The neural correlates of verbal short-term memory in Alzheimer’s disease: an fMRI study

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Although many studies have shown diminished performance in verbal short-term memory tasks in Alzheimer’s disease, few studies have explored the neural correlates of impaired verbal short-term memory in Alzheimer’s disease patients. In this fMRI study, we examined alterations in brain activation patterns during a verbal short-term memory recognition task, by differentiating encoding and retrieval phases. Sixteen mild Alzheimer’s disease patients and 16 elderly controls were presented with lists of four words followed, after a few seconds, by a probe word. Participants had to judge whether the probe matched one of the items of the memory list. In both groups, the short-term memory task elicited a distributed fronto-parieto-temporal activation that encompassed bilateral inferior frontal, insular, supplementary motor, precentral and postcentral areas, consistent with previous studies of verbal short-term memory in young subjects. Most notably, Alzheimer’s disease patients showed reduced activation in several regions during the encoding phase, including the bilateral middle frontal and the left inferior frontal gyri (associated with executive control processes) as well as the transverse temporal gyri (associated with phonological processing). During the recognition phase, we found decreased activation in the left supramarginal gyrus and the right middle frontal gyrus in Alzheimer’s disease patients compared with healthy seniors, possibly related to deficits in manipulation and decision processes for phonological information. At the same time, Alzheimer’s disease patients showed increased activation in several brain areas, including the left parahippocampus and hippocampus, suggesting that Alzheimer’s disease patients may recruit alternative recognition mechanisms when performing a short-term memory task. Overall, our results indicate that Alzheimer’s disease patients show differences in the functional networks underlying memory over short delays, mostly in brain areas known to support phonological processing or executive functioning.

Keywords: Alzheimers disease; Neuroimaging; short-term recognition memory; verbal working memory; fMRI

Abbreviations: fMRI = functional magnetic resonance imaging; FWHM = full-width at half maximum; MMSE = Mini-Mental State Examination; PET = positron emission tomography

Introduction

The memory decline exhibited by patients with Alzheimer’s disease has been the focus of substantial research as it is typically regarded as the most prominent symptom of the disease. In its early stages, Alzheimer’s disease is characterized by several types of explicit memory impairment, such as deficits in episodic memory, semantic memory and short-term memory, whereas other types of memory such as implicit or procedural memory are relatively preserved until late in the disease process.

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(Kaszniaik, 1986; Carlesimo and Oscar-Berman, 1992). An impairment of verbal short-term memory has been consistently observed for various tasks, such as immediate serial recall of word lists or digit span tasks, and the possible cognitive processes which underlie this impairment have been extensively discussed in the neuropsychological literature. In most studies, the short-term memory difficulties in Alzheimer's disease patients have been interpreted within the 'phonological loop' model proposed by Baddeley and Hitch (1974). The phonological loop is comprised of a phonological store which holds verbal information for a brief period of time, and an 'articulatory rehearsal' component, which refreshes the decaying traces by re-introducing them in the phonological store, via sub-vocal articulatory rehearsal. In addition, the phonological loop is assumed to be supervised by an executive control system (called the 'central executive'), responsible for attentional control and coordination of the various processes involved in short-term memory. The verbal short-term memory impairments in mild Alzheimer's disease patients appear to stem from a deficit of executive control systems rather than from impairments in short-term memory. The verbal short-term memory difficulties in Alzheimer's disease patients have been interpreted within the 'phonological loop' model proposed by Baddeley and Hitch (1974). The phonological loop is comprised of a phonological store which holds verbal information for a brief period of time, and an 'articulatory rehearsal' component, which refreshes the decaying traces by re-introducing them in the phonological store, via sub-vocal articulatory rehearsal. In addition, the phonological loop is assumed to be supervised by an executive control system (called the 'central executive'), responsible for attentional control and coordination of the various processes involved in short-term memory. The verbal short-term memory impairments in mild Alzheimer's disease patients appear to stem from a deficit of executive control systems rather than from impairments in mild Alzheimer's disease patients and age-matched healthy controls. Between-group comparisons were performed in order to explore decreased or increased activations in the short-term memory networks of Alzheimer's disease patients, relative to control participants, and random effect statistical analyses were used in order to ensure intersubject consistency of results. In addition, because short-term memory tasks are supposed to involve different cognitive processes during encoding, maintenance and retrieval phases (Cairo et al., 2004; Majerus et al., 2007), we exploited the temporal resolution of fMRI to distinguish between encoding and recognition phases. From neuroimaging studies in healthy young participants, we know that verbal short-term memory tasks yield a consistent pattern of fronto-parietal activation, including the bilateral dorsal prefrontal, middle and superior frontal, premotor and supplementary motor areas, as well as inferior parietal, superior temporal and cerebellar regions (e.g. Paulesu et al., 1993; Salmon et al., 1996; Ungerleider et al., 1998; Linden et al., 2003; Majerus et al., 2006). More precisely, the articulatory rehearsal mechanism has been associated with a network including inferior frontal (mainly Broca's area), premotor and supplementary motor areas. Phonological storage is thought to be sustained by the inferior parietal lobe. More precisely, the bilateral anterior inferior parietal sulcus is responsive to short-term memory load and ensures the encoding of entire sequence information while a more inferior and lateral parietal area (corresponding to the supramarginal gyrus) appears to be involved in phonological processing of the items to be retained (Martin et al., 2003; Majerus et al., 2006). Executive control processes have been associated with middle and superior prefrontal activations and posterior parietal cortex (Collette et al., 1997; Henson et al., 2000; Chein and Fiez, 2001; Majerus et al., 2006, 2007).

