Neural basis for semantic memory difficulty in Alzheimer’s disease: an fMRI study

Murray Grossman,1 Phyllis Koenig,1 Guila Glosser,1 Chris DeVita,1 Peachie Moore,1 Jina Rhee,1 John Detre,1,2 David Alsop2 and Jim Gee 2

Departments of 1Neurology and 2Radiology, University of Pennsylvania, Philadelphia, PA, USA

Correspondence to: Murray Grossman, Department of Neurology – 2 Gibson, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104-4283, USA
E-mail: mgrossma@mail.med.upenn.edu

Summary
Patients with probable Alzheimer’s disease are thought to have a semantic memory deficit. We used functional MRI to evaluate the neural basis for impaired semantic memory for ANIMALS and IMPLEMENTS in 11 patients with Alzheimer’s disease and 16 healthy seniors. For both categories of knowledge, Alzheimer’s disease patients show reduced activation in the left posterolateral temporal-inferior parietal cortex compared with healthy seniors. Activation changes in this heteromodal association region may be related to an impairment of the category-neutral semantic processes involved in integrating feature knowledge that is represented in modality-specific association cortices. We also found increased activation of an area of the left temporal cortex for both categories of knowledge in Alzheimer’s disease that was not activated in healthy seniors. Category-specific changes were also seen in Alzheimer’s disease compared with healthy seniors that may be related to the neural representation of category-specific feature knowledge represented in semantic memory. For ANIMALS, the left ventral temporal cortex was activated in Alzheimer’s disease in an anatomical distribution that was posterior to the left ventral recruitment for this category in healthy seniors. For IMPLEMENTS, frontal-striatal regions were activated in Alzheimer’s disease in a manner that was displaced from the locus of recruitment for this category in healthy seniors. Our findings are consistent with a two-component model of semantic memory involving category-neutral processes operating on category-specific knowledge, and both components appear to be compromised in Alzheimer’s disease. Components of the large-scale neural network underlying semantic memory may modify themselves to maintain performance in the face of a neurodegenerative disease.

Keywords: Alzheimer’s disease; fMRI; semantic; comprehension; cortex

Abbreviations: BA = Brodmann area; fMRI = functional magnetic resonance imaging; SPM = statistical parametric mapping

Introduction
Many studies report difficulty with semantic memory in patients with probable Alzheimer’s disease (Chertkow and Bub, 1990; Grossman et al., 1996). Some attribute this to degradation of the features contributing to semantic knowledge (Lambon Ralph et al., 1997; Garrard et al., 1998; Silveri et al., 1991). Others also point out difficulty with the processes contributing to semantic memory decisions (Grossman et al., 2001a; Koenig et al., 2001; Rhee et al., 2001). In the present study, we use functional MRI (fMRI) to assess the neural basis of semantic memory difficulty in Alzheimer’s disease. We present a two-component model of semantic memory, and use this perspective to review the ways in which semantic memory may be compromised in Alzheimer’s disease.

A two-component model of semantic memory
Briefly, our model of semantic memory posits two major components: long-term knowledge of the features contributing to word meaning, and the processes that operate on this knowledge. Some feature knowledge is likely to be concerned with the perceptual appearance of an object or an action, such as the shape, colour or motion of a word’s exemplar (Miller and Johnson-Laird, 1976; Allport, 1985; Jackendoff, 1990).
There may also be knowledge associated with the function of an object or an action. Knowledge that is neither perceptual nor functional is likely to be retained in semantic memory for word meaning as well, such as an associative network of propositional knowledge that is related particularly to abstract words that have few perceptual features.

