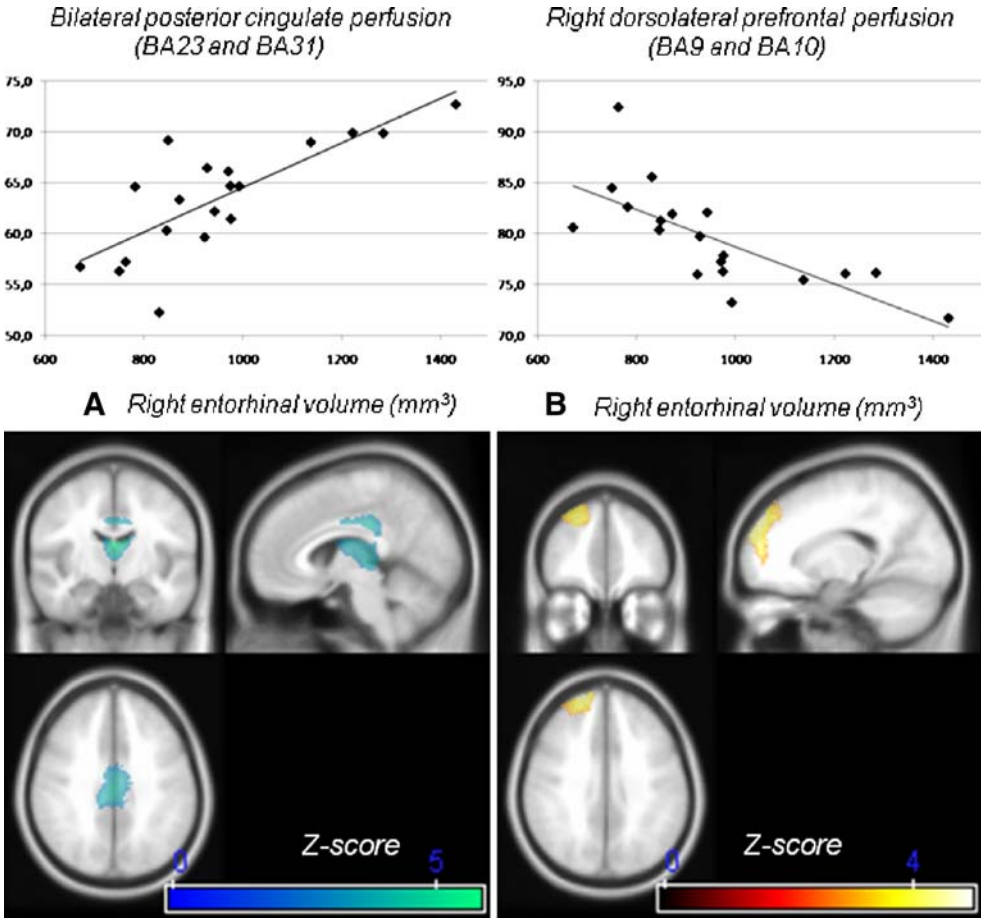

Fig. 3 Anatomical localization of the peaks of significant correlations between right entorhinal MR volumes and whole-brain SPECT perfusion projected onto sections of a normal MRI set, spatially normalized into the standard SPM2 template. The left hemisphere is on the right side (*blue* positive correlations, *yellow–red* negative correlations). **A** Right entorhinal MR volumes correlate positively with perfusion of the posterior cingulate cortex bilaterally and thalami on both sides. **B** Right entorhinal MR volumes correlate negatively with perfusion of the right dorsolateral prefrontal cortex

developing AD has been shown during a memory task [12], and increased choline acetyltransferase activity [34] or serotonergic metabolism [35] has been described in MCI. In the same way, Alsop et al. recently reported a paradoxical hyperperfusion of the hippocampus in AD [36]. This finding may be related to compensatory or pathological elevation of neural activity, inflammation or elevated production of vasodilators [36].

Posterior correlative perfusion

While decreased perfusion and metabolism in the posterior cingulum is usually found in aMCI [6–8], GM loss in this area is inconsistently reported at early stages [30, 37, 38] or to a lesser extent than hypometabolism at the stage of dementia [5, 9]. In addition, hypoperfusion and hypometabolism of the posterior cingulate cortex poorly correlates with atrophy or density of degenerative lesions [39].