In Alzheimer's disease patients, we expected altered brain activation patterns in executive parts of the short-term memory network (lateral prefrontal and posterior parietal cortices) given that neuropsychological studies pointed most consistently to deficits in these aspects of short-term memory control. We were further interested in brain activation profiles in inferior prefrontal and temporo-parietal areas subtending more specific components of the phonological loop (articulatory rehearsal and phonological encoding, respectively).

**Methods**

**Participants**

A total of 16 patients in the mild to moderate stage of Alzheimer's disease (13 female and 3 male; aged 63–82 years) and 16 healthy elderly controls matched for age (14 female and 2 male; aged 62–85 years) gave their written informed consent to take part in this study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège and conforms with ‘The Code of
Table 1 Demographic data (mean and standard deviations) of the two participant groups

<table>
<thead>
<tr>
<th></th>
<th>Elderly</th>
<th>Alzheimer’s disease</th>
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</thead>
<tbody>
<tr>
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<td>16</td>
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<tr>
<td>Age</td>
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<td>77.1 (6.6)</td>
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<tr>
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<tr>
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<td>23.4 (1.7)</td>
</tr>
<tr>
<td>Disease durationa</td>
<td>–</td>
<td>2.35 (1.2)</td>
</tr>
<tr>
<td>Audiometryb</td>
<td>22.6 (7.5)</td>
<td>23.5 (9.7)</td>
</tr>
</tbody>
</table>

a Expressed in years  
b Decibels of hearing lost

Ethics of the World Medical Association (Declaration of Helsinki, 1964). All subjects were right-handed, native French speakers and had normal auditory acuity as measured by tonal audiometry testing. The participants had no history of alcohol abuse, psychotropic drug use, depression or other psychiatric disorders. The diagnosis of Alzheimer’s disease was established in the Memory Clinic of the University Hospital in Liège, by an experienced neurologist (E.S.), based on a semi-structured interview with the patient and a relative, on Mini-Mental State Examination (MMSE; Alzheimer’s disease group mean: 23.4 ± 1.7), laboratory, neurological, neuropsychological and neuroimaging examinations, according to National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Structural neuroimaging did not show focal lesion, but mild leukoaraiosis was not an exclusion criterion for this study. All Alzheimer’s disease patients were given a cholinesterase inhibitor. The elderly volunteers were recruited on a voluntary basis and received a small hourly fee for compensation. The Dementia Rating Scale (Mattis, 1973) was administered to all subjects (Table 1). Each control subject performed above the cut-off score of 130 at the Mattis scale, and Alzheimer’s disease patients had a significantly lower score than controls [Alzheimer’s disease group mean: 122.9 (113–132); Control group mean: 139.2 (133–144); (t = 9.0, P < 0.01)]. There was a small but statistically reliable difference in years of education between the Alzheimer’s disease and the control group (t = 4.94, P < 0.05; Control > Alzheimer’s disease). This factor was statistically controlled in the analyses reported below.

Task description

Each trial consisted of the auditory presentation of a list of four words (the memory list), followed by a fixation cross and then a probe word. Participants indicated if the probe word matched (by pressing the button under the right second finger) or not (by pressing the button under the right middle finger) one of the words presented in the memory list. There were two different conditions: (i) a verbal short-term memory condition in which the subjects were asked to memorize a list of four different items (STM) and (ii) a reference condition in which the same word was presented four times in the memory list and thus only one word had to be retained (REF).

In the STM condition, the words were pseudorandomly sampled from a pool of 100 bisyllabic concrete words. There was a total of 80 different trials, with 32 positive probe trials (the probe was in the memory list) and 48 negative probe trials (the probe was not in the memory list). There was an equal number of negative probe trials in which the probe was phonologically and semantically related to one member of the memory list. In the phonologically related trials, the probe and the related word differed by a single phoneme [e.g. ‘SERPENT–SERGENT’, ‘CAMPAGNE–CHAMPAGNE’ (snake–seargeant, country–champagne)], whereas in the semantically related trials, the probe and the related word had the same or similar meaning [e.g. ‘PELOUSE–GAZON’, ‘DIVAN–SOFA’ (lawn–grass, divan-sofa)]. Mean lexical frequency was matched between phonologically related pairs and semantically related pairs (mean lexical frequency was 2486 (range 140–11205) and 2473 (range 102–13626) occurrences per million words, respectively (Brulex database, Content, Mousty and Radeau, 1990)) as well as between probes and memory lists (mean lexical frequency was 2414 (range 102–13626) and 2787 (range 185–13626) occurrences per million words, respectively). Each of the 100 words of the stimulus set occurred four times in the task, with the restriction that phonologically related or semantically related words could never occur together in the same memory list or in two successive trials.

The REF condition, controlling for perceptual and motor response processes of no interest in this study, consisted in the auditory presentation of one word [e.g. ‘FONTAINE’ or ‘RESSORT’; (fountain or sping)] four times, followed by a fixation cross and the presentation of a probe word. There was a total of 20 trials in the reference condition, with 12 negative probe trials and 8 positive probe trials. In contrast to the memory condition, the negative probes in the reference condition were not related to the target word presented in the list. The negative probes were 12 additional bisyllabic concrete nouns which were presented once, and their mean lexical frequency was matched to the words used in the memory lists [mean lexical frequency was 2445 (range 2225–2901) and 2663 (range 2518–2807) occurrences per million words, respectively]. Mean lexical frequency was also matched between REF and STM conditions [mean lexical frequency was 2619 (range 2225–2901) and 2577 (range 102–13626) occurrences per million words, respectively].

