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The neural substrates of semantic memory deficits in early Alzheimer's disease: Clues from semantic priming effects and FDG-PET

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Abstract

The neural substrates responsible for semantic dysfunction during the early stages of AD have yet to be clearly identified. After a brief overview of the literature on normal and pathological semantic memory, we describe a new approach, designed to provide fresh insights into semantic deficits in AD. We mapped the correlations between resting-state brain glucose utilisation measured by FDG-PET and semantic priming scores in a group of 17 AD patients. The priming task, which yields a particularly pure measurement of semantic memory, was composed of related pairs of words sharing an attribute relationship (e.g. tiger–stripe). The priming scores correlated positively with the metabolism of the superior temporal areas on both sides, especially the right side, and this correlation was shown to be specific to the semantic priming effect. This pattern of results is discussed in the light of recent theoretical models of semantic memory, and suggests that a dysfunction of the right superior temporal cortex may contribute to early semantic deficits, characterised by the loss of specific features of concepts in AD.

Keywords: Alzheimer; Semantic deficits; Superior temporal gyrus; PET

Introduction

Many studies conducted in patients suffering from Alzheimer's disease (AD) report semantic memory impairments (see Hodges, 2006) which may have appeared at an early stage of the disease, possibly even in patients with amnesic mild cognitive impairment (MCI; Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Chételat et al., 2005; Vogel, Gade, Stokholm, & Waldemar, 2005). "Semantic memory" refers to a permanent store of representational knowledge, including facts, objects, words and their meanings. The reported deficits are often attributed to a deterioration in this semantic knowledge (Hodges, Salmon, & Butters, 1992; Salmon, Butters, & Chan, 1999), but this breakdown is progressive and does not appear to be complete, as superordinate concepts are frequently preserved, unlike subordinate information (Martin & Fedio, 1983). The tasks that are generally used to explore semantic memory are not, however, specific and involve cognitive processes other than semantic processing. An alternative way to investigate semantic memory in AD is through the use of a semantic priming paradigm, considered to be an implicit measure of semantic memory (see Neely, 1991, for a review). This paradigm provides a highly relevant method for exploring semantic memory in AD, as it does not call on executive processes or other non-semantic processes, and is highly sensitive to early semantic deterioration. Semantic priming effects refer to a modification in the way a stimulus is processed following the presentation of a related stimulus. Generally speaking, in lexical decision or pronunciation tasks, a target (e.g. chair) is recognized faster if it is preceded by a semantically-related prime (e.g. table) than if it is preceded by an unrelated one (e.g. horse). This processing facilitation depends partly on automatic spread of activation through the semantic network (Collins & Loftus, 1975).

One essential question underlying research into semantic memory in AD concerns the neural substrates of semantic knowledge in the early stages of the disease. After a description of studies that have explored the neural basis of semantic representations in normal subjects, the introduction to this paper reviews semantic dysfunction and related neuroimaging data in AD. This is followed by a description of our novel research in patients suffering from AD. In this FDG-PET study, we looked for correlations between semantic priming scores and metabolic data in order to assess the neural basis of early semantic memory deficits in AD. This is an original approach to AD as, to our knowledge, no previous neuroimaging studies have investigated

semantic priming in this disease. Above all, semantic priming is an experimental paradigm that minimizes the effect of strategic confounds and thus provides a means of assessing semantic memory in a more automatic manner than classic semantic tasks. Accordingly, it can lead to a better understanding of how semantic memory is organized, as well as to a more precise characterization of neural semantic deficits in early AD.

Neural basis of semantic memory in healthy subjects

The neural basis of semantic processing has been investigated in numerous neuroimaging studies. These studies have been conducted with a view to addressing some central questions about conceptual knowledge, such as the organization and structure of semantic memory. Their results point to the existence of a large and distributed network of semantic representations, although the exact nature of the latter's organization is still a matter of debate. This network covers the ventral and lateral temporal cortex, parietal cortex and frontal cortex. To be a little more precise, two main cortical areas have frequently been reported as being critical to the processing of semantic information. These areas are the left inferior prefrontal cortex (e.g. Buckner & Koutstaal, 1998; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001), and the middle and superior temporal gyrus (e.g. Chao, Weisberg, & Martin, 2002; Friederici, Ruschemeyer, Hahne, & Fiebach, 2003; Kuperberg et al., 2000). Although there is little dispute about the involvement of these areas in the semantic system, their precise function has yet to be determined.

