Autonoetic consciousness in Alzheimer's disease: neuropsychological and PET findings using an episodic learning and recognition task.

Géraldine Rauchs, Pascale Piolino, Florence Mézenge, Brigitte Landeau, Catherine Lalevée, Alice Pélerin, Fausto Viader, Vincent de La Sayette, Francis Eustache, Béatrice Desgranges

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Géraldine Rauchs[(1)], Pascale Piolino[(1,2)], Florence Mézenge[(1)], Brigitte Landeau[(1)], Catherine Lalevée[(1,3)], Alice Pélerin[(1,3)], Fausto Viader[(1,3)], Vincent de la Sayette[(1,3)], Francis Eustache[(1)], Béatrice Desgranges[(1)].

[(1)] Inserm - EPHE - Université de Caen E0218 and GIP Cyceron, France; [(2)] CNRS, Université René Descartes - Paris 5, France; [(3)] Service de Neurologie Vastel, CHU Côte de Nacre, Caen, France

Corresponding author:
Dr Béatrice DESGRANGES
Inserm - EPHE - Université de Caen E0218
Laboratoire de Neuropsychologie, CHU Avenue Côte de Nacre,
14033 CAEN cedex, France.
Phone : +33 (0) 2 31 06 51 96
Fax : +33 (0) 2 31 06 51 98
e-mail : desgranges-b@chu-caen.fr

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Abstract:

Objective: This study aims to map in patients with mild Alzheimer's disease (AD) the correlations between resting-state brain glucose utilization measured by FDG-PET and scores reflecting autonoetic consciousness in an episodic learning and recognition task.

Methods: Autonoetic consciousness, that gives a subject the conscious feeling to mentally travelling back in time to relive an event, was assessed using the Remember/Know (R/K) paradigm.

Results: AD patients provided less R responses (reflecting autonoetic consciousness) and more K ones (indicating the involvement of noetic consciousness) than healthy controls. Correct recognitions associated with a R response correlated with the metabolism of frontal areas bilaterally whereas those associated with a K response mainly correlated with the metabolism of left parahippocampal gyrus and lateral temporal cortex.

Conclusions: These data show that recollection is impaired in AD and recognition is more based on a feeling of familiarity than in controls. In addition, the findings of our correlative approach indicate that the impairment of episodic memory is mainly subserved by the dysfunction of frontal areas and of the hippocampal region.

1. Introduction

Impairment of episodic memory is the earliest and most severe cognitive deficit in Alzheimer's disease (AD) [40,47]. According to the current theoretical frameworks of human memory, episodic memory supports the encoding, storage and retrieval of life's events set in a specific spatio-temporal context. Thus, the term episodic memory encompasses not only autobiographical remote memory but also recently learned information, on which this paper will focus on. Episodic memory is also characterized by autonoetic consciousness, which gives a subject the conscious feeling of travelling backwards in time to relive the original event (for review see [64]). This particular state of consciousness during retrieval of information can be assessed with the Remember – Know (R/K) paradigm [23,62]. Thus, a Remember response means that the subject recollects a specific event as a re-experiencing of the source of acquisition with details (feelings, perceptions, …). By contrast, a Know response rather corresponds to a feeling of familiarity. "Remembering" is associated with autonoetic consciousness whereas "knowing" is associated with noetic consciousness, which characterizes semantic memory.

The alteration of autonoetic consciousness in AD has been seldom investigated. Nevertheless, using free and forced-choice recognition tasks, Dalla Barba [9] has shown that "remembering" is more affected than "knowing" in patients with AD. This finding has also been reported using an autobiographical memory task [48]. These results obtained with the Remember/Know paradigm are supported by a series of studies based on other theoretical views but underpinning the idea of a disruption of recollection in AD (see for review [68]). Thus, using an adaptation of the Deese-Roediger-McDermott (DRM) [11,54], a word learning paradigm in which subjects are presented with lists of words in which every item is an associate of a critical non-presented word, Budson et al. [5] showed that AD patients are impaired in their ability to use recollection to reduce, across trials, familiarity-based false

recognitions. Converging evidence also comes from two studies based on the process dissociation procedure of Jacoby [29]. Thus, both Knight [31] and Koivisto et al. [33], using a word-stem completion task in which subjects had to produce the first word that came to mind in response to each stem without using previously studied words, found that AD patients were less likely than control subjects to use recollection to inhibit erroneous responses. In addition, in an investigation of associative recognition in mild AD patients, Gallo et al. [22] presented participants with unrelated word pairs once or three times and found that false alarms to rearranged pairs following repetition increased in AD patients but not in elderly controls. Their results suggest that, contrary to controls, AD patients could not use a recollection-based strategy ("recall-to-reject strategy") to counter the increased familiarity of rearranged pairs and confirm that recollection-based monitoring processes are early impaired in AD. All these studies, carried out with various paradigms, acknowledge that recollection is impaired in AD. However, to the best of our knowledge, none of them has investigated the neural bases of this impairment.