According to one approach, the neural representation of feature knowledge contributing to semantic memory is thought to be in the processing stream most relevant for the feature. The neural representation of visual–perceptual feature knowledge, for example, may be associated with activation of the fusiform gyrus in ventral temporal-occipital visual association cortex (Martin et al., 1995, 2000; Chao et al., 1999; Thompson-Schill et al., 1999; Wiggs et al., 1999; Kellenbach et al., 2001). This theory holds that the representation of a specific category of knowledge in semantic memory is tightly linked to the kind of feature contributing importantly to the category (Warrington and Shallice, 1984; Allport, 1985; Shallice, 1988). The anatomical distribution of activation for a semantic category like ANIMALS (we use capitals to indicate a category) thus may be an emergent property of visual–perceptual feature knowledge that plays a crucial role in natural kinds, also recruiting fusiform portions of the temporal-occipital cortex (Perani et al., 1995; Damasio et al., 1996; Martin et al., 1996; Cappa et al., 1998b; Chao et al., 1999; Moore and Price, 1999; Smith et al., 2001). Likewise, visual–motion feature knowledge is said to be associated with the superior and middle temporal gyri in posterolateral temporal cortex [Brodmann areas (BA) 22, 21 and 37] (Bonda et al., 1996; Patzwal et al., 1996; Puce et al., 1998; Kourtzi and Kanwisher, 2000), and the hypothesized dependence of IMPLEMENTS on knowledge of motion features is thought to explain the recruitment of posterolateral temporal cortex during probes of IMPLEMENTS (Martin et al., 1996; Cappa et al., 1998b; Chao et al., 1999). Knowledge of action features is thought to be represented in premotor and motor association cortices (BA 6, 8, 9 and 44) of the frontal lobes (Decety et al., 1994; Jeannerod et al., 1995; Grafton et al., 1996; Rizzolatti et al., 1996), and the association of IMPLEMENTS with action features is also hypothesized to explain the activation of these frontal brain regions during probes of IMPLEMENTS (Perani et al., 1995; Martin et al., 1996; Grabowski et al., 1998).

While feature knowledge is likely to play an important role in semantic memory, the explanatory strength of a strictly feature-based approach to category-specific knowledge has been questioned from several perspectives. Doubt has been raised concerning the privileged relationship between a kind of feature and a category of knowledge, such as the association of visual–perceptual features with natural kinds (McRae et al., 1997; Caramazza and Shelton, 1998; Tyler and Moss, 2001). Category-specific difficulty for natural kinds without preferential degradation of a particular kind of perceptual feature has been described (Funnell and De Mornay Davies, 1992; Laiacola et al., 1993; Laiacola et al., 1997; Caramazza, 1998; Lambon Ralph et al., 1998b; Moss et al., 1998; Samson et al., 1998). Researchers also find dissociations within categories of knowledge as broad as natural kinds, raising concerns about the coherence of such a large category that indiscriminately depends on a particular kind of feature. Some investigators thus observe greater difficulty with ANIMALS than FRUITS AND VEGETABLES (Caramazza and Shelton, 1998; Hart and Gordon, 1992), while others find the reverse (Hart et al., 1985; Farah and Wallace, 1992). There are also inconsistent combinations of deficits within natural kinds (Caramazza and Shelton, 1998; Caramazza, 2000), such as the variable association of LIVING THINGS with MUSICAL INSTRUMENTS (Warrington and Shallice, 1984; Silveri and Gainotti, 1988; De Renzi and Lucchelli, 1994) or LIVING THINGS with FOODS (Warrington and Shallice, 1984; Hart et al., 1985; Silveri and Gainotti, 1988; Hillis and Caramazza, 1991; Farah and Wallace, 1992; Hart and Gordon, 1992; Caramazza and Shelton, 1998).

Imaging studies have been equally inconsistent. One meta-analysis of category-specific knowledge emphasizes differences in the distribution of activation associated with specific categories of knowledge (Joseph, 2001). Activation for natural kinds is not restricted to ventral temporal-occipital cortex, for example, but is also associated with lateral temporal (Moore and Price, 1999) and frontal (Martin et al., 1996; Cappa et al., 1998b; Grabowski et al., 1998) activation. Likewise, recruitment for manufactured artefacts is not restricted to posterolateral temporal and lateral frontal regions but is also associated with ventral temporal-occipital cortex (Damasio et al., 1996; Cappa et al., 1998b; Chao et al., 1999). Some of these differences may be due in part to the various kinds of tasks and baseline conditions that have been used (Farah and Aguirre, 1999; Joseph, 2001). Additional evidence inconsistent with the sensory and motor representation of feature knowledge comes from investigations of ABSTRACT words. These nouns are impoverished in their sensory–motor features. Nevertheless, ABSTRACT nouns appear to recruit posterolateral temporal and lateral frontal regions of the left hemisphere in a distribution that is very similar to that of objects such as IMPLEMENTS (Beauregard et al., 1997; Kiehl et al., 1999; Grossman et al., 2002a; Noppeney and Price, 2002).

