‘In the course of time’: a PET study of the cerebral substrates of autobiographical amnesia in Alzheimer’s disease

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Summary

Neuroimaging studies in healthy subjects have yielded controversial results about the neural substrates of autobiographical memory. Moreover, the neural networks responsible for autobiographical amnesia remain poorly understood. Since autobiographical memory is frequently altered in Alzheimer’s disease (AD), we used this degenerative disorder as a model and applied a correlational approach between resting cerebral glucose utilization (CMRGlc) and temporally graded memory scores to identify the cerebral structures whose synaptic dysfunction subserves the impairment in autobiographical memory. To this end, we studied a group of 17 AD patients with mild to moderate dementia in whom autobiographical memory was assessed using a specially designed task from three broad time periods [the previous 5 years (period A); middle age (period B); and teenage and childhood (period C)], and measures of resting CMRGlc were obtained with PET. The patients performed less well than a control group for all three time periods and showed the expected temporal gradient, with the most remote period being best preserved (Ribot’s gradient). Qualitative analysis showed that remote memories concerned generic (i.e. semantic) rather than specific (i.e. episodic) events. We found a significant positive correlation between autobiographical scores and the metabolism of the right hippocampus (extending to the lingual gyrus), restricted to period A. In addition, period A scores were significantly correlated with the right middle and inferior frontal gyri and the right middle temporal gyrus. Period B scores correlated chiefly with the prefrontal cortex bilaterally (bilateral superior, bilateral middle and right inferior gyri). Metabolic correlations with period C scores were restricted to the left middle frontal gyrus. These findings show striking differences in metabolic correlations with the autobiographical time period, in agreement with prevalent theories of normal functioning of human memory. Thus, in accordance with theories of long-term memory consolidation, we find the expected implication of the hippocampal region in the recall of recent memories, and a disengagement of this structure when the retention interval is beyond 5 years. Moreover, according to the hemispheric encoding/retrieval asymmetry model based on activation studies in healthy subjects, the fact that recent memories preferentially involved the right prefrontal cortex whereas remote memories involved the left prefrontal cortex supports the notion of semanticization of memories with time interval, such that preserved remote memories in AD have a predominantly semantic character.

Keywords: autobiographical memory; episodic memory; semantic memory; retrograde amnesia; Alzheimer’s disease; hippocampus; frontal lobes; consolidation; SPM; PET

Abbreviations: AD = Alzheimer’s disease; CMRGlc = cerebral glucose utilization; EMT = episodic memory test; SPM = statistical parametric mapping; nCMRGlc = normalized cerebral glucose utilization; SKT = semantic knowledge test

Introduction

Despite the numerous studies carried out in neuropsychology and functional neuroimaging, the neurobiological bases of long-term memory consolidation remain largely unknown (McGaugh, 2000). Activation studies of memory processes have been useful in unravelling the neural bases of active processes (i.e., encoding and retrieval; for reviews see Desgranges et al., 1998a; Cabeza and Nyberg, 2000), but explore with greater difficulty the temporally distributed processes involved in storage and consolidation (Buckner and Koutstaal, 1998), and implementing the activation paradigm in this field has proved particularly difficult (Maguire, 2001a). As a consequence, the results regarding the cerebral regions involved in autobiographical memory have remained unclear (Fink et al., 1996; Conway et al., 1999; Maguire and Mummery, 1999; Maguire et al., 2001; Ryan et al., 2001; Niki and Luo, 2002; Tsukurie et al., 2002; Maguire and Frith, 2003a, b; Pieck et al., 2003). Regarding autobiographical recollection regardless of the time interval, a role for the hippocampal region has been emphasized recently (Tulving, 1989; Conway et al., 1999; Nadel et al., 2000; Ryan et al., 2001; Maguire et al., 2001; but see Haist et al., 2001; Niki and Luo, 2002; Pieck et al., 2003), but the interpretation of this observation remains controversial because when old memories are recalled, they are encoded once again (Persson and Nyberg, 2000; Buckner et al., 2001). Thus, hippocampal activation could reflect the processing of encoding and not the access per se to old memories. The associated activation of the frontal lobes (notably left; see Conway et al., 1999; Maguire and Mummery, 1999) would be also consistent with this hypothesis. Indeed, in the theoretical framework of the HERA (hemispheric encoding/retrieval asymmetry) model (Tulving et al., 1994; Habib et al., 2003), the left prefrontal cortex is involved preferentially in the processing of encoding in episodic memory.