Voxel-based mapping of the correlations between memory performance and resting-state cerebral metabolic rates of glucose (CMRGlc) measured by positron emission tomography (PET) is a sensitive approach to delineate the neural substrates of cognitive impairment in AD [e.g., 13,14,28,45,46,57]. Thus, it has been shown that episodic memory impairments observed in AD are subserved by the dysfunction of not only the hippocampal region but also by the dysfunction of an extensive neural network including the posterior cingulate gyrus ([13], see also [44] for similar conclusions obtained with a different method) and the temporoparietal and frontal association cortices [13]. This methodological approach has been successfully used to unravel the neural substrates of various deficits of episodic memory such as free [19] and cued recall [34], recognition [35], but also for more subtle deficits such as production of intrusions [15] and autobiographical memory impairment for different life-time

periods [20]. Nevertheless, it has never been used so far to investigate, in AD, the impairment of autonoetic consciousness, a prominent feature of episodic memory.

The aim of this study was therefore to unravel the neural substrates of episodic memory and autonoetic consciousness impairment in mild AD. In this purpose, we used PET and statistical parametric mapping (SPM) to map the correlations between CMRGlc and measures of episodic memory and autonoetic consciousness, assessed by means of an episodic learning and recognition task (adapted from the Grober and Buschke's procedure [25]) associated with the R/K paradigm [23].

2. Methods

2.1. Subjects

Thirteen unmedicated patients (7 women, 6 men; mean age ± SD: 76.7 ± 3.8 years) with a MMSE score [21] of 21 or higher (mean MMSE score ± SD: 24.8 ± 2.4, range 21-28) participated in this study. They were all recruited through a memory clinic, and all complained of memory impairment. All were selected prospectively on the basis of a neurological examination and a neuropsychological assessment, using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD [38]. Structural imaging (MRI) showed no focal abnormality. At the time of the study, none of the patients was being or had been treated with specific medication, such as anti-acetylcholinesterase agents.

Neuropsychological data of AD patients were compared to those obtained in a group of ten healthy elderly subjects (6 women, 4 men; mean age ± SD: 76.7 ± 4.1 years) recruited in clubs for retired people. They had no neurological or psychiatric disorders. The mean score (± SD) for the MMSE was 29.4 (± 1). These subjects were paired according to their level of education with AD patients.

All subjects were right-handed, native French speakers and gave their written consent to the study after detailed information was provided to them. The study was done in-line with the Declaration of Helsinki following approval by the Regional Ethics Committee.

2.2. Behavioral paradigm

Episodic memory was assessed using an original task derived from Grober and Buschke's procedure [25] that consisted in learning a series of 15 words in five successive trials. This procedure was designed to limit the interference from semantic memory impairment by using only items whose semantic integrity has been strictly verified individually. To this end, the semantic integrity of the words to learn was controlled for each patient before the learning phase with questions exploring both general and specific knowledge of each item (see [24] for a detailed description of this task). Once this procedure finished, the episodic memory task was proposed after a 4- to 6-hour delay. This task consists in learning 15 words, presented by series of three on separate cards. The subject is asked to point out and to read aloud each item (e.g., salad) in response to the name of its category, verbally given by the examiner as a cue (e.g., vegetable). Once all three words have been correctly named, the three cards are removed and an immediate verbal cued recall is proposed, in the same order as in the previous identification task, again in response to the category cue (e.g., what was the vegetable?). If the subject is unable to recall an item in response to its cue, the pointing and reading aloud procedure is repeated for this item until a correct response is obtained. Once the immediate cued recall for a group of three items has been correctly performed, the next set of items is presented. Immediately following the processing of the 15 items, retrieval is assessed with cued recall using the same cues as in the learning phase. The originality of this task lies in the fact that we proposed five consecutive trials of cued recall to favour the encoding of most of the words and to avoid, as much as possible, floor effects when retesting AD patients the day

after. A delayed cued recall and a yes/no recognition task (with 15 semantic and 15 neutral distractors) were proposed after a night of sleep (i.e., a 12-h delay between learning and recall).

The recognition task was associated with the Remember – Know paradigm [23,62] which requires subjects to give either a "Remember" (R) response if retrieval is accompanied by the recollection of specific experiences present at encoding, or a "Know" (K) response if retrieval is achieved on the basis of a feeling of familiarity. These judgment categories were explained very carefully to the patients until each concept was thoroughly understood. Thus, for each word recognized, subjects had to indicate if they specifically remembered it from the list (R response) or if they merely knew that the word belonged to the list (K response). For example, remembering a word had to be associated with the re-experience of a particular association, or personal feeling (e.g., for the word 'Snail': "I remember seeing it, making an image of it" or "It was a word of the first set of three items", examples adapted from [23]). By contrast, K responses were to be given when the subjects felt confident concerning the recognition of an item but failed to evoke any specific conscious recollection from the learning sequence (e.g., for the item 'Road': "I feel I saw this word but could not find the exact feelings of when I saw the word, but I am sure that I saw it. I cannot find the background", example adapted from [23]). Subjects lacking confidence in a response could indicate it by means of Guess responses. Testing in this way ensured that K responses given by the subject actually reflected memory processes instead of level of uncertainty. Lastly, as done by Gardiner et al. [23], a procedure was performed to check whether the subjects could justify their R responses, proving that they had effectively relived the original event. Thus, for each R response provided, the subjects were invited to give contextual details from the original event, if they had not already provided them spontaneously (see [48] for further use of this score in dementias). These 'R justified' (RJ) responses refer to correct recognitions associated with R

responses and with, at least, one detail relative to the context of encoding (thoughts, feelings or perceptions, associations of ideas, …).