The strong positive correlation between volume of MTL and remote perfusion of the posterior cingulum indicates that with increasing MTL volume loss in the entorhinal and the hippocampal cortex, relative perfusion decreases in the posterior cingulum. To the best of our knowledge, this relationship is exhibited for the first time in patients with aMCI. Recently, Villain et al. have demonstrated such a relationship between hippocampal atrophy and posterior cingulate hypometabolism at the dementia stage of AD [16]. Interestingly, and unlike this previous study [16], we found no significant GM loss of the posterior cingulate cortex in the VBM analysis. Indeed, at the predementia stage of AD, neuropathological studies indicate that NFT and neuronal loss are restricted to the MTL, and that the cingulate cortex remains relatively unaffected [2, 3]. Thus, this correlative finding cannot be explained by local volume loss in the posterior cingulate cortex.

It has been then suggested that either amyloid deposition or deafferentation could explain this pattern of diminished activity [5]. The demonstration of a direct in vivo correlation between the volume of the MTL and remote functional change at the predementia stage is a strong argument in favour of deafferentation. These findings are also in accordance with studies in rodents and baboons reporting remote hypometabolism of the posterior associative cortex after lesions of the MTL cortex [40, 41], and in accordance with a recent study demonstrating a relationship between hippocampal atrophy, posterior cingulate hypometabolism and cingulum bundle disruption [16]. The remote changes observed in our study are also consistent with well-

Table 3 Talairach coordinates of peak significant correlations between MTL volumes and brain perfusion ($p<0.005$ for the voxel, uncorrected; correction was obtained for the cluster). Results from SPM2 are listed in decreasing order of peak *T*-score value; *k* values represent the number of significant voxels in the particular cluster

MR volume correlated to brain SPECT	Type of correlation	Cluster *p*(cor)	*k*	Voxel *T*-score	Coordinates (mm)			Localization
					x	y	z	
Right entorhinal cortex	Positive	<0.001	3407	5.80	0	−7	13	Left thalamus
				5.35	8	−27	1	Right thalamus (pulvinar)
				4.98	0	−18	30	Left cingulate gyrus (BA23)
				4.87	16	−36	26	Right cingulate gyrus (BA31)
				4.66	4	−24	31	Right cingulate gyrus (BA23)
				4.17	−4	−4	32	Left cingulate gyrus (BA24)
	Negative	0.027	1131	4.91	14	55	8	Right medial frontal gyrus (BA10)
				4.76	20	52	32	Right superior frontal gyrus (BA9)
				4.02	24	47	40	Right superior frontal gyrus (BA8)
Right hippocampus	Positive	0.013	1366	4.56	16	−36	26	Right cingulate gyrus (BA31)
				4.08	0	−12	32	Left cingulate gyrus (BA23)
				4.02	2	−8	32	Right cingulate gyrus (BA24)
				3.88	0	−4	32	Left cingulate gyrus (BA24)
				3.79	18	−35	9	Right thalamus (pulvinar)
				3.55	8	−25	34	Right cingulate gyrus (BA23)
	Negative	0.035	1067	4.77	10	55	8	Right medial frontal gyrus (BA10)
				4.05	12	53	18	Right superior frontal gyrus (BA9)

BA Brodmann area, *cor* corrected.

established anatomical connections between MTL and the posterior cingulate cortex [24, 42, 43]. Thus, the relationship between hippocampal volume and cingular perfusion may result from the involvement of the hippocampo-mamillo-thalamo-cingular loop [44]. In this context, it is noteworthy that there was a positive correlation between volumes of the MTL and perfusion of the thalamus and the cingulate cortex, indicating that several components of the Papez circuit are involved [45]. A relationship between the thalamus and episodic memory deficits has been demonstrated in AD [46]. Interestingly, the pathological process underlying this finding remains unclear since the thalamus is usually not described as an early site of neuropathological change in early AD. A deafferentation mechanism from MTL could be also the cause of this thalamic deficit.