Studies of amnesic patients (for reviews see Conway and Fthenaki, 2000; Kopelman and Kapur, 2001; Kopelman, 2002) have given interesting results and are at the source of the modern neurobiological models of long-term memory consolidation (McClelland et al., 1995; Squire and Alvarez, 1995; Murre, 1996; Teng and Squire, 1999; Bayley et al., 2003). According to these theories, the medial temporal lobe, especially the hippocampus, would be involved in the consolidation and in the retrieval of declarative knowledge (in interaction with neocortical areas) during several years [from a few years (Graham and Hodges, 1997), to 10 years (Reed and Squire, 1998), and >10 years (Rempel-Clower et al., 1996)], by ‘binding’ together the multiple cerebral areas that constitute a memory representation. After this period of consolidation, the retrieval of declarative knowledge (episodic and semantic) would be subserved mainly by neocortical regions. However, recent evidence provided by case studies suggests that the hippocampus may be involved in the storage and retrieval of episodic memories regardless of their remoteness (Nadel and Moscovitch, 1997; Fujii et al., 2000; Nadel et al., 2000; Cipolotti et al., 2001; Rosenbaum et al., 2001). Thus, an alternative explanation, termed the ‘multiple trace theory’, has been proposed recently (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1998; Nadel et al., 2000). This theory concurs with the standard model of consolidation for semantic memory, but suggests that the medial temporal lobe plays a permanent role in the recovery of episodic memories regardless of their remoteness. The hippocampus would be involved specifically in the recollection of detailed contextual information such as place, time, temporal sequence, emotional content and perceptual features. Despite its substantial interest, the classic clinico-anatomical method (using structural imaging) is unable to reveal functional changes within these circuits, such as the functional impairment that occurs in structures remote from but connected to the area of primary damage (Feeney and Baron, 1986). Conversely, PET allows the study of physiological parameters such as resting state glucose consumption, which is closely related to synaptic activity and is thus able to identify dysfunction of the neural networks involved in amnesia (Aupée et al., 2001). A powerful approach entails obtaining, within a short time interval (a few days at most), both cognitive tests scores and resting state glucose metabolism. Correlations between these two sets of data across a group of patients can then be computed voxel-wise to map the functional neuroanatomy of the cognitive deficits that characterizes a given disease or syndrome, notably in the field of neurodegenerative diseases where there is a large variability concerning both cognitive performance and cerebral dysfunction (Eustache et al., 2000). This method therefore opens up new avenues in functional neuropsychology, in subjects without focal lesions detectable by the usual structural imaging techniques. Over and above its applications in neurological research, this method is particularly useful for establishing cognitive and neurobiological models of human memory, because it allows the mapping of the neural networks that are essential for memory function. This neural network revealed by the cognitive–metabolic approach can be considered as indispensable to memory functioning because it is directly based in the occurrence of variable but striking memory deficits [notably in neurodegenerative diseases such as Alzheimer’s disease (AD)]. This approach has been used with success in AD to reveal the cerebral structures whose synaptic pathology dysfunction underlies the alteration of different memory systems (Perani et al., 1993; Desgranges et al., 1998b, 2002a, b; Eustache et al., 2001). It is worth noting that the sites of the correlations are related to the severity of dementia, and consequently, during the evolution of the disease, these sites can pin down the cerebral structures implicated in (even if inadequate) compensatory mechanisms (Desgranges et al., 2002a). However, interestingly for the purpose of this study, at a mild to moderate stage of dementia, these maps broadly correspond to the cerebral regions involved in the functioning of memory in normal subjects (Eustache et al., 2001; Desgranges et al., 2002a). By inference, in a formal
theoretical framework, this method can therefore highlight the normal functioning of memory, and this paradigm forms the rationale of the present study of autobiographical memory. In AD, an impairment of autobiographical memory is frequent, though sufficiently variable from patient to patient (Kopelman, 1992; Greene et al., 1995; Graham and Hodges, 1997; Nestor et al., 2002; Piolino et al., 2003a); consequently, using the cognitive–metabolic approach in early AD to reveal the networks subserving autobiographical memory seems particularly relevant.

The aim of the present study was therefore to unravel the cerebral structures involved in the disruption of retrieval of autobiographical memories according to their remoteness in early AD. Specifically, our purpose was to test the putative central role of the whole hippocampus in memory retrieval with respect to the two main theories of long-term memory consolidation (i.e. ‘standard’ and ‘multiple trace’ theories), by means of voxel-based mapping of the correlations between autobiographical memory scores and resting state brain glucose utilization. To this end, memory scores using a novel and reliable task specially designed to assess episodic autobiographical memory throughout three lifetime periods and resting state brain glucose metabolism were both obtained within a short time interval. According to the standard model, which postulates a temporary involvement of hippocampus (in interaction with neocortical areas) in retrieval of declarative memories (either episodic or semantic), we predicted in early AD (where the medial temporal lobe is principally affected) a major involvement of the hippocampus in the retrieval of memories of the most recent lifetime period compared with the other time periods. As predicted by multiple trace theory, this profile would be characteristic of semantic memory, whereas episodic memory would involve the hippocampus regardless of the lifetime periods. Regarding the neocortical regions, we predicted their predominant involvement in the retrieval of memories of the two most remote lifetime periods.

Material and methods

Patients

Seventeen unmedicated AD patients were studied (six men and 11 women; age = 72.8 years; SD = 5.2), all right-handed and with at least 8 years of education. All were selected prospectively on the basis of a neurological examination and a neuropsychological assessment, and using the NINCDS-ADRDA criteria for probable Alzheimer’s disease (McKhann et al., 1984). Standard laboratory examinations were normal for all of them, and structural imaging (with MRI or CT) showed no focal abnormality.