Most words contain knowledge composed of many different kinds of features that vary in the importance of their contribution to the meaning of a word. These multiple features require meaningful integration into a coherent concept so that semantic properties, such as category membership, can be determined (Smith, 1995). The second component of our model is thus concerned with the integrative processes that contribute to semantic memory. One example of this process is rule-based, whereby certain features of an object or abstract word appear to have a special or diagnostic status, since they should be exhibited for it to be an instance of the concept. Another process is similarity-based, where an object or abstract word has sufficient overall
resemblance to a remembered exemplar or a prototype to be considered an instance of the category.

On the basis of neuroanatomical connectivity patterns (Mesulam et al., 1977; Mesulam, 1985), the neural substrates for these integrative processes are hypothesized to include heteromodal association cortices in the posterolateral temporal-inferior parietal (BA 22 and 39) and dorsolateral frontal (BA 9, 10 and 46) brain regions. Heteromodal cortical areas such as these have reciprocal projections with modality-specific association regions where feature knowledge may be represented, and with paralimbic region, such as medial temporal areas important for the long-term consolidation of knowledge in semantic memory. Heteromodal association cortex is implicated in semantic processing, on the basis of structural imaging studies of patients with insult to this region (Hart and Gordon, 1990; Chertkow et al., 1997; Hillis et al., 2001). Functional neuroimaging studies of lexical semantic memory frequently show lateral frontal (BA 9, 44 and 46) and posterolateral temporal (BA 21, 22 and 39) activation for multiple semantic categories (Frith et al., 1991; Martin et al., 1995, 1996; Warburton et al., 1996; Fiez et al., 1996; Price et al., 1997; Mummery et al., 1998; Chao et al., 1999; Kellenbach et al., 2001; Tyler and Moss, 2001; Devlin et al., 2002; Grossman et al., 2002a; Whatmough et al., 2002). Lateral frontal cortices are implicated in reasoning processes relevant to the rule-based approach to word meaning (Goel et al., 1997; Smith et al., 1998; Fischer et al., 1999). An fMRI study during semantic categorization of object descriptions showed that dorsolateral prefrontal activation (BA 9 and 8) was significantly greater during rule-based categorization than similarity-based categorization (Grossman et al., 2002b), and categorization of a novel animal learned on the basis of a rule is associated with dorsal frontal activation (BA 44 and 6) when compared with similarity-based acquisition of the novel animal (Koenig et al., 2002). These studies associate posterolateral temporal and inferior parietal activation (BA 40 and 39) with similarity-based categorization.

**Semantic memory difficulty in Alzheimer’s disease**

Semantic memory difficulty is observed in about 50% of Alzheimer’s disease patients (Grossman et al., 1996; Moore et al., 2002). Evidence supporting semantic memory impairment in Alzheimer’s disease comes from observations of degraded category-specific knowledge (Chertkow and Bub, 1990; Silveri et al., 1991; Gonnerman et al., 1997; Lambon Ralph et al., 1997; Garrard et al., 1998; Grossman et al., 1998b). This work often shows relative difficulty with natural kinds compared with manufactured artefacts. This is attributed by some to the degradation of visual–perceptual feature knowledge on which natural kinds such as ANIMALS are hypothesized to depend (Farah and McClelland, 1991; Silveri et al., 1991). Others attribute relative difficulty with natural kinds to the progressive degradation of a neural network where the overlapping and shared features of category knowledge are represented (Gonnerman et al., 1997; Devlin et al., 1998). However, several studies do not replicate the finding of a category-specific impairment in Alzheimer’s disease patients with a semantic memory deficit (Mickanin et al., 1994; Tippett et al., 1996; Moore et al., 2002). Alzheimer’s disease patients have difficulty with function knowledge as well (Johnson and Hermann, 1995), and this may contribute to their deficit with manufactured artefacts.