2.3. Statistical analyses of behavioral data

As the data were not normally distributed, neuropsychological scores of AD patients were compared to those of control subjects using non parametric Mann Whitney U tests. The Bonferoni correction was used to correct for multiple comparisons. For each score, alpha was stringently set at .007, taking into account the 7 comparisons done (or 0.05/7 ~ 0.007). In a second step, we performed Wilcoxon's tests on R and K responses in order to reveal the existence of a different effect of the kind of response (R *vs.* K) according to the group.

2.4. PET methodology

All the patients underwent a resting PET study using [^{18}F] Fluoro-2-deoxy-D-glucose. Data were collected using the high-resolution PET device ECAT Exact HR+ with isotropic resolution of 4.6 x 4.2 x 4.2 mm (field of view = 158 mm). The patients were fasted for at least 4 hours before scanning. The head was positioned on a headrest according to the cantho-meatal line and gently restrained with straps. [^{18}F] Fluoro-2-deoxy-D-glucose uptake was measured in the resting condition, with eyes closed, in a quiet and dark environment. A catheter was introduced in a vein of the arm for radiotracer administration. Following ^{68}Ga transmission scans, 3-5 mCi of [^{18}F] Fluoro-2-deoxy-D-glucose were injected as a bolus at time 0, and a 10 min PET data acquisition period was begun at 50 min post-injection. Sixty-three planes were acquired with septa out (volume acquisition), using a voxel size of 2.2 x 2.2 x 2.43 mm (x, y, z). During PET data acquisition, head motion was monitored continuously with laser beams.

Actual glucose metabolic values in AD patients measured using PET may be underestimated because of brain atrophy, which accentuates the partial volume effect (PVE) on data collected. In order to avoid this bias, the PET data were corrected for PVE due to both cerebro-spinal fluid and white matter using the optimal voxel-by-voxel method originally proposed by Muller-Gartner et al. [41] with slight modifications proposed by Rousset et al. [55] and described in details in Quarantelli et al. [51].

Using statistical parametric mapping (SPM2; Wellcome Dept of Cognitive Neurology, London, UK), the PVE-corrected PET data were subjected to an affine and non-linear spatial normalization into the standard MNI PET template of SPM2, and to a reslicing of 2 × 2 × 2 mm. The spatially normalized sets were then smoothed with a 14 mm isotropic Gaussian filter to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. The "proportional scaling" routine was applied to the PVE-corrected PET data to control for individual variations in global CMRGlc. In order to minimize "edge effects" without excluding hypometabolic tissue in our AD patients, only the voxels with values >40% of the mean for the whole brain were selected for the statistical analysis.

For the sake of completeness, we compared the normalized CMRGlc (nCMRGlc) data set obtained in our sample of 13 AD patients with that obtained in another group of 20 healthy subjects (mean age ± SD = 63.2 ± 8.5 years). The influence of age was controlled by setting age as a confounding variable, and we used the uncorrected $p < 0.001$ ($Z > 3.18$) as cut-off for statistical significance. Table 1 shows the regions with significantly lower nCMRGlc in the group of AD patients, documenting hypometabolism in the precuneus and posterior cingulate gyrus bilaterally, as well as in the parietotemporal and the frontal areas bilaterally. This pattern of hypometabolism is in accordance with previous findings [12,39,43]. There was no significant reduction of CMRGlc values in medial temporal lobes, also in line with previous reports [13,26].

We then looked for correlations between the cognitive scores and resting nCMRGlc metabolism in the whole brain, using SPM and Pearson's correlation test. The influence of age and of the overall dementia severity was controlled by setting age and the MMSE score as confounding variables in a single linear regression. For each score, only the correlations in the neurobiologically expected direction were assessed, using a statistical threshold (uncorrected for multiple tests) of $p<0.001$ for the voxels, to limit the number of statistical tests and the attending risk of false positives. Anatomical localization was according to both the labellized atlas ('toolbox aal') implemented in SPM2 and developed by Tzourio-Mazoyer et al. [65] and Talairach's Atlas, using M. Brett's set of linear transformations (see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

2.5. Hypotheses

We hypothesized that AD patients would be impaired in this recognition task and that recognition would be more based on a feeling of familiarity than on genuine episodic memory (i.e., more K responses and less R ones than controls). Concerning, the neural substrates of these alterations, based on neuroimaging studies carried out in healthy subjects, we hypothesized that correct recognitions associated with a R response would correlate with the metabolism of frontal [17,69] and parietal areas [70] as well as medial temporal structures, notably the hippocampus ([32,69] and for review [72]). In contrast, recognitions associated with a K response would be linked to the metabolism of the cortex surrounding the hippocampus ([61,63] and for review [72]).