For this study, we purposely selected patients with mild to moderate dementia, based on the Mini-Mental State Examination (Folstein et al., 1975) (mean = 22.2; SD = 2.3) and the Mattis scale (Mattis, 1976) (mean = 119.4; SD = 8.9). Within an interval of 14 days on average, each patient underwent a neuropsychological examination with an experimental assessment of autobiographical memory and a PET measurement of resting cerebral glucose utilization (CMRGlc). Moreover, in order to characterize the well-established atrophy in the AD patients, grey matter loss was mapped by means of voxel-based morphometry on T1-weighted MRI volume sets. The results (for details see Baron et al., 2001) from the AD group (with two additional patients) compared with 16 controls showed a grey matter loss affecting bilaterally and mainly the medial temporal lobe, posterior cingulate gyrus and temporoparietal region, and to a lesser degree the frontal lobe. This profile is consistent with subsequent MRI studies (Good et al., 2002; Busatto et al., 2003; Karas et al., 2003) as well as with histological data in mild to moderate AD (Delacourte et al., 1999).

The patients gave their informed consent to the study, which was done in line with the Declaration of Helsinki, and the PET procedure was approved by the Ethical Committee of the University of Caen.

Neuropsychological assessment

For all the patients, in addition to the Mini-Mental State Examination and Mattis scale, a neuropsychological examination was used to explore explicit semantic memory by means of a word fluency task in which the subject is asked to produce in 2 min as many words as possible (Cardebat et al., 1990) that comply with certain categories (names of animals or fruits, i.e. semantic fluency) or orthographic (words beginning with P or R, i.e. formal fluency) and a semantic knowledge test (SKT; Giffard et al., 2001). The latter, which is derived from Martin’s protocol (Martin et al., 1986) and Desgranges et al. (1996, 1998a), involves three components (i.e. picture naming, categorical knowledge and attribute knowledge of concepts) of 30 concepts belonging to four categories (animals, plants, objects and body parts). First of all, subjects have to name 30 drawings corresponding to the 30 concepts or recognize the name if they cannot do so. They then have to answer ‘yes’ or ‘no’ to a series of questions about the concepts: superordinate category (‘does it occur naturally or is it manmade?’), category membership (‘is it an animal, plant, object or body part?’), subcategory (‘is it a domestic or a wild animal?’) and specific attribute, either functional (‘is it edible?’) or perceptual (‘does it have a mane?’).

A verbal episodic memory test (EMT; Eustache et al., 2001), derived from the procedure of Grober and Buschke (1987), was conducted in order to examine episodic learning, using words whose semantic integrity had been checked previously in the SKT. The subjects learned 15 items presented three at a time on a card, pointing out and naming each item when its category cue was presented verbally. They were then asked for an immediate verbal cued recall. If a subject failed to recall an item, the card was shown again. This encoding phase was followed by three recall tests: first a free recall and, if necessary, a categorical cued recall test, then a recognition memory test. Each trial was preceded by a 20 s delay, during which patients were asked to count backwards. After 20 min, delayed free and cued recalls were tested.

Moreover, verbal episodic memory was tested by the immediate recall of a story (story recall), and visual episodic memory by the reproduction of a geometrical figure (figure reproduction), both taken from Signoret’s ‘Batterie d’efficience mnésique’ (Signoret, 1991).

The three components of working memory (Baddeley, 1991) were evaluated by the serial repetition of a series of digits (verbal span to assess the phonological loop), and the reproduction of spatial sequences (visuospatial span to assess the visuospatial sketchpad), also taken from Signoret’s battery, and a task (Eustache et al., 1995) derived from the Brown–Peterson paradigm (Peterson and Peterson, 1959) to assess the central executive system. In this latter task, the
subject had to read three monosyllabic words per card (25 cards), disposed vertically. Then, after turning over the card revealing a number, he had to count backward two by two starting from this number, for a variable delay (0–18 s), and to recall words immediately.

For this neuropsychological protocol, two groups of strictly age- and education-matched healthy control subjects, with a minimum level of 8 years of primary education, were recruited in retirement homes. On one hand, a group of 20 controls subjects (mean age = 70.60 years; SD = 5.83) performed the verbal EMT and the SKT and, on the other hand, a group of 30 controls (mean age = 70.70; SD = 9.88) undertook the other tests.

The neuropsychological examination (Table 1) revealed that the AD group showed severe disturbance of episodic anterograde memory, as well as working memory, consistent with previous studies on AD patients (Desgranges et al., 1996, 1998b; Hodges et al., 1999). Episodic memory performance revealed a disturbance of encoding mechanisms (immediate recall) which is characteristic of AD (Pasquier et al., 2001). Furthermore, the patients showed semantic memory difficulties, with anomia and impoverished general knowledge on concepts, especially for specific attributes, which corroborate previous works highlighting that semantic memory is impaired early in the course of AD (Hodges and Patterson, 1995).