In recent years, a number of studies have used functional imaging techniques, such as PET and fMRI, to investigate the neural basis of semantic priming. These studies offer a more sensitive vision of the neural architecture of lexical semantic processes, as semantic priming paradigms can reflect the relationship between concepts in a very controlled way. In single-word priming paradigms, a decrease in response times on the target is commonly reported when the prime and the target are related. Most of these studies have revealed that some brain areas (involved in semantic processing) show a decreased haemodynamic response associated with behavioural semantic priming (Mummary, Shallice, & Price, 1999; Rissman, Eliassen, & Blumstein, 2003). These neuroimaging decreases associated with semantic priming may reflect more efficient neural processing, in a manner similar to decreases in activation associated with repetition priming a phenomenon referred to as "repetition suppression" by Desimone (1996) (for

a contradictory result and interpretation, see Raposo, Moss, Stamatakis, & Tyler, 2006). Previous functional semantic priming studies have generally pointed to the involvement of frontotemporal brain regions in semantic processing (e.g. Gold et al., 2006; Wheatley, Weisberg, Beauchamp, & Martin, 2005). Some event-related fMRI studies have reported a repetition suppression effect in the left inferior frontal cortex (e.g. Copland et al., 2003; Kotz, Cappa, von Cramon, & Friederici, 2002), but this region is unlikely to mediate the semantic representations, as lesions in this area do not cause semantic memory deficits (Swick, 1998). The left inferior frontal gyrus, however, is thought to play a role in selection from semantic memory and, more precisely, to mediate selection among competing alternatives (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), or the strategic retrieval of semantic representations from semantic memory (Wagner et al., 2001). The dorsal part of this region seems to be activated by priming paradigms requiring not just automatic processes but also attentional ones, too, involving semantic matching or semantic integration (Matsumoto, Iidaka, Haneda, Okada, & Sadato, 2005). Therefore, this region may serve as a "semantic working memory system", responsible for retrieving, maintaining, monitoring and manipulating semantic representations stored elsewhere (Gabrieli, Poldrack, & Desmond, 1998).

Temporal regions have also been largely reported in semantic priming studies, particularly the bilateral superior and middle temporal areas (Rissman et al., 2003; Wible et al., 2006). Matsumoto et al. (2005) studied the neural distribution of semantic priming using a combination of fMRI and event-related potentials (ERP). The authors reported reduced activity in the left inferior frontal gyrus, anterior cingulate and left superior temporal gyrus for related vs. unrelated conditions. A correlation analysis revealed that the magnitude of the N400 priming effect (ERP component sensitive to semantic deviation) was correlated with the activity of the left superior temporal gyrus. All these results suggest that the middle and superior temporal gyri are associated with the concept's representation and that repetition suppression in these regions is due to the preceding activation of target representation caused by automatic spreading activation.

Semantic memory deficits in Alzheimer's disease

Semantic impairment in early AD takes the form of word finding difficulties and the use of inappropriate words in speech, causing semantic paraphasias (e.g. "banana" for "apple") and superordinate responses (e.g. "fruit" for "apple") in naming tasks (Martin & Fedio, 1983), and the

low production of items from a given semantic category in timed verbal fluency tasks (Diaz, Sailor, Cheung, & Kuslansky, 2004; Henry, Crawford, & Phillips, 2004; Hodges & Patterson, 1995), even at a predementia stage (Chételat et al., 2005). Despite the unequivocal evidence of semantic deficits in AD, one of the recurrent themes over the past decade has concerned the nature of these disturbances, namely a deficit in access or loss of stored representations, and most of the studies have come down in favor of a loss of semantic knowledge in AD (e.g. Bayles & Tomoeda, 1983; Chan, Butters, & Salmon, 1997; Hodges et al., 1992; Ober & Shenaut, 1999; Rohrer, Wixted, Salmon, & Butters, 1995; Salmon et al., 1999). The semantic deterioration observed in AD patients has been shown to be a progressive one, affecting specific attributes first and broader conceptual knowledge thereafter. This pattern of semantic deficits was properly demonstrated for the first time in semantic dementia in the longitudinal study of patient JL (Hodges, Graham, & Patterson, 1995). In the early stages of the disease, this patient correctly named prototypical birds, but failed to differentiate them from more unusual category members. Later on, however, even the names of the most typical members were replaced by the generic name “bird”, and then by the non-specific label “animal”. Confusions between birds and other categories of animals emerged still later in the course of the disease. According to feature-based theories (Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Tyler & Moss, 2001), category-level knowledge is supported by information common to many exemplars of the same category (shared features), whereas exemplar-level knowledge also requires information that is unique to an exemplar member (distinctive features). This suggests that JL’s semantic deterioration was started out as the selective impairment of distinctive features. Examining patients suffering from AD, Garrard, Lambon Ralph, Patterson, Pratt, and Hodges (2005) reported that, in the course of progressive deterioration of semantic knowledge in these patients, the distinctive features of concepts were more vulnerable than the shared ones.