There were a total of 100 trials (80 trials in the STM condition and 20 trials in REF condition). They were presented in two sessions of 50 trials each. For each session, two different pseudo-random trial orders were designed and counterbalanced across subjects. Each trial consisted of the auditory presentation of a memory list (encoding phase), followed by a fixation cross (maintenance phase) and then a probe word (retrieval phase). Before and during the presentation of the memory lists, an instruction screen was displayed reminding the participant to listen to the words being presented. The pre-recorded words were presented audibly via an fMRI compatible audio amplifier system. An interstimulus interval of 900 ms between each item in the memory lists was ensured. A fixation cross then appeared for a random duration of 4000 ± 500 ms during the maintenance phase. Before the auditory presentation of the probe word, a brief instruction mentioning ['Attention', (caution)] appeared on the center of the screen informing the participant that the probe was about to be presented, followed by the question ‘In the list?’ and the auditory presentation of the probe word. The probe screen disappeared immediately after pressing the response button, followed by a fixation cross displayed until the next trial (1500 ms). If the participant did not respond within 5000 ms after the onset of the probe word, a ‘no response’ was recorded, and the next trial was presented. In order to familiarize the participants to the specific task requirements, they were presented with as many practice trials of each condition as necessary, outside the MR environment, using the same response keyboard as in the scanner.
MRI acquisition

Data were acquired on a 3-T scanner (Siemens, Allegra, Erlangen, Germany) using a T2*-sensitive gradient echo EPI sequence (TR = 2130 ms, TE = 40 ms, FA 90°, matrix size 64 × 64 × 32, voxel size 3.4 × 3.4 × 3.4 mm³). Thirty-two 3-mm thick transverse slices (FOV 22 × 22 cm²) were acquired, with a distance factor of 30%, covering the whole brain. Structural images were obtained using a T1-weighted 3D MP-RAGE sequence (TR = 1960 ms, TE = 4.4 ms, FOV 23 × 23 cm², matrix size 256 × 256 × 176, voxel size 0.9 × 0.9 × 0.9 mm³). In each session, between 361 and 447 functional volumes were obtained. The first three volumes were discarded to account for T1 saturation. Head movement was minimized by restraining the subject’s head using a vacuum cushion. Visual stimuli were displayed on a screen positioned at the rear of the scanner, which the participant could comfortably see with a mirror mounted on the standard head coil. Auditory stimuli were presented via an fMRI compatible air-pressure headphone system.

fMRI analyses

Data were pre-processed and analysed using SPM5 software (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks Inc., Sherborn, MA). Functional scans were realigned using iterative rigid body transformations that minimize the residual sum of square between the first and subsequent images. They were normalized to the MNI EPI template (voxel size: 2 × 2 × 2 mm) and spatially smoothed with a Gaussian kernel with full-width at half maximum (FWHM) of 8 mm. For each subject, brain responses were estimated at each voxel, using a general linear model with epoch regressors.

For each condition (STM and REF conditions), three regressors were defined to cover the encoding, maintenance and recognition phases, respectively. Both successful and unsuccessful trials were included in these regressors. Indeed, given that the performance was quite high in both Alzheimer’s disease and control groups, the number of events corresponding to unsuccessful trials was too small to allow a direct comparison between successful and unsuccessful trials. The encoding regressor ranged from the time of the onset of each trial until the end of memory list presentation. The maintenance regressor ranged from the end of encoding phase until the onset of the probe presentation, and the recognition regressor ranged from the onset of probe presentation until the participant’s button press response. Furthermore, in order to make encoding and recognition phases completely independent of the maintenance phase, the maintenance phase was orthogonally related to the encoding and recognition regressors (Andrade et al., 1999). For each condition, three phase-specific regressors were obtained. An additional regressor included all trials for which no response was recorded. In this paper, we focus only on the results corresponding to the encoding and recognition phases. Boxcar functions, representative of encoding and recognition phases for each of the conditions, were convolved with the canonical haemodynamic response. In this context, it should be noted that some previous studies have reported delayed BOLD response in Alzheimer’s disease patients relative to healthy elderly subjects in several brain regions (Buckner et al., 2000; Rombouts et al., 2005). Therefore, we conducted specific analyses to ensure that the use of the canonical haemodynamic response function could not impact our results. The temporal derivative associated with haemodynamic response was modeled for each condition of interest and compared between Alzheimer’s disease and Control groups. These analyses did not reveal any significant difference (resulting maps had a threshold of P < 0.001), indicating that the temporal derivative in each condition was similar among groups, and ensuring that magnitude differences in BOLD response between groups could not be explained by latency differences. The design matrix also included the realignment parameters to account for any residual movement-related effect. A high pass filter was implemented using a cut-off period of 128 s in order to remove the low-frequency drifts from the time series. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model of order 1 (+white noise). On this basis, four linear contrasts were performed. The first two contrasts looked for activation in encoding-specific and recognition-specific phases, [(Enc_stm > Rec_stm); (Rec_stm > Enc_stm)]. The two remaining contrasts assessed the impact of memory load by looking for the differential main effects between STM and REF conditions [(Enc_stm > Enc_ref); (Rec_stm > Rec_ref)]. The resulting set of voxel values constituted a map of t-statistics (SPM(T)). These images were further smoothed (6-mm FWHM Gaussian kernel). They were then entered in a second-level analysis, corresponding to a random effects model, in order to account for inter-subject variance in each contrast of interest. First, one-sample t-tests assessed the significance of the effects within each group separately. Control group: [(ControlEnc_stm > ControlRec_stm), (ControlEnc_ref > ControlRec_ref), (ControlEnc_stm > ControlRec_stm) and (ControlRec_stm > ControlRec_ref); and Alzheimer’s disease group: (Alzheimer’s diseaseEnc_stm > Alzheimer’s diseaseRec_stm), (Alzheimer’s diseaseEnc_ref > Alzheimer’s diseaseRec_ref), (Alzheimer’s diseaseRec_stm > Alzheimer’s diseaseEnc_stm) and (Alzheimer’s diseaseRec_rec > Alzheimer’s diseaseRec_ref)]. Second, between-group comparisons were performed (using two-sample t-tests) to determine which brain regions were differentially activated in the Alzheimer’s disease and control groups, as a function of memory phase: [(ControlEnc_stm > ControlRec_stm) versus (Alzheimer’s diseaseEnc_stm > Alzheimer’s diseaseRec_stm)], [(ControlEnc_ref > ControlRec_ref) versus (Alzheimer’s diseaseEnc_ref > Alzheimer’s diseaseRec_ref)], [(ControlRec_stm > ControlRec_ref) versus (Alzheimer’s diseaseRec_stm > Alzheimer’s diseaseRec_ref)] and [(ControlRec_stm > ControlRec_ref) versus (Alzheimer’s diseaseRec_rec > Alzheimer’s diseaseRec_ref)]. The resulting SPM(T) maps were thresholded at P < 0.001. As a rule, statistical inferences were performed at the voxel or cluster level at P < 0.05, corrected for multiple comparisons across the entire brain volume. When a priori knowledge was available regarding the potential response of a given area in our different short-term memory conditions, a small volume correction (Worsley et al., 1996) was computed on a 10 mm radius sphere, around the averaged coordinates published for the corresponding location of interest (see below).