Focal lesions of the posterior cingulate cortex are known to lead to memory dysfunction [47]. Following this line of thought, functional neuroimaging studies suggest that the retrosplenium is crucial in recall [48], particularly for spatial and autobiographical memory [49, 50]. It is, however, very unlikely that the memory dysfunction during the early stage of AD could exclusively be attributed to retrosplenial dysfunction [7]. Furthermore, functional activation studies have shown activation of the posterior cingulate cortex in AD patients, in favour of its relative functional integrity [51]. Further studies are necessary to confirm this hypothesis. This could be reminiscent of cerebellar diaschisis, in which hypoperfusion in the cerebellum is not associated with a clinical cerebellar syndrome [52].

Anterior correlative perfusion

The strong negative correlation between MTL volumes and medial and dorsolateral prefrontal perfusion provides evidence for an increased relative perfusion of the prefrontal cortex with increasing MTL atrophy. To our knowledge, such a relationship has never been demonstrated for the basal state. These findings are in accordance with a significant hyperperfusion of the prefrontal cortex in MCI patients who converted to dementia of the AD type over a 2-year period, compared to both control subjects and MCI patients who did not convert [53]. The present study goes further and suggests that such a phenomenon is strongly associated with MTL volumes. This contrasts with the findings of patients at the dementia stage of AD, where hippocampal atrophy is correlated with a decrease in metabolism in the dorsolateral frontal cortex [14], indicating that mechanisms of reorganization may be more active in patients at the stage of aMCI [12]. Whether this relationship is efficient and whether it