3. Results

3.1. Behavioral data

Mann Whitney U tests revealed that patients were significantly impaired on both delayed cued recall and recognition, albeit the difference did not survive the Bonferoni correction (Table 2). From a more qualitative point of view, AD patients also made more errors than healthy subjects as shown by a significant increase in false recognitions. These false recognitions are essentially recognitions of semantic distractors (Table 2). These analyses also revealed a significant effect of the group factor (controls *vs.* AD patients) on R responses ($p<0.001$), a trend for K responses ($p<0.01$), but no effect on G ones (Table 2). It is noteworthy that for R responses (and also for the number of false recognitions), all the patients exhibited performance lower than 1.65 standard deviation from the mean of healthy subjects. Thus, AD patients gave significantly fewer R responses and tended to give more K ones than controls. Then, Wilcoxon's tests were performed on R and K responses in order to reveal the existence of a different effect of response according to the group. Thus, we showed that elderly healthy subjects gave significantly more R responses than K ones ($p<0.01$) while there was no significant difference between the percentage of R and K responses in AD group. Finally, AD patients also exhibited significantly poorer capacities to justify their R responses with details (RJ responses) about the learning context compared to controls (Table 2).

3.2. Correlations between memory scores and nCMRGlc

Since this study focuses on autonoetic consciousness, cognitivo-metabolic correlations were only searched for correct recognitions associated with a R response and compared to those associated with a K response.

The proportion of correct recognitions associated with R responses, relative to the total number of correct recognitions, was significantly and positively correlated to the metabolism of frontal areas in a bilateral and strikingly symmetric manner (Figures 1 and 2, and Table 3).

In contrast, correct recognitions associated with K judgments, relative to the total number of correct recognitions, significantly and positively correlated with the metabolism of the parahippocampal gyrus and temporal neocortex, with a left predominance. Others correlations were also found in the left cuneus and the pre- and post-central gyri (Table 4 and Figures 3 and 4). Interestingly, even at a very liberal statistical threshold ($p<0.05$ uncorrected), no significant correlation between frontal activity and K responses nor between the metabolism of the medial temporal lobes and R responses was found (data not shown).

4. Discussion

We will first discuss the neuropsychological performance and then turn near the neural substrates of the impairment of both autonoetic and noetic consciousness in mild AD.

4.1. Behavioural data

Delayed cued recall performance was lower in the group of patients, in line with previous studies who had demonstrated the sensitivity of delayed recall measures to AD (for review see [3,59]). Recognition performance also strongly decreased as testified by the decrease in correct responses and the significant increase in false recognitions, more particularly for semantic distractors. These poor performances reflect troubles from the encoding phase. AD patients encode and store an insufficient and unspecific representation of the items that does not enable them to characterize each word in an unique way and may result in confusion with other semantically-related items [25].

The patients gave significantly less R responses and tended to give more K ones than controls. These results are in agreement with those reported by Dalla Barba [9] showing a decrease in R responses during free and forced-choice recognition tasks. A diminution of R responses has also been observed in mild AD patients during an autobiographical memory

task [48]. The high number of K responses suggests that recognition is more based on a feeling of familiarity than in controls and concurs with the observation of preserved familiarity processes contrasting with the alteration of recollection in AD [22,35]. These results are also in line with the disruption of recollection reported in patients with medial temporal lobe amnesia [2,66,71], medial temporal lobes being the area earliest and most severely affected by neuropathological lesions in AD [4,10].

RJ responses (R responses justified by details about the encoding context) are a useful measure to better understand the phenomenon of recollection because they prove the existence of the mental travel in time permitting the retrieval of contextual details. Noteworthy, AD patients presented an altered autonoetic consciousness (significant reduction in R responses) and gave very few RJ responses highlighting their major difficulties to recollect contextual details. This result is in line with those obtained using notably the DRM paradigm, that enables to produce high levels of false recognition or recall of a critical non-presented word by presenting to subjects lists of words in which every item is an associate of the critical non-presented word, and demonstrating recollection deficits in AD patients [22]. Since patients are unable to retrieve the specific learning context of an item, they may thus mistake it for a semantically-linked item on the basis of a feeling of familiarity explaining the increase in false recognitions in the group of AD patients compared to elderly controls.