### Table 1 Neuropsychological data (mean ± SD) for the AD patients and the controls

<table>
<thead>
<tr>
<th>Tests</th>
<th>AD</th>
<th>Controls</th>
<th>Group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>27.70 (9.38)</td>
<td>40.63 (9.83)</td>
<td>***</td>
</tr>
<tr>
<td>Formal fluency</td>
<td>27.70 (13.30)</td>
<td>35.87 (10.15)</td>
<td>*</td>
</tr>
<tr>
<td>SKT: naming (/60)</td>
<td>58.04 (1.47)</td>
<td>59.34 (0.74)</td>
<td>**</td>
</tr>
<tr>
<td>SKT: categorical knowledge</td>
<td>84.99 (0.86)</td>
<td>84.74 (1.01)</td>
<td>ns</td>
</tr>
<tr>
<td>SKT: attribute knowledge</td>
<td>86.94 (0.96)</td>
<td>87.94 (1.18)</td>
<td>**</td>
</tr>
<tr>
<td>Episodic memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Story recall</td>
<td>2.67 (1.47)</td>
<td>6.22 (2.12)</td>
<td>***</td>
</tr>
<tr>
<td>Figure reproduction</td>
<td>2.79 (1.67)</td>
<td>7.05 (2.17)</td>
<td>***</td>
</tr>
<tr>
<td>EMT: immediate recall (/15)</td>
<td>13.12 (1.5)</td>
<td>15.00 (0.00)</td>
<td>***</td>
</tr>
<tr>
<td>EMT: total recall (/45)</td>
<td>28.37 (7.88)</td>
<td>43.85 (1.18)</td>
<td>***</td>
</tr>
<tr>
<td>EMT: delayed recall (/15)</td>
<td>9.5 (4.32)</td>
<td>14.90 (0.31)</td>
<td>***</td>
</tr>
<tr>
<td>EMT: recognition (/45)</td>
<td>37.25 (5.63)</td>
<td>44.05 (1.39)</td>
<td>***</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal span</td>
<td>5.23 (1.20)</td>
<td>6.00 (0.83)</td>
<td>*</td>
</tr>
<tr>
<td>Visuospatial span</td>
<td>4.17 (0.73)</td>
<td>5.53 (1.07)</td>
<td>***</td>
</tr>
<tr>
<td>Brown–Peterson paradigm</td>
<td>33.17 (14.06)</td>
<td>60.80 (11.78)</td>
<td>***</td>
</tr>
</tbody>
</table>

Differential effects between the AD patients and controls are reported (ANOVA). ns = non-significant; *P < 0.05; **P < 0.01; ***P < 0.001. The results of a one-way ANOVA (group) are shown according to performances on each test. Data are provided for the 17 AD patients [except for the test derived from the Grober and Buschke test (EMT), n = 16] and two groups of controls: a group of 20 control subjects (for EMT and SKT) and a group of 30 controls (for the other tests).

### Experimental autobiographical memory protocol

Autobiographical memory was assessed with a sophisticated novel personal event task derived from Kopelman et al. (1989), Borrini et al. (1989) and Piolino et al. (2003a, b). Three broad time periods were examined: the previous 5 years except the last 12 months (period A); middle age (period B); and teenage and childhood (period C). For each period studied, subjects were required to produce specific detailed personal event memories and to state when and where the event happened, regarding four topics: a meeting or an event linked to a person; a school and a professional event; a trip or journey; and a family event. Subjects were instructed to describe personal events in as much details as they could. For example, ‘relate precisely a particular event which took place in your family life during the previous 5 years’. If the subject could not recollect a specific event spontaneously, cues were provided and/or encouragement given to be specific when the memory was generic (without a specific spatio-temporal context such as a repeated or extended event). After three trials of cueing and/or encouragement, another topic was proposed. A re-test was carried out 15 ± 2 days after the task, in order to check each memory. This consisted of a cued recall task where subjects had to recall in random order the content and the time and spatial location of each recollected event. When possible, a family member also checked each memory.

Each event was scored on a 4-point episodic scale based on that of Baddeley and Wilson (1986), which takes into account the specificity of the content (single or repeated event), spatio-temporal situation and the presence of details (perceptions, thoughts, feelings, etc.). A specific event with details situated in time and space was given a score of 4 points. For example: ‘I was informed of my unemployment by a colleague. I was 56 years old and 3 months...that day, I worked at the shop of fruits and vegetables and we had received important documents from the director. Thus, all employees were summoned at syndicate head-office. But, I could not leave my work because I must help customer. When my colleague came back, she said to me: ‘well, L. you’re unemployed!’ I asked: “It’s because I didn’t go to the meeting?” She answered: “No, you’re too old!” It was in September, in a morning because we had to deliver the bad news immediately. A specific event without detail situated in time and space was given a score of 3 points. A repeated or extended event was given a score of 2 points or 1 point according to whether or not it was situated in time and space. For example: ‘I was

All patients underwent a PET study using [18F]fluoro-2-deoxy-D-glucose. Data were collected using the high-resolution PET device ECAT Exact HR+ with isotropic resolution of 4.6 × 4.2 × 4.2 mm [FOV (field of view) = 158 mm]. The patients were fasted for at least 4 h before scanning. The head was positioned on a headrest according to the cantho-meatal line and gently restrained with straps. [18F]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 68Ga transmission scans, 3–5 mCi of [18F]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 (acquisition), using a voxel size of 2.2 × 2.2 × 2.2 mm. During PET data acquisition, head motion was monitored continuously with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn over the skin of the forehead.

In order to control for the variance in global CMRGlc, the CMRGlc images were divided pixel by pixel by the individual value for the cerebellar vermis, yielding normalized CMRGlc (nCMRGlc) images (Desgranges et al., 1998b, 2002a, b).