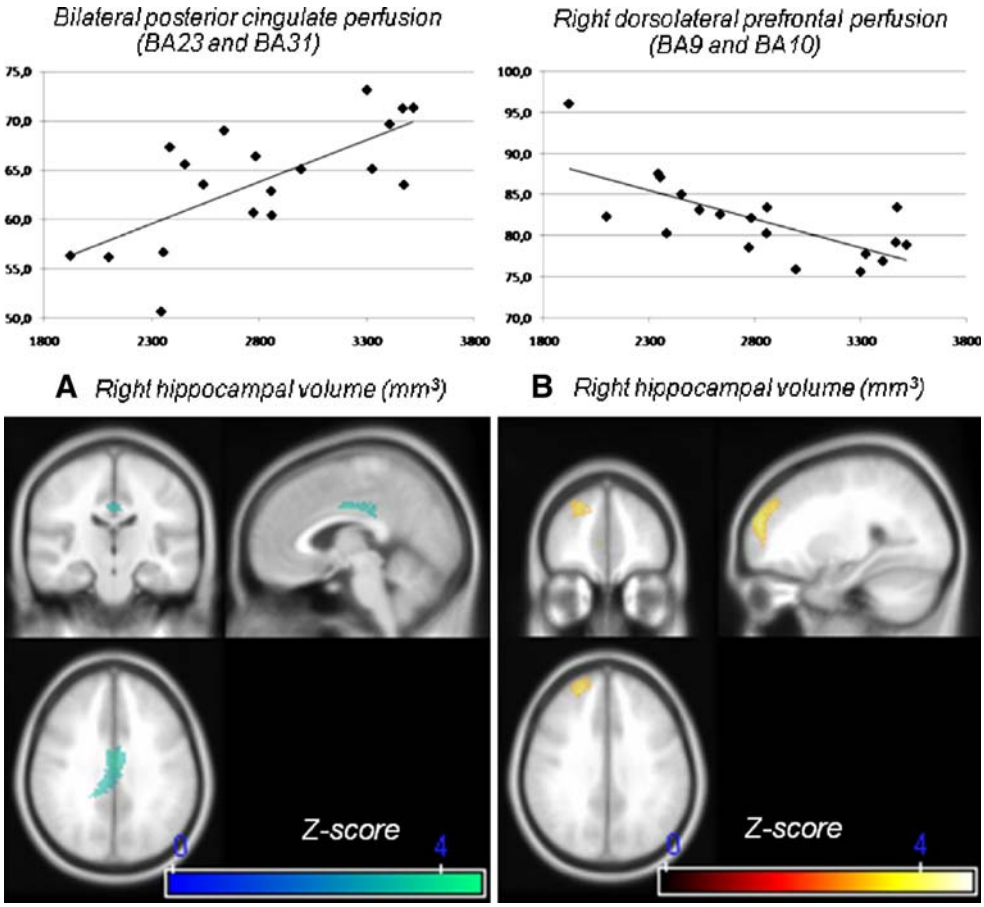

Fig. 4 Anatomical localization of the peaks of significant correlations between right hippocampal MR volumes and whole brain SPECT perfusion projected onto sections of a normal MRI set, spatially normalized into the standard SPM2 template. The left hemisphere is on the right side (*blue* positive correlations, *yellow–red* negative correlations). **A** Right hippocampal MR volumes correlate positively with perfusion of the posterior cingulate cortex bilaterally. **B** Right hippocampal MR volumes correlate negatively with perfusion of the right dorsolateral prefrontal cortex

compensates for cognitive dysfunction in an appropriate way remain to be further investigated with connectivity studies. This relationship may also illustrate maladaptive mechanisms related to lack of normal connectivity.

However, the finding of a relatively enhanced perfusion of the dorsolateral frontal cortex in the basal state may be of critical importance for activation studies [8]. Several functional activation studies in patients with MCI [54] and mild AD [55, 56], but also in asymptomatic subjects at risk of AD, carrying the APOE4 allele [57], have shown prefrontal task-related hyperactivation, in particular in dorsolateral areas. Moreover, the intensity and extent of task-related prefrontal activations are directly correlated with MTL atrophy [55]. This hyperactivation has been related to cognitive compensatory mechanisms. The dorsolateral prefrontal cortex plays a key role in effortful cognitive processes and this system might be spontaneously activated when other systems, such as episodic memory become deficient because of degenerative change [58]. The dorsolateral prefrontal cortex is also known to be critical for encoding and retrieval strategies in episodic memory. Several studies have shown poor performance in free recall after lesions to this region [59]. The dorsolateral prefrontal cortex could thus be involved in maintaining memory function in the event of dysfunction of the hippocampus. In the same way, Wang et al. have recently shown that patients with mild AD have increased resting-state activity in the prefrontal cortex and hippocampus, suggesting increased functional connectivity [42]. Subsequently, progression of the degenerative process may result in a loss of functional connectivity between MTL and frontal cortices, thereby disrupting this compensatory mechanism [60].

Conclusion

The findings reported here provide further insight into the functional changes associated with MTL volume loss during the predementia phase of AD. The positive correlation between MTL volumes and posterior perfusion could be the result of the deafferentation of a posterior temporocingulate network related to mediotemporal degeneration. The paradoxical negative correlation between MTL volumes and prefrontal cortex perfusion may result from recruitment of an alternative anterior temporofrontal network. However, it remains to be investigated how the "net sum" of this perfusion modulation affects memory and other cognitive domains through a possible compensatory perspective.

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Conflict of interest None.