The processes operating on this knowledge in semantic memory may also be compromised in Alzheimer’s disease. Recent work has focused on the integrative categorization processes that are central to the establishment of word meaning. Healthy adults are flexible in their use of both rule-based and similarity-based approaches to integrating features represented in a word (Rips, 1989; Smith and Sloman, 1994; Hampton, 1998; Smith et al., 1998). However, Alzheimer’s disease patients appear to be particularly impaired using a rule-based approach to categorize objects. For example, patients with Alzheimer’s disease encounter difficulty identifying and using diagnostic features that contribute crucially to the semantic categorization of object descriptions (Rhee et al., 2001). They also have difficulty learning a new category in a rule-based manner (Koenig et al., 2001). There is some evidence that Alzheimer’s disease patients also have deficits with similarity-based categorization (Grober et al., 1985; Chan et al., 1993a, b; Grossman and Mickanin, 1994).

For example, Alzheimer’s disease patients appear to be relatively dependent on highly representative exemplars of a category during similarity-based categorization, and are less efficient when similarity-based categorization depends on less representative exemplars (Bozoki et al., 2001).

Histopathological abnormalities in Alzheimer’s disease include neurofibrillary tangles and neuritic plaques. The neuroanatomical distribution of these abnormalities overlaps in part with the regions implicated in these components of semantic memory (Arnold et al., 1991; Braak and Braak 1991), including the temporal, parietal and frontal association cortices. Correlative studies relate impaired performance on measures of semantic memory in Alzheimer’s disease to reduced activity at rest in several of these brain regions—particularly the posterolateral temporal-inferior parietal association cortices—using SPECT (Grossman et al., 1997, 1998a), PET (Desgranges et al., 1998) and perfusion fMRI (Alsop et al., 2000).

It is important to assess the contribution of these brain regions in Alzheimer’s disease by the use of activation studies during semantic memory challenges because areas of reduced activity at rest may still be recruited during a semantic challenge. Activation studies can also establish whether other brain regions are recruited in a manner that may help compensate for regions of limited activation. In one neuroimaging study with fMRI, Alzheimer’s disease patients and healthy control subjects made semantic or phonological decisions about pairs of aurally presented words (Saykin et al., 1999). Healthy subjects recruit inferior and middle frontal
cortex of the left hemisphere when judging the category membership of word pairs that include a semantic superordinate category and an exemplar from the category. By comparison, this study reports that Alzheimer’s disease patients recruit right frontal cortex to a significantly greater extent than control subjects during the semantic task. The authors infer that limited activation of left frontal brain regions in Alzheimer’s disease is due to impaired word meaning, and that areas of increased activation in right frontal cortex during this challenge compensate in part for the patients’ semantic difficulty. The interpretation of changed activation in Alzheimer’s disease during this study is confounded, however, by the behavioural abnormalities shown by the patients. For example, it is unclear whether the pattern of activation in Alzheimer’s disease is due to the resources involved in performing a task that is difficult for the patients, or to the degradation of semantic knowledge. A profile of impaired recruitment in neuroimaging studies during cognitive tasks, such as memory challenges, also shows compensatory redistribution of activation in Alzheimer’s disease patients, although a cognitive deficit is also evident during these imaging studies (Becker et al., 1996; Woodard et al., 1998; Grady et al., 2001).

More recently, healthy seniors and Alzheimer’s disease patients were asked to make ‘pleasantness’ judgements of printed verbs (M. Grossman, P. Koenig, G. Glosser, P. Moore, J. Gee, J. Detre and D. Alsop, unpublished). This pleasantness decision has few resource demands, does not require explicit category membership judgements, and involves the same decision for both categories of knowledge. Moreover, this decision is performed equally easily and accurately by Alzheimer’s disease patients and healthy seniors, so the interpretation of differences in neural activation patterns across these groups is less confounded by task difficulty during the imaging study. This kind of decision nevertheless entails a semantic assessment of the stimulus word (Warrington and Weiskrantz, 1968). This study shows reduced posterolateral temporal-parietal and inferior frontal activation in the left hemisphere of Alzheimer’s disease patients compared with healthy seniors during pleasantness judgements, implying a role for these brain regions in the verb-meaning impairments reported in Alzheimer’s disease (Robinson et al., 1996; White-Devine et al., 1996; Bushell and Martin, 1997; Cappa et al., 1998a). Moreover, Alzheimer’s disease patients show greater activation than healthy seniors in an adjacent, mid-lateral temporal region of the left hemisphere, suggesting a compensatory redistribution of recruitment to an adjacent brain region in Alzheimer’s disease.