Previous AD group studies using FDG-PET (Desgranges et al., 1998, 2002; Eustache et al., 2004; Hirono et al., 2001; Teipel et al., 2006; Zahn et al., 2004), SPECT (Grossman et al., 1998, 1997) or fMRI (Grossman et al., 2003) have highlighted the involvement of left hemispheric regions, such as the inferior and superior temporal, and inferior parietal cortices in semantic memory tasks. Other studies have also been consistent with prior functional imaging studies of semantic processing in normal adults, showing the involvement of inferior frontal regions in semantic tasks (Hirono et al., 2001; Saykin et al., 1999). The tasks used in these

studies, such as the category fluency task, are not specific and require cognitive processes other than semantic processing, such as sustained attention, active searching and overt retrieval, in addition to the more basic processes of accessing and using information from semantic memory. And yet, these cognitive processes are often disturbed in AD. Another method that is widely used to assess the integrity of semantic memory in AD is the semantic priming paradigm which has the advantage of being more independent of executive or word production than explicit tasks.

Semantic priming paradigms have, however, yielded contradictory cognitive results in AD: less-than-normal priming (Ober & Shenaut, 1988), equivalent priming (Nebes, Martin, & Horn, 1984) or even increased priming effects (hyperpriming; Chertkow, Bub, & Seidenberg, 1989). These contrasting results may reflect not only the clinical heterogeneity of the sample population studies, but also differences in the priming methodologies used (Giffard, Desgranges, & Eustache, 2005). In a previous study, we reported a combination of both intact priming and hyperpriming in a group of AD patients (Giffard et al., 2001): in order to explore different levels of the semantic structure, and taking feature-based models into account, related words had either coordinate (tiger–lion) or attribute (tiger–stripes) relationships. The results for the AD group as a whole revealed hyperpriming in the coordinate condition and normal priming effects in the attribute one. The magnitude of the semantic priming effects in the coordinate condition varied according to the degree of attribute loss: the greater the impairment of attribute knowledge, the greater the increase in semantic priming effects. In a subsequent longitudinal cognitive study (Giffard et al., 2002), we explored semantic memory in AD using the same priming task. We observed changing patterns over the course of AD: in the attribute condition, priming effects underwent a linear decline, whereas in the coordinate condition, priming effects increased abnormally (hyperpriming) before collapsing. To date, imaging has never been used to investigate the neural basis of semantic priming in AD, even though, the semantic priming measurement is crucially assumed to provide a very pure assessment of semantic memory from the onset of semantic deficits in AD. In the present study, the method of voxel based mapping of correlations between the resting-state cerebral metabolic rate for glucose (CMRGlc) and priming scores was used. The effectiveness of cognitive-metabolism correlations has been comprehensively demonstrated. This is a sensitive approach to assessing the neural substrates of cognitive impairment in AD (Desgranges et al., 2002; Eustache, Desgranges, Giffard, de la Sayette, & Baron, 2001; Hirono et al., 2001; Salmon et al., 2005), and MCI (Chételat et al.,

2003). Furthermore, this methodological approach has been successfully used to unravel the neural substrates of various and extremely subtle cognitive deficits in AD (Eustache et al., 2004; Rauchs et al., 2007).

In a separate session from the neuropsychological examination, seventeen AD patients drawn from our previous study (Giffard et al., 2001) underwent a PET exam. The semantic priming paradigm is particularly suitable for identifying the specific brain areas responsible for semantic deficits only, using statistical parametric mapping (SPM2) to establish correlations between CMRGlc and priming scores in the attribute condition. We chose to restrict our study to attribute semantic priming, as this makes it possible to assess the fine-grained subordinate level of semantic memory that is known to be disrupted first in AD. Moreover, as shown in our longitudinal data (Giffard et al., 2002), scores in the attribute condition evolve in a linear way, contrary to the pattern observed in the coordinate condition, where priming scores are initially similar to controls', before increasing abnormally, returning to normal and finally collapsing. This non-linear pattern in the coordinate condition would make the correlations difficult to interpret. We hypothesized that the pattern of attribute priming effects would depend on the degree of semantic impairment and that attribute priming would thus be affected by the dysfunction of cerebral areas classically involved in semantic memory tasks, particularly the posterolateral temporal regions (e.g. Fiez, Raichle, Balota, Tallal, & Petersen, 1996; Martin, Wiggs, Ungerleider, & Haxby, 1996; Mummery, Patterson, Hodges, & Price, 1998).