A priori locations of interest

The following a priori locations of interest were used for small volume corrections, based on published coordinates in the literature for verbal short-term memory recognition tasks similar to that used in the present study. These regions concerned primarily the left intraparietal sulcus and lateral inferior parietal cortex, but also the right parietal, bilateral prefrontal, dorsolateral prefrontal, insular, subcortical and cerebellar regions which are consistently activated in verbal short-term memory recognition tasks. Other regions of interest were concerned more specifically with activation in areas in the temporal lobe, documented to underlie phonological, orthographic and lexico-semantic processing and which we hypothesized to also be recruited.
All stereotactic coordinates refer to the MNI space. The a priori locations of interest were the following:

- Inferior frontal gyrus (−63, 8, 11; −48, 16, 0; −50, 22, 30; 32, 24, −2) (Chen and Fiez, 2001; Chen and Desmond, 2005; Majerus et al., 2006); precentral gyrus (−52, −2, 48; −32, −9, 46; 29, −2, 64; 29, −3, 46) (Chen and Desmond, 2005); middle frontal gyrus (−33, 54, 3; −39, 22, 40; −44, −9, 56, 46, 30, 23) (Henson et al., 2000; Cairo et al., 2004; Ravizza et al., 2004); insula (−34, 32, 23; −32, 22, 2; 32, 27, −3; 48, 5, 2) (Cairo et al., 2004; Ravizza et al., 2004; Arnott et al., 2005; Majerus et al., 2006); posterior parietal cortex (42, −75, 43) (Ravizza et al., 2004); caudate (−8, −8, 24, 18, 5, 20) (Ravizza et al., 2004); cerebellum (38, −67, −38; −23, −58, −29; 28 −41 −33; 20, −57, −27) (Cairo et al., 2004; Ravizza et al., 2004; Chen and Desmond, 2005); and inferior parietal sulcus (−24, −60, 42; −34, −50, 48, 38, −48, 44, 44, −39, 50) (order information; Becker et al., 1999; Henson et al., 2000; Marshuetz et al., 2000). In addition, a priori locations specific to language information were the: superior temporal gyrus and planum temporale (−61, −4, −12; 61, −5, −6; −53, 26, 9; 48, −24, 12) (phonological/phonetic processing: Binder et al., 2000; Scott et al., 2000); temporal pole (−30, 9, −21) (general semantic processing: Bright et al., 2004); fusiform gyrus (−34, −51, −17; −40, −55, −17; 40, −53, −17) (orthographic processing: Price et al., 1996); and lateral inferior parietal cortex (−52, −27, 22) (Becker et al., 1999). Lastly, some medial temporal lobe structures have also been related to verbal short-term memory processing in a number of previous studies, such as hippocampus (−19, −26, −9) (Cabeza et al., 2002) or parahippocampus (−20, −30, −10) (Sakai et al., 2002).

## Results

### Behavioural data

We performed a mixed ANOVA with group condition (Controls versus Alzheimer’s disease) as between-subject factor and list condition [memory condition (STM) versus reference condition (REF)] as within-subject factor. Mean proportion of correct responses was used as a dependent variable (Table 2). The results showed significant main effects for the list condition [$F(30,1) = 5.84$, $P < 0.001$; REF > MEM], but there was no significant main effect for the group [$F(30,1) = 1.93$, $P > 0.05$] and no significant interaction between list and group conditions [$F(30, 1) = 2.74$, $P > 0.05$].