References

1. Xu Y, Jack CR Jr, O'Brien PC, Kokmen E, Smith GE, Ivnik RJ, et al. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology 2000;54:1760–77.
2. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–59.
3. Delacourte A, David JP, Sergeant N, Buée L, Wattez A, Vermersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–65.
4. Ishii K, Sasaki M, Yamaji S, Sakamoto S, Kitagaki H, Morie E. Paradoxical hippocampus perfusion in mild-to-moderate Alzheimer's disease. J Nucl Med 1998;39:293–8.
5. Chételat G, Desgranges B, Landeau B, Mézenge F, Poline JB, de la Sayette V, et al. Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. Brain 2008;131:60–71.
6. Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease. Neurology 2003;60:1374–7.
7. Nestor PJ, Fryer TD, Ikeda M, Hodges JR. Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). Eur J Neurosci 2003;18:2663–7.
8. Huang C, Wahlund LO, Svensson L, Winblad B, Julin P. Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment. BMC Neurol 2002;2:9.
9. Matsuda H, Kitayama N, Ohnishi T, Asada T, Nakano S, Sakamoto S, et al. Longitudinal evaluation of both morphologic and functional changes in the same individuals with Alzheimer's disease. J Nucl Med 2002;43:304–11.
10. Mosconi L, Tsui WH, De Santi S, Li J, Rusinek H, Convit A, et al. Reduced hippocampal metabolism in MCI and AD: automated FDG-PET image analysis. Neurology 2005;64:1860–7.
11. Scheff SW, Sparks L, Price DA. Quantitative assessment of synaptic density in the entorhinal cortex in Alzheimer's disease. Ann Neurol 1993;34:356–61.
12. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 2005;65:404–11.
13. Jobst KA, Smith AD, Barker CS, Wear A, King EM, Smith A, et al. Association of atrophy of the medial temporal lobe with reduced blood flow in the posterior parietotemporal cortex in patients with a clinical and pathological diagnosis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1992;55:190–4.
14. Yamaguchi S, Meguro K, Itoh M, Hayasaka C, Shimada M, Yamazaki H, et al. Decreased cortical glucose metabolism correlates with hippocampal atrophy in Alzheimer's disease as shown by MRI and PET. J Neurol Neurosurg Psychiatry 1997;62:596–600.
15. Meguro K, LeMestric C, Landeau B, Desgranges B, Eustache F, Baron JC. Relations between hypometabolism in the posterior association neocortex and hippocampal atrophy in Alzheimer's disease: a PET/MRI correlative study. J Neurol Neurosurg Psychiatry 2001;71:315–21.
16. Villain N, Desgranges B, Viader F, de la Sayette V, Mézenge F, Landeau B, et al. Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. J Neurosci 2008;28:6174–81.
17. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
18. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–46.
19. Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, et al. Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. Neurology 2007;69:1859–67.
20. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988;38:900–3.
21. Barbeau E, Didic M, Tramoni E, Felician O, Joubert S, Sontheimer A, et al. Evaluation of visual recognition memory in MCI patients. Neurology 2004;62:1317–22.
22. Guedj E, Barbeau EJ, Didic M, Felician O, de Laforte C, Ceccaldi M, et al. Identification of subgroups in amnestic mild cognitive impairment. Neurology 2006;67:356–8.
23. Eustache F, Desgranges B, Giffard B, de la Sayette V, Baron JC. Entorhinal cortex disruption causes memory deficit in early Alzheimer's disease as shown by PET. Neuroreport 2001;12:683–5.
24. Duvernoy HM. The human brain: surface, three-dimensional sectional anatomy with MRI, and blood supply. New York: Springer; 1998.
25. Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, et al. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 1998;19:659–71.
26. Barbeau E, Sontheimer A, Joubert S, Didic M, Felician O, Tramoni E, et al. The human perirhinal cortex. Rev Neurol (Paris) 2004;160:401–11.
27. Eritaia J, Wood SJ, Stuart GW, Bridle N, Dudgeon P, Maruff P, et al. An optimized method for estimating intracranial volume from magnetic resonance images. Magn Reson Med 2000;44:973–7.
28. Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC. Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. Neuroreport 2002;13:1939–43.
29. de Leon MJ, Convit A, DeSanti S, Bobinski M, George AE, Wisniewski HM, et al. Contribution of structural neuroimaging to the early diagnosis of Alzheimer's disease. Int Psychogeriatr 1997;9:183–90.
30. Chetelat G, Baron JC. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. Neuroimage 2003;18:525–41.
31. Teipel SJ, Flatz WH, Heinsen H, Bokde AL, Schoenberg SO, Stöckel S, et al. Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. Brain 2005;128:2626–44.
32. Frisoni GB, Testa C, Zorzan A, Sabattoli F, Beltramello A, Soininen H, et al. Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. J Neurol Neurosurg Psychiatry 2002;73:657–64.
33. Mevel K, Desgranges B, Baron JC, Landeau B, De la Sayette V, Viader F, et al. Detecting hippocampal hypometabolism in mild cognitive impairment using automatic voxel-based approaches. Neuroimage 2007;37:18–25.
34. DeKosky ST, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, et al. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol 2002;51:145–55.
35. Truchot L, Costes SN, Zimmer L, Laurent B, Le Bars D, Thomas-Antérion C, et al. Up-regulation of hippocampal serotonin metabolism in mild cognitive impairment. Neurology 2007;69:1012–7.
36. Alsop DC, Casement M, de Bazelaire C, Fong T, Press DZ. Hippocampal hyperperfusion in Alzheimer's disease. Neuroimage 2008;42:1267–74.