Methods

Subjects

Seventeen unmedicated patients were examined (6 men and 11 women; age 72.5 ± 5.6 years; range 63–85 years). We deliberately selected probable AD patients with mild-to-moderate dementia (McKhann et al., 1984), using a standard neuropsychological assessment, including the Mini Mental Status Examination (MMSE, Folstein, Folstein, & McHugh, 1975; 23.1 ± 1.9 ; range 20–26) and the Dementia Rating Scale (DRS, Mattis, 1976; 121.6 ± 7.1 ; range 108–136). After an interval of a few days at most, each patient underwent specially-designed semantic memory tasks and a PET measurement of resting state CMRGlc using standard procedures and a high-resolution device that allowed the imaging of the entire brain. The patients gave their consent to

the study after detailed information had been provided to them, and the study was conducted in line with the Declaration of Helsinki, following approval by the Regional Ethics Committee.

Neuropsychological data of AD patients were compared with those obtained in a group of 15 healthy elderly subjects (7 men and 8 women; age 72.7 ± 5.1 years; range 67–86 years) recruited in clubs for retired people. They were paired according to age, education and gender distribution with the AD patients ($p = 0.96, 0.92, 0.75$, respectively). They had no neurological or psychiatric disorders. MMSE (28.9 ± 1.1 ; range 27–30) and DRS (138.3 ± 2.6 , range 135–143) scores were significantly higher than those of the AD group ($p < 0.0001$ for both comparisons).

Neuropsychological assessment

Lexical decision task

A lexical decision task was administered, in order to assess automatic semantic priming effects in the patients and their controls (see also Giffard, Desgranges, Kerrouche, Piolino, & Eustache, 2003; Giffard et al., 2002, 2001).

Stimuli

The material was composed of 30 related pairs of words: 20 semantically-related word pairs of the same semantic level (coordinate relation, e.g. tiger–lion) and 10 pairs in which the target was a specific attribute of the prime (attribute relation, e.g. zebra–stripe). These pairs were drawn from word association norms (Lieury, Iff, & Duris, 1976; Ol'eron & Legall, 1962; Rosenzweig, 1970). Prior to the experiment, we showed 60 of the first written words stemming from these norms to 100 subjects, who had to supply the first word that came to mind for each of them. From the resulting word pairs, we selected the 30 most homogeneous ones in terms of their association frequency. The nouns, which were all concrete and imageable, were between 3 and 10 letters long, and their mean lexical frequency was 60 per million (Brulex, Content, Mousty, & Radeau, 1990). In both sets of pairs, the words were balanced in terms of length (coordinate: 6.1 letters; attribute: 5.3 letters), lexical frequency (coordinate: 75 per million; attribute: 82 per million) and association frequency (coordinate: 43%; attribute: 47%), checking that there were no extreme values in any condition. The word pairs were always related semantically and were also slightly associated, as associative strength has been shown to be a key determinant of the degree of priming (Moss, Ostrin, Tyler, & Marslen-Wilson, 1995): semantically-related and associated

words have a priming advantage over semantically-related but non associated words. To ensure that none of the priming could be overly attributed to the frequency of a co-occurring word, association frequency was never maximal and was the same in both related conditions.

These 30 related pairs were included in a list of 300 pairs of words and nonwords. All the primes were words. 20% of the pairs in which the target was a word were semantically related (coordinate or attribute condition) but 80% did not share any semantic or associative link, thus helping to avoid any expectations on the part of the subjects as to the nature of the target. In order to minimize the intervention of postlexical attentional processes, the likelihood of encountering a word vs. a nonword in the target position was 50%. The nonwords, which were all pronounceable, were created by replacing one letter in each syllable of a concrete word taken from the word association norms. The task was divided into four blocks, each lasting approximately 5 min and separated by a few minutes interval. The distribution of the pairs (coordinate, attribute, unrelated words and word/nonword) was the same in all four blocks. In each block, the pseudo-randomized distribution of the stimuli was the same for all subjects and met the following constraints: there were never more than five occurrences of word or nonword targets in a sequence, the related pairs never occurred at the beginning of a block and never occurred one next to another.