A second mixed ANOVA was conducted with reaction times as dependent variable. The results revealed a main effect of group [$F(30, 1) = 12.65$, $P < 0.05$; Alzheimer’s disease > Control] whereas the main effect of list condition was not significant [$F(30,1) = 3.08$, $P > 0.05$]. However, we found a significant interaction between group and list conditions [$F(30, 1) = 5.50$, $P < 0.05$]. Further Tukey’s post hoc revealed that reaction times were longer in the Alzheimer’s disease group than in the control group, but only in the REF condition ($P > 0.05$). Lastly, given the group difference in educational level, we replicated these statistical analyses in a mixed ANCOVA model, with the number of years of education taken as a covariate. The results replicated all the findings reported above, suggesting that educational level had no impact on the performance in our verbal short-term memory task.

## Imaging data

### Within-group analyses

#### Encoding

In both groups, the encoding phase (relative to the recognition phase) yielded activation in the bilateral middle temporal gyrus and in the right superior temporal gyrus ([$Enc_{stm}$]>Rec_{stm}; Table 3 for coordinates and SPM(Z) values). Relative to the reference condition, in which there was a minimal memory load ([$Enc_{stm}$]>Rec_{ref}]), controls presented enhanced activation in the bilateral insula, the left inferior frontal gyrus (posterior Broca’s area), supplementary motor areas, and the right caudate nucleus (Table 3); additional activation foci were also observed in language processing areas including the anterior part of the left superior temporal and the right middle temporal gyrus. In contrast, we did not observe any significant activation in the Alzheimer’s disease group for this contrast ([$Enc_{stm}$]>Enc_{ref})).

#### Recognition

Relative to the encoding phase ([$Rec_{stm}$]>Rec_{stm}), the recognition phase activated several bilateral frontal regions (including fronto-insular, superior medial frontal and precentral cortex) and the postcentral area, as well as left inferior frontal, middle cingulate/SMA, and supramarginal areas in the control group (Table 4). In the Alzheimer’s disease group, the recognition phase yielded greater activation in the left inferior and middle frontal gyri as well as in the right superior medial frontal gyrus; additional activation was observed in the right fusiform gyrus (extending to the right lingual gyrus). When comparing the recognition phase between the memory and the reference condition ([$Rec_{stm}$]>Rec_{ref}]), memory condition was associated with bilateral inferior frontal activations in the control group. In the Alzheimer’s disease group, for the same contrast, activation was observed in the left insula, caudate nucleus, hippocampus, parahippocampus, fusiform gyrus and cerebellum.
Between-group analyses

Encoding phase

Peak activations of between-group comparison are listed in Table 5. No group difference was found in the encoding phase as compared to the recognition phase [(ControlEnc_stm 4 ControlRec_stm) versus (Alzheimer’s disease Enc_stm 4 Alzheimer’s diseaseRec_stm)]. However, when the reference condition was subtracted from the memory condition [Enc_stm 4 Enc_ref], the Alzheimer’s disease group showed less activation in bilateral middle frontal, left inferior frontal and transverse temporal gyri, as well as the right precuneus (Fig. 1). In contrast, no significantly enhanced activation was found in Alzheimer’s disease patients as compared to normal elderly participants.

Recognition phase

Relative to the Control group [(Alzheimer’s disease versus Control) for (Rec_stm 4 Enc_stm)], the Alzheimer’s disease group showed less activation in a number of frontal regions, including the bilateral superior frontal gyrus, supplementary motor areas, the precentral gyrus, the left postcentral gyrus and the right middle frontal gyrus. Significantly lower brain activity was also observed in bilateral supramarginal gyri. At the same time, Alzheimer’s disease patients activated the right fusiform gyrus to a greater extent than controls. Lastly, enhanced activation was also found in a small area of the left anterior fusiform gyrus in the Alzheimer’s disease group relative to control group when contrasting the memory and reference conditions [(Alzheimer’s disease 4 Control) for (Rec_stm 4 Rec_ref)].

Discussion

This study examined the neural correlates of verbal short-term memory in a group of mild Alzheimer’s disease patients and a group of aged-matched healthy elderly controls. Although reaction times were longer in Alzheimer’s disease patients than in control participants, memory performance did not differ significantly between groups. In both groups, the short-term memory task elicited activity in a network that encompassed bilateral inferior frontal, insular, supplementary motor, precentral and postcentral areas, consistent with previous studies in normal young participants. At the same time, Alzheimer’s disease patients showed reduced activation in bilateral middle frontal areas and left
inferior frontal and transverse temporal gyri during the encoding phase, and in the bilateral supramarginal, supplementary motor, precentral and postcentral areas during the recognition phase. Increased brain activity was observed in two different locations of the fusiform gyrus in Alzheimer’s disease patients relative to control participants during the recognition phase.

### Cortical activation for the encoding phase

In healthy elderly participants, regions showing activation during the encoding phase were generally consistent with the findings of previous studies of verbal short-term memory in young adults. These regions included the left inferior frontal gyrus, supplementary motor areas as well as the bilateral insula which are thought to reflect the operation of the articulatory rehearsal process (Paulesu et al., 1993; Fiez et al., 1996; Salmon et al., 1996; Cairo et al., 2004; Ravizza et al., 2004; Chen and Desmond, 2005). In addition, activation in the middle and superior temporal gyri bilaterally was observed in both Alzheimer’s disease and elderly groups of participants. These regions are typically associated with language processing in young healthy populations, and more specifically with sublexical and lexical phonological processing of the items to be retained in a verbal short-term memory task (Majerus et al., 2002; Raetig and Kotz, 2008).