### Voxel-based analysis

The nCMRGlc images were transferred to a SUN workstation. Manipulations of the image matrix (stereotaxic normalization) and statistical calculations were carried out with MATLAB (Mathworks Inc., Sherborn, MA). With the Statistical Parametric Mapping 99 (SPM99) software (Wellcome Department of Imaging Neuroscience), individual images were transformed into Montreal Neurological Institute (MNI) stereotactic space, and smoothed in three dimensions using a three-dimensional Gaussian filter of 14 mm. In order to minimize ‘edge effects’ without excluding hypometabolic tissue in our AD subjects, only those voxels with values >40% of the mean for the whole brain were selected for the statistical analysis (Desgranges et al., 1998b).

For the sake of completeness, we compared the nCMRGlc data set obtained in our sample of 17 AD patients with that obtained in a group of 13 strictly healthy subjects (mean age = 63.8 ± 9.4 years). The influence of age was controlled by setting age as the confounding variable, and we used the uncorrected P < 0.001 (Z ≥ 3.09) as cut-off for statistical significance. Table 2 shows the regions with significantly (P < 0.001, uncorrected) lower nCMRGlc in the patients group, documenting the expected hypometabolism in the inferior parietal lobule, precuneus and posterior cingulate gyrus, bilaterally, as well as in the left inferior temporal gyrus and the right superior frontal gyrus. This pattern of hypometabolism is in accordance with previous findings (for reviews, see for example Minoshima et al., 1994; Ibanez et al., 1998; Demetriades, 2002; Wolf et al., 2003).

Then, we looked for correlations between the cognitive scores obtained for each period and resting nCMRGlc metabolism using

### Table 2  Significant decreases in normalized regional metabolic activity in AD patients compared with healthy subjects

<table>
<thead>
<tr>
<th>Regions</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z</th>
<th>Cluster size (no. of voxels)</th>
<th>Corrected P (cluster level)</th>
<th>Corrected P (voxel level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L inferior parietal lobule</td>
<td>40</td>
<td>-42</td>
<td>-64</td>
<td>40</td>
<td>4.76</td>
<td>7145</td>
<td>0.000</td>
<td>0.01</td>
</tr>
<tr>
<td>R inferior parietal lobule</td>
<td>40</td>
<td>42</td>
<td>-66</td>
<td>46</td>
<td>3.37</td>
<td></td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>-54</td>
<td>43</td>
<td>3.22</td>
<td></td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>-50</td>
<td>41</td>
<td>3.20</td>
<td></td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>L inferior temporal gyrus</td>
<td>37</td>
<td>-53</td>
<td>-66</td>
<td>2</td>
<td>4.24</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>L precuneus</td>
<td>7</td>
<td>-10</td>
<td>-61</td>
<td>33</td>
<td>4.42</td>
<td></td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>R precuneus</td>
<td>7</td>
<td>20</td>
<td>-58</td>
<td>40</td>
<td>4.14</td>
<td></td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>R posterior cingulate</td>
<td>31</td>
<td>-4</td>
<td>-39</td>
<td>31</td>
<td>3.96</td>
<td></td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>R superior frontal gyrus</td>
<td>8</td>
<td>30</td>
<td>51</td>
<td>40</td>
<td>3.34</td>
<td></td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>L ant cingulate</td>
<td>24</td>
<td>-12</td>
<td>33</td>
<td>8</td>
<td>3.20</td>
<td></td>
<td>0.82</td>
<td>0.84</td>
</tr>
</tbody>
</table>

BA = Brodmann area; x, y, z = coordinates of peaks in Talairach’s system; L = left; R = right; n = 17 for AD patients; n = 13 for healthy controls. Significant P < 0.001, uncorrected. (Corrected values are also indicated in the table.)

young when my brothers showed me how to ride a bicycle; they held me and then let me go. I so much wanted to get my own bicycle!’ Absence of memory or general information about a topic was given a score of 0. Recollections scoring 4 referred to strictly episodic memories, whereas other kinds of recollections referred rather to personal semantic memories (Graham and Hodges, 1997; Piolino et al., 2003a). Even specific non-detailed memories (a score of 3) were not truly episodic since the details alone made it possible to assess reliably whether a memory had an episodic character (Moscovitch et al., 1999).

An autobiographical memory score (maximum 4 × 4 = 16) which takes into account all types of recall, both specific and generic, was recorded per lifetime period examined. This score was established on the basis of the information supplied in the test and corroborated in the re-test and, when possible, by a family member. Two independent experts rated each memory until a consensus was reached.

For the autobiographical memory test, 14 strictly age- and education-matched healthy control subjects (mean age = 71.6 years; SD = 4.9; minimum level of 8 years of primary education) were recruited in retirement homes. Statistical analysis of the data recorded for the autobiographical memory task, expressed in terms of total score per period, was processed with a repeated measure analysis of variance (ANOVA) followed by post hoc tests (Bonferroni multiple comparison) to examine the influence of the factors group (between-factor AD and controls) and period (within-factor A, B and C).
SPM 99. The influence of age was controlled by setting age as the confounding variable in a single linear regression. Only the correlations in the neurobiologically expected direction (i.e. positive; i.e. the lower metabolic value the more severe the memory deficit) as searched. We retained significant correlations at $P < 0.01$ (uncorrected). The results were obtained in two forms: (i) projection of the significant voxels onto an MNI-MRI template; and (ii) peaks with their Talairach coordinates, using Mathew Brett’s set of linear transformations (www.mrc-cbu.cam.ac.uk/imaging/mnispace.html).