Procedure

Stimuli were presented using Superlab 1.68 software (Cedrus Corporation, Phoenix, AZ, USA) which allows response times to be measured accurately to within 1 ms. During the trials, subjects were shown a fixation point on a screen for 500 ms, followed by a prime word for 200 ms. Thereafter, the screen remained empty for 50 ms. Stimulus onset asynchrony (SOA) was 250 ms—a time interval too short for subjects to anticipate the nature of the target. Subsequently, the target stimulus was displayed until a response was forthcoming. The screen then remained empty for 1500 ms and another trial began. In order to enhance the automaticity of the task, subjects were instructed to respond for the target only: if they recognized French word in the series of letters, they had to press the “yes” key as fast as possible with their dominant hand. If the target did not mean anything to them, they had to press the “no” key with their other hand. Priming effects, based on differences in response times between unrelated and related conditions, were expressed as a percentage for each subject (priming effect divided by mean response times for the

unrelated condition $\times 100$); this approach helped to avoid a slowing effect on the priming effects (see Giffard et al., 2003).

Complementary cognitive tasks

An episodic memory task and an explicit semantic memory task (category fluency task) were also administered to the subjects. Along with the MMSE score, these tasks were conducted in order to characterize the patients, study links between the scores on these tasks and semantic priming effects, and determine whether these scores correlated with the metabolism of areas similar to those linked with the semantic priming effects, i.e. to control for the specificity of the correlations between FDG-PET changes and semantic priming scores. Episodic memory was assessed using an original task (Eustache et al., 2001) derived from Grober and Buschke's procedure (1987). This procedure was designed to limit interference from semantic memory impairment by using only items whose semantic integrity has been strictly verified individually (see Giffard et al., 2001, for a detailed description of this task). Our task consists in learning a series of 15 words presented in series of three on five separate cards. After a deep encoding phase for each word, three recall tests are administered to the subjects, each recall test comprising free recall for 2 min and, if necessary, a categorical cued recall test. Each trial is preceded by 20 s interference, when patients are asked to count backwards. During the category fluency task, subjects were given 2 min to produce as many words as possible belonging to a given category (names of animals and fruit) (Cardebat, Doyon, Puel, Goulet, & Joanne, 1990). The sums of correct and unique responses are reported.

PET methodology

All patients underwent a PET study using ^{18}F FDG. Data were collected using the high-resolution ECAT Exact HR+ PET device with isotropic resolution of $4.6\text{mm} \times 4.2\text{mm} \times 4.2\text{mm}$ (FOV= 158 mm). Patients were fasted for at least 4 h before scanning. The head was positioned on a headrest according to the canthomeatal line and gently restrained with straps. ^{18}F FDG uptake was measured in the resting condition, with eyes closed, in a dark, quiet environment. A catheter was inserted into a vein of the arm for radiotracer administration. Following ^{68}Ga transmission scans, 3–5 mCi of ^{18}F FDG were injected as a bolus at time 0, and a 10-min PET data acquisition session was begun after a 50-min. post-injection period. Sixty-three planes were acquired with septa out (volume acquisition), using a voxel size of $2.2\text{mm} \times 2.2\text{mm} \times 2.43\text{mm}$ (x, y, z). During

PET data acquisition, head motion was continuously monitored with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn on the forehead.

Using SPM2 (Wellcome Dept of Cognitive Neurology, London, UK), the PET data were subjected to an affine and non-linear spatial normalization to SPM2's standard MNI PET template, and were resliced to $2\text{mm} \times 2\text{mm} \times 2\text{mm}$. 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 PET data to control for individual variations in the overall CMRGlc. In order to minimize "edge effects" without excluding hypometabolic tissue in our AD patients, only the voxels with values above 60% of the mean for the whole brain were selected for the statistical analysis.

For the sake of thoroughness, we compared the normalised CMRGlc (nCMRGlc) data set obtained for our sample of 17 AD patients with that obtained for another group of 14 age-matched healthy subjects (mean age \pm S.D. = 70.5 \pm 5.8 years). We used the uncorrected $p < 0.001$ ($Z > 3.09$) as a cut-off for statistical significance. Hypometabolism was revealed in the bilateral parietal and left temporal areas, the precuneus and the middle and posterior cingulate gyrus bilaterally, and the bilateral parahippocampal regions. This pattern of hypometabolism is in line with previous findings (Desgranges et al., 1998; Kawachi et al., 2006; for reviews, see Mosconi et al., 2005; Nestor, Scheltens, & Hodges, 2004).