In the present study, we asked Alzheimer’s disease patients to make pleasantness decisions about a continuously presented series of written words that included blocks of ANIMALS and IMPLEMENTS. We chose these categories of knowledge since they may be compromised in patients with Alzheimer’s disease, and some reports suggest relatively greater difficulty with ANIMALS than IMPLEMENTS (Chertkow and Bub, 1990; Silveri et al., 1991; Gonnerman et al., 1997; Lambon Ralph et al., 1997; Garrard et al., 1998; Grossman et al., 1998b). Pleasantness judgements about ANIMAL and IMPLEMENT categories of knowledge are associated with distinct anatomical distributions in healthy young adults—the left ventral temporal cortex for ANIMALS and the left lateral temporal and frontal cortex for IMPLEMENTS (Grossman et al., 2002a). On the basis of the considerations presented above, we hypothesized that Alzheimer’s disease patients would have limited activation in modality-specific frontal and temporal association cortices compared with healthy subjects, depending on the specific category of knowledge being probed. By comparison, the activation of heteromodal cortical regions that we and others observe in healthy subjects during semantic challenges (Frith et al., 1991; Martin et al., 1995, 1996; Fiez et al., 1996; Warburton et al., 1996; Price et al., 1997; Mummery et al., 1998; Chao et al., 1999; Kellenbach et al., 2001; Tyler and Moss, 2001; Devlin et al., 2002; Grossman et al., 2002a; Whatmough et al., 2002) may implicate category-neutral semantic processes important for word meaning. In this context, we hypothesized that impairment of a category-neutral process related to semantic categorization and feature integration would be associated with limited recruitment of heteromodal temporal-parietal association cortex for both ANIMAL and IMPLEMENT categories of knowledge in Alzheimer’s disease. We also expected increased activation in Alzheimer’s disease in an anatomical distribution adjacent to the recruitment seen in healthy seniors that may help Alzheimer’s disease patients maintain semantic memory performance in the face of their disease.

**Methods**

**Subjects**

We studied 16 healthy, right-handed seniors and 11 patients with mild to moderate dementia diagnosed as probable Alzheimer’s disease according to NINCDS–ADRDA (National Institute of Neurological and Communicative Diseases and the Stroke, Alzheimer’s Disease and Related Disorders Association) criteria (McKhann et al., 1984). Other neurological, psychiatric and medical conditions that can interfere with cognitive performance were ruled out in these patients by structural imaging and serum studies, and the patients were not taking any medications that can impair cognition or interfere with blood flow. The demographic features of the Alzheimer’s disease patients and the healthy seniors are summarized in Table 1. These subjects and their legal representatives participated in an informed consent procedure approved by the Institutional Review Board of the University of Pennsylvania.

The patients completed a brief battery of tasks assessing several cognitive domains, which are outlined below. These data are summarized in Table 2 for individual Alzheimer’s disease patients. For comparative purposes, we also report
performance in 15 healthy, age- and education-matched seniors.

Semantic memory
Subjects performed a simple category membership judgement task requiring a dichotomous decision about the category membership of 48 printed words and colour photographs (Grossman et al., 1996). Subjects judged half of the stimuli for their membership in a natural category (‘Is it a vegetable?’; VEG CATEG) and the remaining half for their membership of a manufactured category (‘Is it a tool?’; TOOL CATEG). Half of the stimuli were members of the test category and half were foils. We report the percentage of correct judgements. Subjects also named 15 line drawings of natural kinds and manufactured artefacts from the Boston Naming Test (NAMING) (Kaplan et al., 1983). We report the percentage named accurately.