**Results**

**Experimental autobiographical memory protocol**

The analysis of the data processed with a two-way ANOVA of group (AD versus controls) × period (A, B, C) showed a significant group effect [$F(1,29) = 76.45, P < 0.0001$] which indicated lower overall performances in the AD group in comparison with the controls (mean ± SD: 8.02 ± 3.54 and 13.24 ± 1.22, respectively) and a period effect [$F(2,58) = 19.58, P < 0.0001$] which indicated an increase of performances with time interval (A, B, C: 9.03 ± 13.07 ± 3.54 and 3.61 ± 9.90 ± 1.14, respectively) and a period effect [$F(2,58) = 10.36, P < 0.001$] demonstrated that the period effect was different for the AD and controls (see Fig. 1). Thus, a one-way ANOVA (period) for the two groups revealed that, for controls, the period effect was not significant [$F(2,26) = 1.92, P = 0.16$], the three periods (A, B, C) being performed similarly (12.92 ± 1.20, 13.07 ± 1.14 and 13.71 ± 1.26, respectively). In contrast, the performances of the AD subjects [$F(2,32) = 21.14, P < 0.0001$] showed a significant temporal gradient such that the remote memories were better recalled than the recent ones. The results of the post hoc tests showed for AD that period A was clearly more deficient ($P < 0.0001$) than periods B and C (5.82 ± 3.48, 7.29 ± 2.734 and 10.94 ± 2.22, respectively).

In order to obtain a better understanding of the Ribot’s temporal gradient observed in the AD group, we subsequently sought to elucidate the processes underlying the autobiographical memory deficits by examining the relationship between autobiographical memory test performances and other neuropsychological measures, namely of semantic, episodic and working memory. Therefore, we carried out a stepwise regression analysis for the measures of autobiographical memory obtained for each time period using the 14 neuropsychological measures (see Table 1) as independent variables. The results (see Table 3) show that semantic measures were the best predictors of the autobiographical measures for the two most remote periods (C and B), while an episodic measure predicted the recent period (A). In addition, we made a qualitative analysis of the performances obtained for the two most remote periods, which highlighted that remote memories were obviously semanticized far more than strictly episodic memories. Indeed, the number of generic memories (scoring ≤3) reached 79.42%, whereas the number of episodic memories (scoring 4) was 20.58%.

**Cognitive–metabolic correlations**

The results are shown in Table 4 and Fig. 2. Regarding period A, SPM revealed significant correlation between autobiographical scores and normalized metabolism of the posterior part of the right hippocampus (extending to the right lingual gyrus), right middle and inferior frontal gyri and the anteroinferior part of the right middle temporal gyrus (near the hippocampus and parahippocampal gyrus). Regarding period B, the correlations concerned principally the bilateral prefrontal cortex (bilateral superior, bilateral middle and right inferior gyri), while for period C they concerned only the left middle frontal gyrus.

**Table 3** Stepwise regression analysis using neuropsychological measures as the independent variables for autobiographical measures on the three time periods explored

<table>
<thead>
<tr>
<th>Autobiographical measures</th>
<th>Neuropsychological measures</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period A</td>
<td>EMT (delayed recall)</td>
<td>35.1**</td>
</tr>
<tr>
<td>Period B</td>
<td>SKT (categorical knowledge)</td>
<td>24.7*</td>
</tr>
<tr>
<td>Period C</td>
<td>Semantic fluency</td>
<td>24.9*</td>
</tr>
<tr>
<td></td>
<td>Semantic fluency, SKT (attribute knowledge)</td>
<td>47.1**</td>
</tr>
</tbody>
</table>

For neuropsychological measures, see also Table 1. The 14 independent variables were: semantic measures [semantic and formal fluencies, SKT (naming, categorical knowledge, attribute knowledge)], episodic measures [story recall, figure reproduction, EMT (immediate recall, total recall, delayed recall, recognition)], working memory (verbal and visuospatial spans, Brown–Peterson paradigm); period A (previous 5 years); period B (middle age); period C (childhood and teenage); *$P < 0.05$; **$P < 0.01$. 

![Fig. 1 Autobiographical memory performances in AD according to time interval compared with controls (mean and SD). Period A = previous 5 years; period B = middle age; period C = childhood and teenage. Pathological scores: **$P < 0.01$; ***$P < 0.001$.](image-url)
Discussion
Consistent with previous studies using an autobiographical memory questionnaire (Kopelman, 1992; Graham and Hodges, 1997; Piolino et al., 2003a), this study in a group of patients with AD at the mild to moderate stage of dementia documents an autobiographical retrograde amnesia that obeys Ribot’s law (Ribot, 1881), i.e. characterized by a relative preservation of remote compared with recent memories. Using a correlation approach between resting nCMRGlc and temporally graded memory scores, this study identified the cerebral structures whose synaptic dysfunction subserved the impairment of autobiographical memory in AD. Our findings revealed an involvement of the right hippocampus, restricted to the most recent period (the previous 5 years except the last 12 months). Secondly, they showed that the most recent period was, in addition, significantly correlated with right prefrontal cortex metabolism, while the intermediate period (middle age) was correlated with prefrontal cortex metabolism bilaterally, and the most remote period (teenage and childhood) with left prefrontal cortex metabolism. We will discuss the limited involvement of the hippocampal region in the most recent period in the framework of models of long-term memory consolidation. We will then examine the other results showing a shift with time interval from the right to the left prefrontal cortex in the light of studies of memory, especially autobiographical memory, retrieval.