37. Karas GB, Scheltens P, Rombouts SA, Visser PJ, van Schijndel RA, Fox NC, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. Neuroimage 2004;23:708–16.
38. Barbeau EJ, Ranjeva JP, Didic M, Confort-Gouny S, Felician O, Soulier E, et al. Profile of memory impairment and gray matter loss in amnestic mild cognitive impairment. Neuropsychologia 2008;46:1009–19.
39. De Carli C, Atack JR, Ball MJ. Post mortem regional neurofibrillary tangle densities but not senile plaque densities are related to regional cerebral rates for glucose during life in Alzheimer's disease patients. Neurodegeneration 1992;1:113–21.
40. Hayashi T, Fukuyama H, Katsumi Y, Hanakawa T, Nagahama Y, Yamauchi H, et al. Cerebral glucose metabolism in unilateral entorhinal cortex-lesioned rats: an animal PET study. Neuroreport 1999;10:2113–8.
41. Meguro K, Blaizot X, Kondoh Y, Le Mestric C, Baron JC, Chavoix C. Neocortical and hippocampal glucose hypometabolism following neurotoxic lesions of the entorhinal and perirhinal cortices in the non-human primate as shown by PET. Implications for Alzheimer's disease. Brain 1999;122:1519–31.
42. Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L, et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage 2006;31:496–504.
43. Ranganath C, Heller A, Cohen MX, Brozinsky CJ, Rissman J. Functional connectivity with the hippocampus during successful memory formation. Hippocampus 2005;15:997–1005.
44. Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry 1937;38:725–43
45. Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 1999;22:425–89.
46. Desgranges B, Baron JC, de la Sayette V, Petit-Taboué MC, Benali K, Landeau B, et al. The neural substrates of memory systems impairment in Alzheimer's disease. A PET study of resting brain glucose utilization. Brain 1998;121:611–31.
47. McDonald CR, Crosson B, Valenstein E, Bowers D. Verbal encoding deficits in a patient with a left retrosplenial lesion. Neurocase 2001;7:407–17.
48. Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000;12:1–47.
49. Berthoz A. Parietal and hippocampal contribution to topokinetic and topographic memory. Philos Trans R Soc Lond B Biol Sci 1997;352:1437–48.
50. Maddock RJ, Garrett AS, Buonocore MH. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience 2001;104:667–76.
51. Backman L, Andersson JL, Nyberg L, Winblad B, Nordberg A, Almkvist O. Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology 1999;52:1861–70.
52. Nguyen DK, Botez MI. Diaschisis and neurobehavior. Can J Neurol Sci 1998;25:5–12.
53. Huang C, Wahlund LO, Almkvist O, Elehu D, Svensson L, Jonsson T, et al. Voxel- and VOI-based analysis of SPECT CBF in relation to clinical and psychological heterogeneity of mild cognitive impairment. Neuroimage 2003;19:1137–44.
54. Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, et al. Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. Neurobiol Aging 2007;28:404–13.
55. Garrido GE, Furuie SS, Buchpiguel CA, Bottino CM, Almeida OP, Cid CG, et al. Relation between medial temporal atrophy and functional brain activity during memory processing in Alzheimer's disease: a combined MRI and SPECT study. J Neurol Neurosurg Psychiatry 2002;73:508–16.
56. Remy F, Mirrashed F, Campbell B, Richter W. Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. Neuroimage 2005;25:253–66.
57. Bondi MW, Houston WS, Eyler LT, Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. Neurology 2005;64:501–8.
58. Backman L, Small JB, Fratiglioni L. Stability of the preclinical episodic memory deficit in Alzheimer's disease. Brain 2001; 124:96–102.
59. Moscovitch M. Memory and working-with-memory: a component process model based on modules and central systems. J Cogn Neurosci 1992;4:257–67.
60. Mosconi L, Pupi A, De Cristofaro MT, Fayyaz M, Sorbi S, Herholz K. Functional interactions of the entorhinal cortex: an 18F-FDG PET study on normal aging and Alzheimer's disease. J Nucl Med 2004;45:382–92.