4.2. Neural substrates of the impairment of consciousness in mild AD

As recognition can be made either by re-experiencing the learning episode or on the basis on a feeling of familiarity, we focused our analysis of PET data on correct recognitions associated with R or K responses, reflecting the involvement of autonoetic and noetic consciousness respectively. Significant positive correlations between correct recognitions associated with K responses and CMRGlc were found mainly in the parahippocampal and the

lateral temporal cortices, in line with previous studies ([8,63] and for review see [61]), confirming that familiarity judgments are mainly subserved by the cortex surrounding the hippocampus. In contrast, correct recognitions associated with R responses correlated with the frontal cortex bilaterally (mainly Brodmann area 10). One may hypothesize that the correlation between R responses and the metabolism of frontal areas is modulated by another variable such as an executive dysfunction. Nevertheless, this assumption appears unlikely since a new correlation analysis setting a measure of executive functions (backward digit span) as confounding variable yielded similar results (data not shown). This result indicates that the correlation with frontal areas is not related to an executive dysfunction nor to overall severity of dementia, since all correlations were searched setting the MMSE score as confounding variable, but actually reflects the impairment of autonoetic consciousness.

The correlation with frontal areas is in line with other studies obtained with various methodological approaches. Thus, it has been shown that patients with frontal lesions present deficits during source (or contextual) memory tasks, thought to rely mainly on recollection [30,52]. In the same way, frontal dysfunction also induce reductions in R judgments during episodic [36] and autobiographical [50] memory tasks. Event-related potentials studies have also strengthen the role of frontal areas in recollection since R responses have been consistently associated with a late frontal positivity ([16,17] and for review see [56]). This correlation with frontal areas may reflect the involvement of monitoring processes in recognition tasks [7] as well as effortful retrieval [58] and successful recollection [27] processes. Based on these arguments, we suggest that the recruitment of frontal areas, particularly involved in effortful and monitoring processes, may be a crucial step in the initiation of the process of recollection.

Other studies carried out in healthy subjects suggested that the frontal cortex is not the only area involved in recollection and that medial temporal lobe structures, notably the

hippocampus, may also take part to this phenomenon (for review see [61], but see also [37] for divergent findings). Thus, Ranganath et al. [53] have demonstrated that neural activity in the rhinal cortex during encoding predicts subsequent familiarity-based recognition whereas activity in the hippocampus and posterior parahippocampal cortex selectively predicts recollection (associated with autonoetic consciousness). Episodic memories are composed of several elements (event, perceptions, smells,…) stored in various cortical areas, but all linked by the hippocampus that serves as an index to retrieve all the facets of the memory [20,42,49,60]. The fact that we do not report any significant correlation between R responses and the metabolism of the hippocampus might suggest that AD patients do not recollect contextual details and only have the subjective feeling of reliving the event, i.e. 'sense of pastness' but no recollection of the episodic details. This suggestion is supported by the difficulties of AD patients to justify their R judgments with specific details of the encoding context. Our results are also corroborated by an observation reported by Budson and colleagues [5,6] who demonstrated, using an adaptation of the DRM paradigm, that AD patients were unable to suppress their false recognitions over trials due to an inability to develop any item-specific recollection. We suggest that frontal areas may subserve this impression of reliving the original event (i.e., autonoetic consciousness) but not the access to contextual elements *per se*.

We do not report any significant correlation with parietal areas that are generally activated during recollection (e.g., [18,27,70,73] and for review [67]). Our data suggest therefore that the dysfunction of frontal areas explains to a large extent the impairment of autonoetic consciousness observed in our group of AD patients. Nevertheless, as suggested by the literature in healthy subjects, we cannot exclude than other brain areas are also involved in the disruption of autonoetic consciousness in AD.

On a more clinical point of view, our results extend our knowledge of the neural substrates of memory impairment in AD by focusing on more subtle measures of memory performance and targeting specific cognitive components. Such investigations should also provide a detailed analysis of residual abilities, which could be then used to help patients in their everyday life activities despite their anterograde amnesia. Indeed, therapeutic strategies in AD patients designed to increase dependence on familiarity-based memory in daily living may help to cope, at least in the early stages of the disease, with the consequences of memory decline [68]. In addition, as autonoetic consciousness is critical to shape one's own identity and a feeling of continuity, data about recollection and familiarity processes could also inform us on the interest of further investigations on self awareness, often impaired in AD [1], by means of autobiographical memory tasks for example.

To conclude, we have shown that AD patients presented poor recognition performances linked, in part, to an alteration of autonoetic consciousness and to major difficulties to reinstate the context in which information was encoded. Using voxel-based mapping of the correlations between memory performance and resting-state cerebral metabolism measured by PET, we have shown that their impairment of autonoetic consciousness is mainly subserved by the dysfunction of frontal areas. This result suggests that frontal areas are crucial in the subjective feeling of reliving an event (i.e. "reliving" component of episodic memory). However, since AD patients were unable to justify their R responses with details concerning the context of encoding (other than the cue given by the experimenter), we suggest that frontal areas together with, at least, medial temporal lobes and parietal areas, may be necessary to achieve a genuine episodic recollection comprising the event itself, the mental travel in time and phenomenological details. In addition, as frontal areas are particularly involved in monitoring processes during recognition tasks [7], effortful retrieval [58] and successful recollection [27], we suggest that a dysfunction, even subtle, of these areas may disrupt the

effortful process of research in memory that is critical to enable a subject to have access, in a second step, to the contextual details of a memory. These results remain nevertheless to be confirmed on a larger sample of patients using, for example, event-related fMRI.