### Table 4 Within group analyses: recognition phase

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<th>Contrasts</th>
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Maxima within regions showing BOLD signal changes in the recognition phase in a group of 16 healthy elderly participants (controls) and 16 patients with Alzheimer’s disease.

BA: Brodmann area; enc_stm: encoding phase in the memory condition; enc_ref: encoding phase in the reference condition; rec_stm: retrieval phase in the memory condition; rec_ref: retrieval phase in the reference condition.

++ Significant at $P<0.05$, corrected for whole brain volume (at the voxel and/or cluster level).

+ Significant at $P<0.05$ after applying small volume corrections (see Methods section for details).
At the same time, between-group comparisons for the encoding phase revealed that the left inferior and bilateral middle frontal gyri, as well as the transverse temporal gyrus, were less activated in Alzheimer’s disease patients compared to healthy elderly participants. Although activation of the anterior middle frontal gyrus has been observed in various short-term memory tasks (Collette et al., 1999b; Nyberg et al., 2003; Owen et al., 2005), this region is also involved in executive control processes such as divided attention or information integration (Badre and Wagner, 2004; Johnson and Zatorre, 2006; for a review see Ramnani and Owen, 2004). This result is consistent with previous neuropsychological studies showing deficits of information integration or coordination in mild Alzheimer’s disease patients (Collette et al., 1999a; Peters et al., 2007). In addition, Alzheimer’s disease patients also showed reduced activation in the left inferior frontal (BA 44) and transverse temporal gyrus (BA 22). Activation of these regions has previously been reported in various speech processing tasks, the anterior superior temporal gyrus being associated with basic speech language perception (Scott et al., 2000; Belin et al., 2002), whereas the pars triangularis of the inferior frontal gyrus, and more generally Broca’s area, appears to be involved in attentional control while processing verbal information (Zatorre et al., 1992; Pugh et al., 1996; Burton et al., 2000, 2005; Heim et al., 2003). Taken as a whole, these impaired activations in fronto-temporal areas support our hypothesis that Alzheimer’s disease patients are

<table>
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<td>enc_stm &gt; enc_ref</td>
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<tr>
<td>rec_stm &gt; rec_ref</td>
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<td>Parahippocampus/Fusiform gyrus</td>
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</table>

Maxima within regions showing BOLD signal changes after between-group analyses: contrast of brain activation related to encoding and recognition phases in a group of 16 healthy elderly participants (controls) and 16 patients with Alzheimer’s disease. BA: Brodmann area; enc_stm: encoding phase in the memory condition; enc_ref: encoding phase in the reference condition; rec_stm: retrieval phase in the memory condition; rec_ref: retrieval phase in the reference condition.
++ Significant at P < 0.05, corrected for whole brain volume (at the voxel and/or cluster level).
+ Significant at P < 0.05 after applying small volume corrections (see Methods section for details).
characterized by an executive control deficit during verbal short-term task, with some additional involvement of speech perception processes.

**Cortical activation for the recognition phase**

With respect to the recognition phase, the fronto-parietal network we identified in healthy elderly participants was consistent with previous studies of short-term memory in young subjects using similar recognition task (Rypma and D’Esposito, 2000; Cairo et al., 2004; Chen and Desmond, 2005). This network encompassed several regions that were already activated during the encoding phase, including supplementary motor, insular and inferior frontal areas, suggesting sustained activation of these regions across successive memory stages. These findings are consistent with previous verbal short-term memory studies in which both supplementary motor and inferior frontal areas showed encoding,
maintenance and retrieval-based activity (Kruggel et al., 2000; Chein et al., 2001). As already noted, the inferior frontal and supplementary motor areas are part of a distributed network associated with subvocal rehearsal processes, supporting the claim that this articulatory rehearsal is activated during successive phases of verbal short-term memory tasks (Rypma and D’Esposito, 2000). Other areas were specifically recruited only during the recognition phase, including areas in the bilateral superior frontal gyri associated with executive control processes, as well as the left inferior parietal areas involved in phonological processing and manipulation processes (Rypma and D’Esposito, 2000; Martin et al., 2003; Cairo et al., 2004; Majerus et al., 2006). Although some of these regions (left inferior frontal, middle frontal and precentral areas) were also activated in Alzheimer’s disease patients during the recognition phase, marked decreases of activation were observed in the left supplementary motor and premotor areas, suggesting that articulatory rehearsal mechanisms might be less extensively recruited in Alzheimer’s disease patients during recognition. Decreases of activation were also observed in the bilateral inferior parietal lobe, and more precisely the ventral part of supramarginal gyrus. As noted in the introduction, activation of the left supramarginal gyrus during verbal short-term memory tasks has often been interpreted as reflecting phonological storage (Paulesu et al., 1993; Awh et al., 1996; Henson et al., 2000). However, although the left supramarginal gyrus appears relatively specific for processing phonological information, the precise role of this region in temporary storage of phonological information is still not clear (see Becker et al., 1999 and Ravizza et al., 2004 for discussion). Its activation is not systematically reported in different neuroimaging studies of verbal short-term memory while this region is also activated in various phonological tasks when no or minimal memory load is involved, such as in passive listening or phonological discrimination tasks (Zatorre et al., 1992; Jacquetmot et al., 2003). Martin et al. (2003) demonstrated that, in a group of young participants, the activity in the left supramarginal gyrus did not vary as a function of short-term memory load, but responded more to a delayed rhyme judgment task than a delayed synonym judgment task, suggesting that this region actually responds to manipulation of phonological information in short-term memory (see Ravizza et al., 2004 for similar findings using n-back and item recognition tasks; see also Buchsbaum and D’Esposito, 2008, for a recent review reaching similar conclusions). Our results showed that this ventral supramarginal area was involved to a greater extent during probe recognition than item encoding, in accordance with previous studies (Veltman et al., 2003). This suggests that phonological discrimination processes associated with left supramarginal gyrus activation are recruited during the retrieval phase, possibly related to increased phonological processing demands when comparing a probe word and the target words which could differ by a single phoneme. In Alzheimer’s disease patients, reduced activity in this region could reflect difficulties to process and compare multiple phonological information. Difficulties in item-comparison processes could also be related to reduced activation observed in the right middle prefrontal gyrus during recognition. This lateral prefrontal region has been associated with executive processes required for response selection (Bunge et al., 2002; Veltman et al., 2003), and more specifically with experimental conditions in which response conflict or competition was high (Milham et al., 2001; Bunge et al., 2002; Hazeltine et al., 2003). Hence, activation in the left supramarginal and the middle frontal gyrus in control subjects is likely to reflect item comparison, decision and selection processes. Alzheimer’s disease patients may have difficulties at this level. When inspecting the behavioural results more closely, we observed that there was a tendency for the Alzheimer’s disease group to actually be more impaired for rejecting phonologically than semantically related probes. This is also consistent with previous studies that reported impairments in Alzheimer’s disease patients for tasks in which a decision on phonologically related information had to be made (Lambert et al., 1996; Crook et al., 2000).