Executive functioning
Patients named as many different animals as possible in one minute (ANIMAL FLUENCY) and as many different words beginning with letters ‘F’, ‘A’ and ‘S’ during three 1-min trials (FAS FLUENCY) (Mickanin et al., 1994). We report the number of unique words produced in 1 min that conformed to the category instructions. The subjects performed an 80-item version of the Stroop test (STROOP) that required naming the colour of the font used to print a different colour term (e.g. saying ‘red’ in response to the word ‘GREEN’ printed in a red font) (Stroop, 1935). We report the number of accurate items out of the total number of items completed, divided by their performance time, up to 300 s. The subjects also performed the Trails B test (TRAILS B), which required subjects to draw a line alternately connecting an ascending series of letters and numbers randomly distributed on a sheet of paper (Reitan, 1958). We report the number of accurate items for the total number of items completed divided by their performance time, up to 300 s.

Anterograde memory
The patients performed a 10-word supraspan aurally presented list-learning task over three trials, and were asked to recall the words 1 min after presentation (Welsh et al., 1991). We report the number of items reproduced on the third learning trial minus the number of reproduced items on the first trial (LIST LEARNING), and we report the number of items recalled after 1 min (LIST RECALL).

Materials and procedure
We presented blocks of printed words to subjects, which included ANIMAL and IMPLEMENT nouns. There were 60 words of each noun type, matched for mean (± SD) frequency (Francis and Kucera, 1982) [IMPLEMENT = 11.3 ± 27.4; ANIMALS = 13.1 ± 20.9; t(118) = 0.41; not significant]. A cohort of 42 native English-speaking undergraduates assessed the words for familiarity. All word meanings were known to all students and were judged to be familiar by over 93% of these students (one ANIMAL was judged familiar by only 86% of the undergraduates). The words were either unambiguously nouns or, if not, a word’s frequency of occurrence as a noun was at least five times that of its verb homophone, according to form class-sensitive frequency measures (Francis and Kucera, 1982). Each stimulus word was available for 3 s followed by a 1 s interstimulus interval. Words were presented sequentially, blocked by category, and each 10-word block lasted 40 s. Blocks were presented in a fixed random order with no overt indication of where blocks began or ended. Subjects were not informed that different categories of words were being administered. Two baseline blocks of pronounceable pseudoword stimuli and five blocks of filler words (verbs, abstract nouns) were interspersed among the noun blocks. We used pronounceable pseudoword stimuli as a baseline for pleasantness judgements of words during direct comparison of healthy senior citizens and Alzheimer’s disease patients to minimize activation differences between groups that may have been due to visual±perceptual or reading deficits in Alzheimer’s disease. [Direct comparison of healthy seniors and Alzheimer’s disease patients for pseudoword pleasantness judgements reveals relatively greater activation in the right frontal cortex of healthy seniors (peak coordinates, x = 28, y = 20, z = 16; Z ~4.63), but no areas of significantly greater relative activation in Alzheimer’s disease.] Two runs containing non-repeated stimuli were presented, each run including two blocks of each word category and two pronounceable pseudoword blocks.

To minimize the potential confounds of covarying categories of knowledge and processes for probing this knowledge, to limit memory and task-switching demands of

| Table 1 Demographic characteristics of Alzheimer’s disease patients and healthy seniors |
|---------------------------------------------|---------------------------------------------|
|                                            | Healthy seniors (n = 16) | Alzheimer’s disease patients (n = 11) |
| Age [years; mean (SD)]                     | 73.9 (3.6)                | 73.0 (4.9)                      |
| Education [years; mean (SD)]               | 13.8 (1.8)                | 15.3 (2.9)                     |
| MMSE score [max. = 30; mean (SD)]          | –                         | 20.2 (6.1)                     |
| Sex (M/F)                                  | 9/7                       | 8/3                           |

MMSE = Mini-Mental State Examination.
subjects while in the bore of the magnet, and to use a task that Alzheimer’s disease patients can perform as easily and as accurately as healthy seniors, we employed a single neutral probe for all categories. Subjects were thus asked to make pleasantness decisions for each stimulus. This task has been used for over 30 years to probe ‘deep’ or ‘semantic’ knowledge about words while avoiding a request for specific information (Warrington and Weiskrantz, 1968). Subjects indicated their judgement of each word by right- and left-hand button press for, respectively, ‘pleasant’ and ‘not pleasant’. Response and latency were recorded by the computer presenting the stimuli. Before each run, subjects were acclimatized to the MRI environment by viewing the words ‘Get Ready’ on the screen for 20 s. This also allowed the MRI environment to achieve longitudinal magnetization stability. These data were discarded. Brief rest periods were included between runs.