We then looked for correlations between the priming effects in the attribute condition and resting-state nCMRGlc metabolism in the whole brain, using SPM and Pearson's correlation test. The influence of age and overall dementia severity was controlled by using age and the MMSE score as confounding variables in a simple linear regression. Analyses of correlation between CMRGlc and MMSE, episodic memory and semantic memory (category fluency task) measures were also conducted to determine whether the brain regions involved in the attribute priming process were really specific. For each score, only the correlations in the neurobiologically expected (i.e. positive) direction were assessed using a statistical threshold (uncorrected for multiple tests) of $p < 0.01$. This threshold has been used in previous studies by our group, with the same correlative approach (Chételat et al., 2003; Desgranges et al., 1998) as well as by other groups (Teipel et al., 2006; Zahn et al., 2004). Furthermore, this threshold seems especially suitable regarding expected regions, such as temporal regions, which play a well-known role in

semantic memory. Anatomical localization was based on Talairach's Atlas, using M. Brett's set of linear transformations (see URL www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

Results

Cognitive tasks

In keeping with other studies on semantic priming effects in AD (Chertkow et al., 1994; Ober, Shenaut, Jagust, & Stillman, 1991), we only report results for "yes" responses. Likewise, in order to ensure that performances were not influenced by extreme scores, in each condition, response latencies exceeding 3 standard deviations (S.D.) above each participant's mean were treated as outliers and the mean was calculated again. We conducted an analysis of variance to compare priming effects in the attribute condition between the controls and the AD group. This analysis failed to reveal any significant difference between the two groups (AD group: $8.23 \pm 5.28\%$, control group: $9.5 \pm 3.90\%$, $F(1,30) = 0.57$, $p = 0.45$), but thanks to the longitudinal study, we know that the priming scores of these 17 AD patients were just about to decrease (mean priming effects of the 17 patients at the second session: $7.73\% \pm 5.68$), while several of the patients already had pathological scores (6 patients with pathological Z-scores compared with attribute priming effects of the control group), explaining in part the important standard deviation compared to the one of the controls.

Concerning the episodic memory task, taking the total number (free recall + cued recall scores) of correct answers as the dependent variable, an ANOVA showed a significant group effect [$F(1,29) = 44.05$; $p < 0.0001$] in favor of the controls, and the absence of a trial effect [$F(2,58) = 1.15$; $p = 0.32$]. The interaction between these two effects was significant [$F(2,58) = 4.89$; $p = 0.01$], due to the controls (but not the patients) significantly improving their performance.

The verbal fluency scores (sum of words produced in the animal and fruit categories) differed significantly between the AD and control groups [$t(29) = 4.31$; $p = 0.0002$] in favor of the controls (43.8 ± 9.03 vs. 29.87 ± 8.96).

In the AD group, Pearson correlations between attribute semantic priming and MMSE showed that the measure of priming was not highly associated with severity ($r = 0.37$; $p = 0.14$). Similarly, a distinction between implicit and explicit semantic measures was supported by the

absence of any significant correlation between attribute semantic priming and categorical fluency scores ($r = 0.24$; $p = 0.36$).

Cognitive-metabolic correlations

In the patient group, significant positive correlations ($p = 0.01$) were observed between the attribute priming scores and nCMRGlc (Fig. 1). They concerned the bilateral superior temporal gyrus, predominantly in the right hemisphere (Brodmann areas 21/22; right hemisphere: 48, -34, 4 for x, y, z; cluster size = 59 voxels; Z-score = 2.65; left hemisphere: -42, -42, 10; cluster size = 5 voxels; Z-score = 2.41). Significant positive correlations ($p = 0.001$) between CMRGlc values and the patients' MMSE scores concerned the left posterior cingulate/precuneus areas (-4, -56, 32; cluster size = 65 voxels; Z-score = 3.40).

Positive correlations between CMRGlc values and episodic memory scores (sum of all three trials) were obtained ($p = 0.01$), in the left parahippocampal, fusiform and hippocampal areas (-24, -28, -28; cluster size = 357 voxels; Z-score = 3.75). Significant positive correlations ($p = 0.001$) were found between the semantic verbal fluency scores (sum of words produced in the animal and fruit categories) in the left inferior (-44, -10, -36; cluster size = 440 voxels; Z-score = 4.10) and middle temporal regions (-58, -42, -14; cluster size = 412 voxels; Z-score = 4.07), encroaching upon the neighboring left STG when considering the less strict threshold $p = 0.01$.