The role of hippocampus in autobiographical memory
Voxel-based mapping of the correlations between autobiographical memory scores and nCMRGlc restricted to the area predicted according to the consolidation memory theory (i.e. the hippocampus) is consistent with the idea of a disengagement of the hippocampal region with time. Effectively, the present observation of an implication of the hippocampal region restricted to the recall of recent memories (the previous 5 years) would support the standard model of long-term memory consolidation (McClelland et al., 1995; Squire and Alvarez, 1995; Murre, 1996). According to this model, the retrieval of recent declarative memories (i.e. both episodic and semantic) initially relies upon the medial temporal lobe, but, over time, the repeated reinstatement of this region results in the formation of a more permanent representation in the neocortical networks. Thus, the hippocampal memory system would serve as a temporary index for the retrieval of myriad aspects of the memory trace, whereas the neocortex would be the permanent repository of long-term memory. Based on the HIPER model (Lepage et al., 1998), our results which show the involvement of the posterior hippocampus are compatible with the role of this region in the retrieval of episodic memory.

Our finding contrasts with several previous functional neuroimaging studies in healthy young or elderly subjects.
using the activation paradigm (Tulving, 1989; Conway et al., 1999; Nadel et al., 2000; Maguire et al., 2001; Ryan et al., 2001) that failed to find a differential activation of the medial temporal lobe with the remoteness of autobiographical memories (see Introduction). Our finding nevertheless is consistent with a few recent functional neuroimaging studies of autobiographical memories, even though these studies concerned semantic information of famous faces (Haist et al., 2001) or more generic than specific remote personal events memory [personal topographical autobiographical memory (Niki and Luo, 2002); childhood memory (Piefke et al., 2003)]. Interestingly, the behavioural evidence we reported in this study supports the view that the relatively better preservation of remote memory compared with recent memory in AD patients was linked to their semantic nature (see also Piolino et al., 2003a). Hence, the lack of significant correlation with the hippocampal region observed here for the two remote periods, which is compatible with the standard model of long-term memory consolidation, is also compatible with the alternative multiple trace theory, since the latter assumes that semantic remote memories, unlike episodic ones, become independent of the medial temporal lobe.

The remaining issue is that of the asymmetry in the hippocampal correlation. Indeed, we observed a right hemispheric instead of the predicted bilateral involvement for the hippocampal region. Several previous reports have highlighted the specific involvement of the right hippocampus in visuospatial memory retrieval and of the left hippocampus in verbal memory retrieval (for reviews see Desgranges et al., 1998a; Cabeza and Nyberg, 2000). Furthermore, in the same AD group (with two additional patients), the cognitive–metabolic approach showed that verbal episodic memory performance (i.e. word learning) was also correlated with the metabolism of the hippocampal region, although left sided (Eustache et al., 2001). Specific aspects of the material (i.e. autobiographical versus word list) are likely to explain those differences. As far as autobiographical memory is concerned, several studies reported bilateral, but preferentially left sided, hippocampal activations (Maguire and Mummery, 1999; Maguire et al., 2001, 2001; Ryan et al., 2001), whereas others demonstrated right-sided hippocampal activation (Fink et al., 1996; Tsukiura et al., 2002). Moreover, Maguire and Frith (2003a) recently demonstrated, in a large group of young and older adults, that the right and left hippocampi diverged in their response to remoteness. The activity of the right hippocampus decreased with the passage of time, in contrast to the left hippocampus, which was consistently involved. Furthermore, these authors (Maguire and Frith, 2003b), studying the effects of ageing on the engagement of the hippocampus during memory retrieval, reported a left hippocampal activation in young adults, but a bilateral hippocampal activation in older subjects. The greater activation of the right hippocampus was specific to autobiographical event memory compared with autobiographical facts or non-self semantic memory retrieval, arguing, according to the authors, in favour of compensatory processes for
episodic memory difficulties in normal ageing. In keeping with these findings, our data may imply that the right hippocampal correlation in AD patients reflects both the specific involvement of this structure in the retrieval of their recent past and the dynamic course of normal ageing.

The role of the prefrontal cortex in autobiographical memory retrieval

We found correlations which differed according to the three time periods tested: they concerned principally the right prefrontal cortex for the previous 5 year period, the bilateral prefrontal cortex for the middle age period, and the left prefrontal cortex for the teenage and childhood period. These correlations between prefrontal cortex and autobiographical memory scores across the three time periods would be consistent with the role of this cerebral region in autobiographical recollection (Conway and Pleydell-Pearce, 2000; Conway, 2001), and more generally in tasks involving a process of controlled retrieval. Indeed, the critical role of the prefrontal cortex in autobiographical memory retrieval is supported by numerous studies (for reviews see Maguire, 2001; Giffard-Quillon et al., 2001), as well as by many neuropsychological studies on retrograde amnesia (Calabrese et al., 1996; Kroll et al., 1997; Levine et al., 1998; for reviews see Markowitsch, 1995; Conway and Pleenaki, 2000; Kopelman and Kapur, 2001; Kopelman, 2002).