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Figure captions

Table 1:

The influence of age was controlled by setting age as a confounding variable, and we used the uncorrected $p < 0.001$ ($Z > 3.18$) as cut-off for statistical significance. BA: Brodmann area; x, y, z : MNI space stereotactic coordinates of the peak in mm; L: left; R: Right; n= 13 for AD patients; n= 20 for healthy elderly subjects. Significant $P< 0.001$, uncorrected.

Table 2:

Neuropsychological data in the AD group were compared to those obtained in the group of ten elderly control subjects, using non parametric Mann-Whitney U tests, and were corrected for multiple comparisons using Bonferoni correction.

Table 3:

BA: Brodmann area; x, y, z : MNI space stereotactic coordinates of the peaks in mm; L: left; R: Right. The clusters are listed in decreasing order of peak Z-score. Significant $P< 0.001$, uncorrected.

Table 4:

BA: Brodmann area; x, y, z : MNI space stereotactic coordinates of the peaks in mm; L: left; R: Right. The clusters are listed in decreasing order of peak Z-score. Significant $P< 0.001$, uncorrected.

Figure 1:

SPM2 surface rendering depicting in red the significant ($P<0.001$, uncorrected) clusters of significant positive correlations, in 13 AD patients, between the proportion of correct

recognitions associated with a R judgment and nCMRGlc (normalized resting-state cerebral metabolic rates of glucose), controlling for the confounding effect of age and of dementia severity (MMSE score), projected on a standard T1-weighted MRI for anatomical orientation, according to six views indicated on the side of each image.

Figure 2: Scatter plots of the correlations between nCMRGlc values and the proportion of correct recognitions associated with a R judgment, in left (-32 54 2) and right (30 54 10) frontal areas.

Figure 3: Results from SPM2 analysis: positive correlations ($P<0.001$ uncorrected, SPM maps thresholded at $Z> 3.26$) between the proportion of correct recognitions associated with a K response and nCMRGlc controlling for the confounding effect of age and of dementia severity (MMSE score). For anatomical orientation, the significant correlations are shown as coloured voxels superimposed on a normal MRI set spatially normalized on the Montreal Neurological Institute (MNI) template. The MRI set has been cut out to show only the analysed voxels, i.e. in which nCMRGlc was >40% of mean nCMRGlc across all patients. The right side of the figure corresponds to the right hemisphere.

Figure 4: Example of a scatter plot of the correlations between nCMRGlc values and the number of correct recognitions associated with a K response in the left parahippocampal gyrus (-22 –14 -26).

Table 1: Significant decreases in normalized regional metabolic activity in AD patients compared with healthy subjects.

Regions		Cluster size (no. of voxels)	BA	x	y	z	Z
R	precuneus	1740	7/31/19	8	-52	30	5.3
L	precuneus						
R	middle cingulate gyrus						
L	posterior cingulate gyrus						
L	cuneus						
L	middle cingulate gyrus						
R	posterior cingulate gyrus						
R	cuneus						
L	inferior temporal gyrus	302	20/21	-50	14	-40	4.58
L	middle temporal gyrus						
L	inferior parietal gyrus	539	40	-36	-54	42	4.24
L	angular gyrus						
L	insula	478	22/42	-38	-16	8	4.22
L	superior temporal gyrus						
L	Heschl gyrus						
L	rolandic operculum						
R	angular gyrus	1340	40	48	-62	46	4.10
R	inferior parietal gyrus						
R	supramarginal gyrus						
R	middle frontal gyrus	84	11	28	46	-18	3.48
R	inferior frontal gyrus						
L	superior temporal gyrus	35	42/22	54	-32	20	3.40
L	supramarginal gyrus						
L	middle frontal gyrus	41	10	-32	48	2	3.37
L	inferior frontal gyrus						

Table 2: Neuropsychological performance of the AD patients and elderly controls.

Neuropsychological score	Alzheimer's patients		Elderly controls	
	Mean ± SD	Median (range)	Mean ± SD	Median (range)
Delayed cued recall (max 15)	10.1 ± 3.7 (a)	10 (4 -15)	14.7 ± 0.7	15 (13 -15)
Correct recognitions (max 15)	12.8 ± 2.3	14 (9 -15)	14.6 ± 0.7	15 (13 -15)
False recognitions	7 ± 4.4***	6 (1 -17)	0.2 ± 0.4	0 (0 -1)
- % of FR for semantic distractors	82.9	x	100	x
- % of FR for neutral distractors	17.1	x	0	x
% of R responses (on correct recognitions)	44.1 ± 32.6***	33.3 (0 -100)	94 ± 5.8	93.3 (86.6 -100)
% of K responses (on correct recognitions)	38 ± 34.4 (a)	22.2 (0 -100)	3.5 ± 4.8	0 (0 -13.3)
% of G responses (on correct recogntions)	11.6 ± 18.1	0 (0 -55.5)	0.7 ± 2.1	0 (0 -6.6)
% of RJ responses (on correct recognitions)	1.1 ± 2.7***	0 (0 -7.7)	39.3 ± 27.4	40 (0 -78.6)

*** : p<0.001, corrected for multiple comparisons.

(a) : p<0.01

*

t

Table 3: Peaks of significant correlations between the proportion of correct recognitions associated with a R response and nCMRGlc.