Discussion

This study sought to identify the neural substrates of early semantic memory impairment in AD by establishing correlations between CMRGlc and attribute priming scores. As previously observed in a larger group of patients (Giffard et al., 2002, 2001), the priming analysis showed statistically comparable performance for the present AD group and the fifteen controls. As semantic priming effects reflect the level of semantic memory deterioration and are sensitive to the early signs of this deficit, we rather expected a decrease in semantic priming in the attribute condition, when in fact priming scores remained intact. Nevertheless, several AD patients displayed significantly abnormal priming effects, and we know from our longitudinal data (Giffard et al., 2002) that attribute priming in the whole AD group was about to undergo a significant decrease. Additionally, this absence of any significant difference in priming effects

can be explained by the fact that AD patients have greater difficulty with some semantic relations than with others, demonstrating that concept features are not lost in an all-or-nothing manner, but that the loss may be progressive and incomplete at the start of the disease. Computational models based on distributed networks make it easier to understand this result. These models suggest that concepts are represented by an overlap of features and assume that category structure is based on similarity, i.e. the degree to which semantic properties overlap. This indicates the existence of two kinds of attributes: those that are common to a large number of concepts and also tend to co-occur across exemplars, and those that are specific to one concept and usually occur in isolation (Tyler & Moss, 2001). In AD, common features may be preserved longer than distinctive features (Devlin et al., 1998). Hence, in the present study, semantic priming effects were still normal because the pairs in this condition were partly composed of common features. We hypothesize that patients with lower semantic priming may have reached the stage where distinctive attributes start to be affected. Thereafter, as semantic memory impairment worsens still further, not only distinctive attributes, but common attributes, too, gradually deteriorate. The spread of activation between a concept and its attribute (distinctive or shared) then becomes weaker and weaker.

This is the first time that voxel-based mapping of the correlations between priming scores and resting-state nCMRGlc measured by PET has been applied in AD. Correlations showed that the patients with lower priming scores had lower nCMRGlc in the bilateral superior temporal areas, mainly on the right side. This result highlights the involvement of the superior temporal cortex in the semantic priming process, all the more that the metabolism of this region was specifically correlated with this cognitive process, and not with non-semantic cognitive tasks: MMSE scores correlated with the metabolism of the left posterior cingulate/precuneus areas, as has already been reported in other studies (Salmon et al., 2005), while episodic memory scores correlated with the parahippocampal areas, almost mirroring the findings of Eustache et al. (2001) study. On the other hand, a different semantic test (semantic verbal fluency task), which was explicit and not as specialized as the attribute priming task, also correlated to some degree with FDG levels in the left superior temporal gyrus.

Areas within the bilateral superior temporal gyrus have been shown to play an important role during the semantic integration of inferential information (Jung-Beeman, 2005). For example, activity in the superior temporal gyrus increases when individuals read sentence pairs that are causally linked (Mason & Just, 2004), detect inconsistencies in story information (Ferstl,

Walther, Guthke, & von Cramon, 2005), carry out syllogistic reasoning (Goel & Dolan, 2001), or comprehend short stories featuring inference events (Virtue, Haberman, Clancy, Parrish, & Jung Beeman, 2006). It has also been shown that certain categories of semantic information are bilaterally represented in the temporal lobes (Tranel, Damasio, & Damasio, 1997). Dronkers, Wilkins, Van Valin, Redfern, and Jaeger (2004) have also claimed that the posterior temporal lobe is needed for word level comprehension, but whether this comprehension is specific to the semantic level, the phonological level or the link between form and concept is unclear. Our results suggest that it may not be specific to the phonological level. Lesion and functional imaging studies have also pointed to a bilateral posterior superior temporal representation of lexemes (see Poeppel, Idsardi, & van Wassenhove, 2008 for a review). In the present semantic priming study, we cannot exclude the possibility that lexical associativity between primes and targets may have influenced the priming scores, and this factor may therefore have affected the correlation with posterior superior temporal areas. However, associativity was controlled for and was always very minor, compared with the conceptual-semantic relations between primes and targets which should, therefore, have exerted the greatest influence on the semantic priming scores. In an ERP and fMRI study, Matsumoto et al. (2005) reported reduced activity in the left superior temporal cortex for related vs. unrelated conditions during a semantic priming paradigm—an activity that was correlated with the N400 component. This finding was partly consistent with MEG data suggesting that the source of N400 was the bilateral superior temporal lobe. Swaab, Baynes, and Knight (2002) showed that the N400 effect was strongest over the right posterior electrode sites—a topographic distribution typical for the N400 (Kutas & Hillyard, 1980).