Our findings also highlight a shift in the laterality of correlations with the prefrontal cortex from the right to the left hemisphere, with increasing time interval. This finding might reveal a transition from episodic to semantic retrieval, consistent with both the HERA model (Tulving et al., 1994; Habib et al., 2003) based on activation studies in healthy subjects, and the theory of ‘semanticization’ of episodic memories with time interval proposed by Cermak (1984). Activation studies in healthy subjects have shown that the right prefrontal cortex subverts the retrieval of episodic information (regardless of its verbal or visuospatial nature), whereas the left prefrontal cortex subverts the retrieval of semantic information (for a review see Cabeza and Nyberg, 2000). This interpretation is in accordance with Cermak’s proposal of the ‘semanticization’ of episodic memories with time interval, according to which memories become independent of specific temporal and spatial contexts. According to this author (1984, p. 58), normal retention of autobiographical or public events memory ‘represents a shift in time from specific retention involving episodes to a more general retention of knowledge about names and events’. With respect to this model, remote retrieval would involve mainly episodic memory for the recent past and semantic memory for the distant past. Other authors have corroborated that semanticization of episodic memories with time interval and repetition of similar events is a normal process of forgetting (Barclay, 1986; Linton, 1986). Cermak first expounded the idea that episodic memory and semantic memory form a continuum in order to explain Ribot’s gradient seen in amnesic syndrome (Cermak and O’Connor, 1983; Butters and Cermak, 1986). Accordingly, Ribot’s temporal gradient would be due to the greater vulnerability to amnesia of episodic relative to semantic memory and, ‘even those distant episodes that do appear vivid may actually be more familial folklore than truly retained episodes’ (Cermak, 1984, p. 59). Our PET analysis, as well as our regression analysis [showing that recent memories are predicted by verbal episodic memory (i.e. delayed recall) whereas remote memories are predicted by verbal semantic memory] in line with further neuropsychological findings (Piolino et al., 2003a), support the view that preserved remote memories in AD have a predominantly semantic character, especially for the oldest ones. Pulling together the HERA and Cermak models, our data may reflect the transition from episodic to semantic memory with time interval, demonstrating that recent memories imply episodic memory retrieval (involving the right prefrontal cortex) while remote memories imply semantic memory retrieval (involving the left prefrontal cortex). Intermediary memories would involve both episodic and semantic memory retrieval. Interestingly, the shift with time interval from the right to the left frontal cortex may also be considered in conjunction with other results (Desgranges et al., 1998b) using the same cognitive–metabolic approach in AD patients showing that verbal episodic memory impairment was related not only to limbic structures but also to right-sided anterior and posterior cingulate and temporoparietal and frontal cortices, whereas verbal semantic memory impairment was related to the left-sided temporoparietal and frontal cortices and cingulate cortex. Therefore, the deficit in episodic memory in early AD may be partially compensated with respect to the remote past by resorting to semanticized memories (see Desgranges et al., 2002a). In line with this interpretation, the global autobiographical amnesia without a temporal gradient reported in AD with more severe dementia may be explained by an additional deficit in semantic memory (Sagar, 1991).

Altogether, these findings illustrate the transition from episodic to semantic memory with time interval, but this change is not systematic since some old episodic memories may persist in normal elderly subjects (Piolino et al., 2002) and even in AD patients (Piolino et al., 2003a; this study).

In addition, our findings may also be considered in conjunction with the view that episodic memory is essential for the retrieval of recent memory whereas semantic memory is essential for the retrieval of remote memory. Another explanation would be, therefore, that semantic memory is essential to recollect remote episodic memory (for the development of this hypothesis in semantic dementia see Piolino et al., 2003a, b). According to a recent constructive model of autobiographical memory (Conway and Pleydell-Pearce, 2000; Conway, 2001), a complex cyclic retrieval process which depends on the frontal lobe, especially the left
side, allows one to access sensory/perceptual event-specific knowledge through the personal knowledge base. Autobiographical memory would reflect the integration of the episodic information with knowledge structures in long-term memory. Thus, an alternative interpretation would be that our results traduce a semantic establishment with time interval of a retrieval route to the episodic knowledge structures in other areas of the brain.

Finally, the fact that our results map a restricted number of regions (i.e. hippocampus and prefrontal cortex) involved in autobiographical amnesia of AD patients, compared with the large number of regions involved in autobiographical memory in studies of normal subjects (reviewed in Maguire, 2001b), emphasizes the difference between studies of patients and normal subjects, and more fundamentally the difference between correlation and subtraction analysis revealing ‘how’ and ‘what’ sites, respectively (Tulving et al., 1999). The activity of the ‘how’ sites would reveal how well the brain is performing a given task (retrieval success), whereas that of ‘what’ sites would reveal what the brain is doing. Therefore, using the correlational approach in patients with impaired performance appears to be a valid approach to shed light on the mechanisms underlying time-related differences in autobiographical memory that offers a powerful complementary approach to the activation paradigm.

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