More generally, the relative preservation of performance in Alzheimer’s disease patients, associated with altered neural responses, suggests that different recognition mechanisms might be recruited by Alzheimer’s disease patients when performing a short-term memory task. We considered two locations of increased activity in the Alzheimer’s disease group that may correspond to alternative recognition pathways. Firstly, within-group analyses of the retrieval phase revealed that several regions of the anterior medial temporal lobe, including hippocampus and parahippocampal gyrus, were significantly activated in Alzheimer’s disease patients, but not in elderly controls. Many studies have reported medial temporal lobe activation in short-term memory tasks (Ranganath and D’Esposito, 2001; Cabeza et al., 2002). Among the activated medial temporal regions in Alzheimer’s disease patients, a brain area overlapping the most anterior portion of the left parahippocampal area and fusiform gyrus was significantly more active in Alzheimer’s disease patients than in elderly control participants. The function of the anterior parahippocampal area has been related to familiarity-based recognition of both verbal and non-verbal information, rather than recollection, which is associated with activation of the hippocampus and the posterior parahippocampal gyrus (Davachi et al., 2003; Ranganath et al., 2004; Weis et al., 2004; Montaldi et al., 2006; Diana et al., 2007). Thus, increased brain activity in the anterior parahippocampal area in Alzheimer’s disease patients may reflect the recruitment of a familiarity-based recognition pathway rather than effortful explicit memory recognition, which is consistent with previous studies showing that Alzheimer’s disease patients’ recognition performance using familiarity judgments correlates with the metabolism of anterior parahippocampal area (Rauchs et al., 2007). However, it should be noted that, when the same contrast was performed using a slightly more liberal threshold before applying small volume correction, the hippocampus and a more posterior parahippocampal area were more active in Alzheimer’s disease patients than in elderly controls. This suggests that enhanced activation in the medial temporal lobe was, in fact, not restricted to the anterior parahippocampal area, but rather encompassed hippocampus and different parahippocampal areas. Therefore, our data does not allow us to rule out the possibility that Alzheimer’s disease patients also recruited a recollection-based recognition pathway, since the hippocampus, which is reliably associated with recollection (Diana et al., 2007) was also activated during the recognition phase in Alzheimer’s disease patients. Interestingly, Nee and Jonides (2008) have recently shown that
the hippocampus and the parahippocampus gyrus were specifically activated when subjects had to recognize items that are no longer in their focus of attention in short-term memory, as opposed to recognition of items that are still in their focus of attention which was associated with the activation of a fronto-parietal network. In this context, our results suggest that recognition in Alzheimer’s disease patients may primarily rely on medial temporal lobe activation because the fronto-parietal recognition network we identified in healthy elderly participants (associated with attentional and phonological processes) is not available for Alzheimer’s disease patients. Second, enhanced activation in the Alzheimer’s disease group was also observed in the right lateral fusiform gyrus, when comparing recognition and encoding phases [(Rec_stm - Enc_stm)]. In healthy young subjects, brain activity in the right fusiform gyrus has been associated with the processing of different types of visual information, such as characters, shapes or objects (Slotnick and Schacter, 2004; Pernet et al., 2005; Xue et al., 2006; Wilson and Farah, 2006). Most importantly, this region appears to be important for visual semantic features of familiar entities (Murtha et al., 1999; Bright et al., 2004; Vandenbulcke et al., 2006). Therefore, increased activation of the right fusiform gyrus in Alzheimer’s disease patients during the recognition phase might be tentatively interpreted as reflecting the reactivation of visuo-semantic features of the concrete probe words. Taken together, our results suggest that Alzheimer’s disease patients recruited a ‘semantic’ recognition pathway to a larger extent than healthy elderly individuals, possibly due to their altered phonological processing of short-term memory lists. Given that the performance of Alzheimer’s disease group was essentially preserved, we can tentatively propose that these increased activations reflected alternative recruitment of a medial temporal lobe recognition pathway that allowed them to recognize words from the visuo-semantic features corresponding to presentation of the list.