The lesser involvement of left temporal areas observed in the present study may seem surprising, given the published neuropsychological and neuroimaging literature. Nevertheless, many experimental, neuroimaging and patient studies have now demonstrated that areas of the right hemisphere also contribute to language comprehension, despite the obvious superiority of the left hemisphere in most language tasks. The right temporal lobe has been shown to contribute to the processing of language and, more specifically, of semantic knowledge. There is considerable evidence to show that several lexical-semantic functions are located in the right and/or bilateral temporal regions, and there are reports showing that the right hemisphere is far more involved in metaphoric meaning, connotative meaning and abstract semantic concepts

(Bottini et al., 1994; Gagnon, Goulet, Giroux, & Joanne, 2003; Larsen, Baynes, & Swick, 2004). It has been amply demonstrated that right hemisphere-damaged patients have problems understanding complex discourse, and have specific difficulty in drawing inferences that conceptually connect two sentences—a necessary process for maintaining coherence (Beeman, 1993; Brownell, Potter, Bihle, & Gardner, 1986). Moreover, these patients cannot take full advantage of a theme sentence to arrange subsequent sentences into a coherent paragraph, as left hemisphere-damaged patients and controls can (Schneiderman, Murasugi, & Saddy, 1992). These deficits suggest that right hemisphere-damaged patients have difficulty maintaining or imparting coherence, i.e. connecting those elements of discourse that should be connected. Normal subjects organize their representations of discourse into thematically related substructures which are then linked together within a coherent macrostructure (Gernsbacher, Varner, & Faust, 1990). Right hemisphere-damaged patients may fail to activate some items of semantic information and therefore be less effective in building structures and completing processes that depend on sensitivity to semantic relations. These observations may partly explain why, in the present study, AD patients with the lowest metabolism in the right superior temporal region were those who achieved the lowest attribute priming scores, as it may have been difficult for them to relate primes to their targets.

Recently, using neuroimaging in normal subjects, several semantic priming studies similar to ours have revealed that the right superior temporal gyrus is activated by semantically related pairs in a lexical decision task (Rossell, Bullmore, Williams, & David, 2001; Wible et al., 2006). Similarly, Kotz, von Cramon, and Friederici (1999) noted right superior temporal gyrus activation during semantic categorization, using fMRI. Rossell et al. (2001) claimed that this lateralization suggests that the right superior temporal gyrus is involved more extensively in within-category semantic processes, as also implied in neuropsychological studies using divided visual field presentation (Chiarello, Burgess, Richards, & Pollock, 1990) to infer hemisphere differences in semantic networks. It has been shown that, in semantic priming tasks, when a low proportion of pairs are related, normal subjects respond faster to target words related to the prime, but only for target words presented to the left visual field-right hemisphere, although subjects viewing target words in the right visual field-left hemisphere do benefit from seeing category coexemplar prime words if they are also associatively related to the prime (Chiarello et al., 1990; Chiarello & Richards, 1992). On the basis of ERP experiments, Deacon and co-workers (Deacon

et al., 2004; Grose-Fifer & Deacon, 2004) proposed a new model of semantic memory, in which the left hemisphere represents semantic information locally and priming occurs exclusively through associative links, whereas the right hemisphere represents concepts on the basis of distributed individual features. Deacon et al. (2004) demonstrated that associated words without shared semantic features (dog–bone) prime each other in the left hemisphere but not in the right one. Conversely, words that share semantic features but are not associates (tree–broccoli), prime each other in the right hemisphere, but not in the left. Their study clearly showed that priming via an associative relationship and priming via a physical/functional feature overlap are not subserved equally by the cerebral hemispheres. In the right hemisphere, priming only occurs when patterns of activation overlap, i.e. when items share attributes. The authors concluded that feature representations are maintained by the right hemisphere. In our paradigm, as we used actual semantic features as targets, selecting ones which were not overly associated with the prime, the attribute condition bore a close resemblance to the feature overlap condition described by Deacon and co-workers. If features representations do indeed depend on the right hemisphere, the correlation observed in a right temporal region in AD patients becomes easier to understand: after the presentation of the prime-concept, the lexicality decision for a related target-feature was only marginally faster than in an unrelated condition, because the features were partly represented in deficient right temporal areas.

Overall, these results provide valuable clues to the nature of early deterioration of semantic memory in AD. Semantic priming studies have shown that semantic deterioration begins with the selective loss of specific attributes of concepts. The correlative approach adopted here to FDG changes and semantic priming scores for attribute targets would appear to reveal the specific involvement of the right superior temporal cortex, demonstrating that a dysfunction in this area is therefore partly responsible for the early stages of the semantic deterioration in AD.

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Figure

Fig. 1. Anatomical localization of the significant positive correlations between the percentage of semantic priming effects in the attribute condition and nCMRglc, controlling for the confounding effects of age and dementia severity, in the bilateral temporal region. On the left: correlations projected onto sagittal, axial, and coronal sections of a normal MRI set spatially normalized into the standard SPM2 template. On the right: scatter plots of the correlations.