Region	Cluster size (number of voxels)	BA	x	y	z	Z
L middle frontal gyrus	1428	10	-32	54	2	4.72
L superior frontal gyrus						
L frontal superior orbital gyrus						
L frontal middle orbital gyrus						
R middle frontal gyrus	1190	10	30	54	10	4.47
R superior frontal gyrus						
R frontal superior orbital gyrus						
R frontal middle orbital gyrus						
R median superior frontal gyrus	96	8	14	50	44	4.27
R superior frontal gyrus						
L frontal inferior orbital gyrus	44	47	-48	46	-14	3.33
L frontal middle orbital gyrus						

Table 4: Peaks of significant correlations between the proportion of correct recognitions associated with a K judgment and nCMRGlc.

Region	Cluster size (number of voxels)	BA	x	y	z	Z
L parahippocampal gyrus	232	28/36	-22	-14	-26	3.96
L Hippocampus						
L fusiform gyrus						
L postcentral gyrus	47	3/4	-24	-32	56	3.88
L precentral gyrus						
R temporal pole: middle temporal gyrus	20	38	24	14	-36	3.36
R temporal pole: superior temporal gyrus						
R postcentral gyrus	45	4	16	-26	62	3.35
R precentral gyrus						
R temporal inferior gyrus	20	20	50	-30	-32	3.31
L calcarine region	46	18	-10	-78	16	3.26
L cuneus						

Figure 1 :

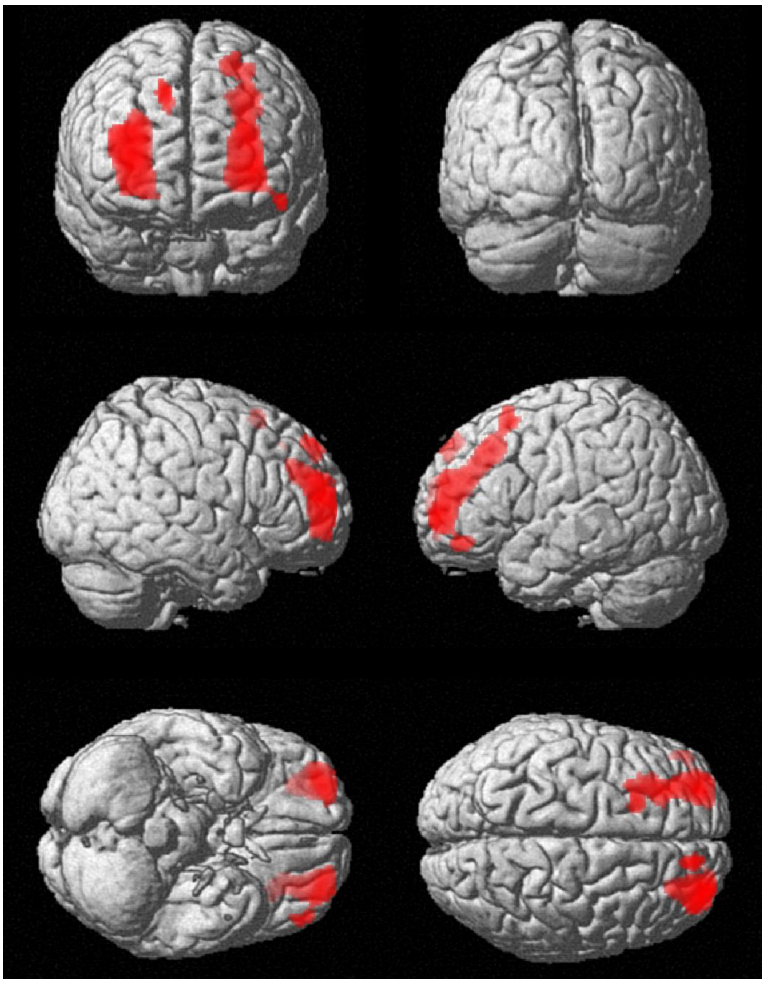
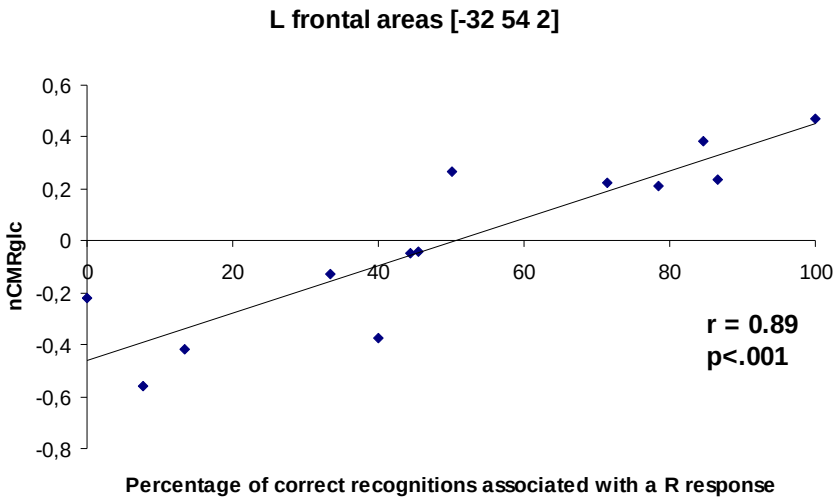