Our stimulus presentation system, compatible with high magnetic fields, back-projected the printed words onto a screen at the magnet bore. The subject viewed the screen through a system of mirrors. A portable computer (Macintosh 1400C or G3) outside the magnet room used PsyScope presentation software (Cohen et al., 1993) to present stimuli and record response accuracy and latency. Subjects were familiarized with the task prior to entering the magnet bore, and the task was practised by each subject.

### Imaging data acquisition and statistical analysis

The experiment was carried out at 1.5 T on a General Electric (Milwaukee, WI, USA) Echospeed scanner capable of ultrafast imaging. We used a standard clinical quadrature radio-frequency head coil. Firm foam padding was used to restrict head motion. Each imaging protocol began with a 10–15 min acquisition of 5 mm thick adjacent slices for determining regional anatomy, including sagittal localizer images [repetition time (TR) = 500 ms, echo time (TE) = 10 ms, 192 × 256 matrix], T2-weighted axial images [fast spin echo (FSE), TR = 2000 ms, effective echo time (TEff) = 85 ms] and T1-weighted axial images of slices used for fMRI anatomical localization (TR = 600 ms, TE = 14 ms, 192 × 256 matrix). Gradient echo echoplanar images were acquired for detection of blood oxygenation level-dependent (BOLD) alterations that accompany increased mental activity. All images were acquired with fat saturation, a rectangular field of view of 20 × 15 cm, flip angle 90°, 5 mm slice thickness, an effective TE of 50 ms and a 64 × 40 matrix, resulting in a voxel size of 3.75 × 3.75 × 5 mm. The echoplanar acquisitions consisted of 18 contiguous transaxial slices covering the entire brain every 2 s, and the data contributing to each analysed subject consisted of 320 brain volumes. There was a risk of biasing parameter estimates, resulting in artificially increased or decreased contrasts, since this TR was a fixed multiple of the stimulus onset asynchrony (4 s). A separate acquisition lasting 1–2 min was needed for phase maps to minimize distortion in
echoplanar images (Alsop, 1995). We also inspected raw data for individual subjects. Raw data were stored by the MRI computer on DAT tape and then processed off-line.

Initial data processing was carried out with Interactive Data Language (Research Systems, Natick, MA, USA) on a Sun (Cupertino, CA, USA) Ultra 60 workstation. Raw image data were reconstructed using 2D fast Fourier transformation with a distortion correction to reduce artefact due to magnetic field inhomogeneities. Individual subject data were then prepared and analysed statistically using statistical parametric mapping (SPM99) developed by the Wellcome Department of Cognitive Neurology (Frackowiak et al., 1997). This system, operating on a MatLab platform, combines raw difference images from individual subjects into a statistical t map. We used a fixed-effects analysis to test our hypotheses. This limits the generalizability of our findings, but we feel that a conservative approach to generalization is most appropriate at this early stage of activation neuroimaging assessments in Alzheimer’s disease, particularly given potential inter-individual differences. Inspection of individual patient fMRI images used a ±3 SD criterion to evaluate the number of activated voxels in regions of interest on the basis of areas activated in the group-wise analysis. The regions are illustrated in Fig. 1. This analysis did not reveal any extreme outliers that could have biased the imaging data. The images in each subject’s time series were registered to the initial image in the series. The images were then aligned to a standard coordinate system (Talairach and Tournoux, 1988). Global perfusion was included as a covariate across groups, the data were smoothed spatially with a 12 mm Gaussian kernel to account for small variations in the location of activation and gyral anatomy across subjects, and low-pass filtering was implemented to control autocorrelation with a first-order autoregressive method. We used a factorial design to analyse the imaging data parametrically, with a group (healthy seniors, Alzheimer’s disease patients) × category (ANIMALS, IMPLEMENTS) design. Hypothesized category-specific differences were investigated in the context of this model by comparing groups for each category of knowledge and by comparing categories of knowledge within each group. We designed contrasts to involve very similar materials (comparing two word categories or comparing a word category with pronounceable pseudowords within a group, or comparing groups for identical materials).