Methodological considerations

A specific feature of our probe short-term memory recognition task (as opposed to more conventional short-term memory recall tasks) is that good performance can be obtained either from an explicit recollection of the items or from a familiarity-based recognition (via controlled or automatic cognitive processes, respectively), whereas the performance on recall tasks depends heavily on the ability to explicitly retrieve the precise phonological input information. This difference could explain why their reduced brain activity in the frontal and transverse temporal regions during the encoding did not result in a decrement in memory performance. Indeed, one could argue that attentional and phonological processes associated with these regions are more critical for tasks requiring subjects to repeat items, as phonological memory trace corresponding to the sequence of words must remain stable until the retrieval phase. This is supported by previous studies showing that brain activity in the auditory cortex and the inferior and middle frontal areas during encoding predicts later recall or consolidation in long-term memory of the items (Rosen et al., 2002; Blumenfeld and Ranganath, 2006; Mainey et al., 2006). This raises the question of how the word lists were encoded in Alzheimer’s disease patients before the probe recognition task. Our within-group analyses revealed that a large bilateral middle temporal region was activated in both Alzheimer’s disease and elderly control groups during the encoding phase. The middle temporal gyrus is associated with both verbal and visual semantic knowledge (Vandenbergh et al., 1996), suggesting that access to semantic knowledge was preserved in patients during the encoding phase. Overall, these data are consistent with our interpretation that Alzheimer’s disease patients might recognize the word from semantic features activated during the presentation of the word list. Finally, it should be mentioned that some of the characteristics of individuals with Alzheimer’s disease may have influenced our data. First, all Alzheimer’s disease patients were treated with a cholinesterase inhibitor. A number of previous studies have demonstrated that cholinesterase inhibitor treatment improves performances in various memory tasks, such as verbal learning, free recall or recognition tasks (Ebbeie et al., 1992; Crowell et al., 2006; Stefanova et al., 2006). More specifically, enhancement of memory performances induced by cholinesterase inhibitor appears to be mediated primarily by more task-related activity in sensory and frontal cortical brain areas during the encoding phase (Furey et al., 2000; Bentley et al., 2008). However, in the present study, these regions were less activated in Alzheimer’s disease patients during the encoding phase, suggesting that the treatment effect was unlikely to explain their reduced activation in the transverse temporal and the inferior and middle frontal gyri. Second, one cannot exclude an influence of the brain atrophy on brain activity in Alzheimer’s disease patients. Indeed, several previous studies have shown that brain activation was related to the grey matter atrophy in Alzheimer’s disease. However, the exact nature of this relationship is still unclear, some previous studies showing a negative correlation between the cerebral atrophy and brain activity (Remy et al., 2005), whereas others observe a positive relationship between the two measures or no relationship (Johnson et al., 2000). For this study, unfortunately, the grey/white contrast in our structural MRI image was not sufficient to allow for evaluation of local grey matter atrophy. Third, one should be cautious when comparing brain activity in Alzheimer’s disease patients and elderly control with the same canonical hemodynamic response function, since the neurovascular coupling may differ between groups (Buckner et al., 2000; Rombouts et al., 2005). However, as mentioned in the Methods section, we have compared the temporal derivative of the haemodynamic response function in Alzheimer’s disease patients and control participants for each condition, but these analyses did not reveal any significant difference, suggesting that reduced activation observed in Alzheimer’s disease patients (as compared to elderly controls) can be confidently interpreted in terms of magnitude differences. Lastly, as mentioned in the Results section, the group of Alzheimer’s disease patients had a lower mean duration of education than the group of elderly controls participants. However, we included years of education as a covariate in both the behavioural and imaging statistical analyses, hence controlling for any possible linear relationship between level of education and brain activity. Therefore, the differences of brain activity between Alzheimer’s disease patients and elderly controls were unlikely to be explained by this variable.
Conclusions

To conclude, the present study aimed at investigating the neural substrates of verbal short-term memory in a group of mild Alzheimer’s disease patients and a group of healthy elderly controls. In both groups, the recognition task used elicited a distributed fronto-parieto-temporal network that was consistent with previous studies of verbal short-term memory in young subjects. However, several areas of this network were less activated in Alzheimer’s disease patients relative to elderly controls, including encoding-specific activation in the inferior and middle frontal gyri and in the transverse temporal gyrus, respectively, associated with executive control and language perceptual processes. In addition, possibly as a consequence of deficits during the encoding phase, activation decrease was also found in several frontal regions associated with subvocal rehearsal. Diminished brain response was also observed in Alzheimer’s disease patients during recognition, involving the left inferior parietal and right posterior middle frontal areas, reflecting manipulation and decision processes necessary to discriminate between the probe word and the short-term memory traces. Consequences of these results are threefold: (i) our study supports previous neuropsychological studies showing that executive control processes most probably underlie reduced short-term memory performance in Alzheimer’s disease patients (and more specifically integration and coordination processes); (ii) altered phonological processes could further contribute to verbal short-term memory difficulties and (iii) alternative recognition pathways might be recruited, involving recognition of semantic features corresponding to presentation of the list rather than explicit retrieval of precise phonological input information.

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