Figure 2 :


L frontal areas [-32 54 2]
nCMRglc
0,6
0,4
0,2
0
-0,2
-0,4
-0,6
-0,8
0
20
40
60
80
100
r = 0.89
p<.001
Percentage of correct recognitions associated with a R response

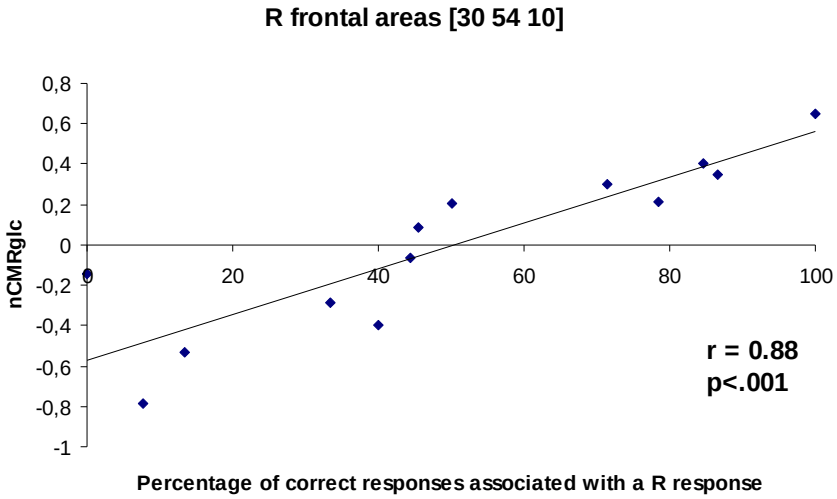

R frontal areas [30 54 10]
nCMRglc
0,8
0,6
0,4
0,2
0
-0,2
-0,4
-0,6
-0,8
-1
0
20
40
60
80
100
r = 0.88
p<.001
Percentage of correct responses associated with a R response

Figure 3 :

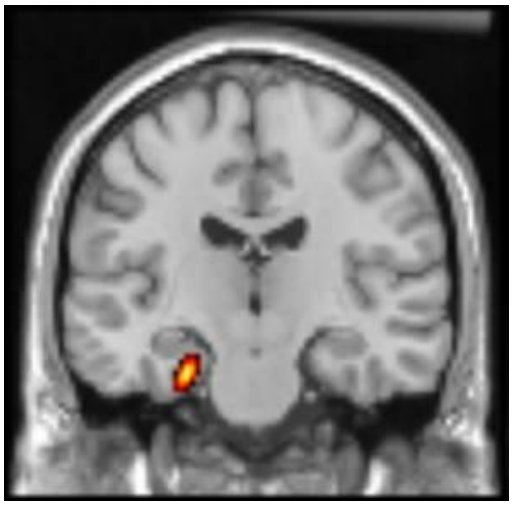
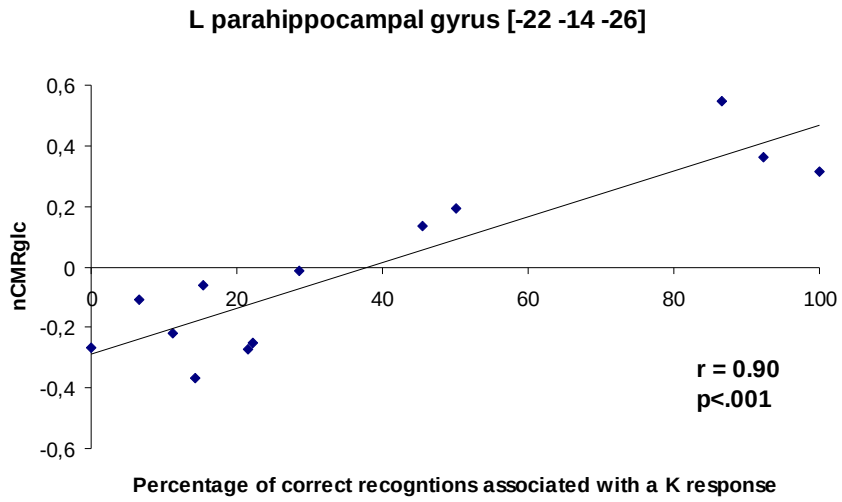


Figure 4 :


L parahippocampal gyrus [-22 -14 -26]
nCMRglc
0,6
0,4
0,2
0
-0,2
-0,4
-0,6
0
20
40
60
80
100
r = 0.90
p<.001
Percentage of correct recogntions associated with a K response