Fig. 1 Patterns of activation illustrating main effects for the group (healthy seniors, Alzheimer’s disease patients) × category (ANIMALS, IMPLEMENTS) analysis of variance. Activations are rendered on lateral and medial normalized brains and a transaxial slice through the activation (Z level of slice provided in parentheses below). (A) Main effect illustrating group difference for reduced activation in Alzheimer’s patients compared with healthy seniors (Z = +16). (B) Main effect illustrating group difference for greater activation in Alzheimer’s disease patients compared with healthy seniors (Z = –4). (C) Main effect illustrating category difference for greater activation in ANIMALS compared with IMPLEMENTS (Z = –4). (D) Main effect illustrating category difference for greater activation in IMPLEMENTS compared with ANIMALS (Z = +12).
Confidence in the interpretation of our results was based on the specificity and meaningfulness of these contrasts, guided by a priori hypotheses, using a statistical threshold of $P < 0.001$ uncorrected for multiple comparisons.

**Results**

**Behavioural observations**

Patterns of cognitive functioning in Alzheimer’s disease are summarized in Table 2. It can be seen that Alzheimer’s disease patients were impaired relative to healthy control subjects in language, memory and/or executive domains, consistent with their diagnosis. While impaired on confrontation naming and semantic judgement tasks, this group of Alzheimer’s disease patients did not show differential impairment for natural kinds compared with manufactured artefacts. Z-score analyses of individual patient performance profiles relative to the healthy seniors revealed that two Alzheimer’s disease patients had significant impairment judging VEGETABLES (Z-score < −1.96) without a deficit for IMPLEMENTS, and one Alzheimer’s disease patient had significant impairment judging IMPLEMENTS (Z-score < −1.96) without a deficit for VEGETABLES.

Pleasantness judgements associated with each category of knowledge and latencies for making these judgements are summarized in Table 3. Repeated-measures ANOVA (analysis of variance) with a group × category design did not reveal any significant main or interaction effects during pleasantness judgements. A repeated-measures ANOVA with the same design also did not reveal any significant main or interaction effects for latencies to make pleasantness judgements. These healthy seniors and Alzheimer’s disease patients thus appeared to have similar cognitive profiles on this task.

**Imaging observations**

Table 4 summarizes the spatial coordinates of peak activation within each cluster of voxels and the BA locus of each significant cluster for the main effects minus the pronounceable pseudoword baseline, according to the Talairach and Tournoux (1988) reference system. Activations illustrating the contrasts of these main effects are provided in Table 4 and Fig. 1. Figure 1A shows significantly less recruitment in Alzheimer’s disease patients relative to healthy seniors in posterolateral temporal, lateral frontal and occipital regions of the left hemisphere and in temporal and caudate regions of the right hemisphere during pleasantness judgements across both categories. Figure 1B shows greater recruitment of the left inferior temporal cortex during pleasantness judgements for Alzheimer’s disease patients compared with healthy seniors. Figure 1C illustrates the distribution of greater activation in the left ventral temporal cortex for the category of ANIMALS compared with IMPLEMENTS, while Fig. 1D shows marginally greater activation for IMPLEMENTS than ANIMALS in the right caudate and right medial frontal cortex.

Table 5 summarizes the mean number of activated voxels [(number of activated voxels/total number of voxels in a region) × 100] in each of the clusters recruited in the analysis comparing main effects illustrated in Fig. 1. It can be seen that Alzheimer’s disease patients had fewer activated voxels than healthy seniors in left temporal-parietal, left lateral frontal, left occipital and right temporal regions, while Alzheimer’s disease patients had more activated voxels than healthy seniors in left inferior temporal cortex. The table also summarizes a regions-of-interest analysis of the percentage of activated voxels in each group for each category (the regions are illustrated in Fig. 2). An ANOVA examining the percentage of activated voxels in regions, with a group (Alzheimer’s disease, healthy seniors) × category (ANIMALS, IMPLEMENTS) design, showed a significant interaction effect [$F(1.25) = 7.30; P < 0.01$]. Alzheimer’s disease patients had fewer activated voxels than healthy seniors in the left temporal-parietal cortex for both ANIMALS and IMPLEMENTS. However, Alzheimer’s disease patients had more activated voxels than healthy seniors in left ventral temporal cortex during pleasantness decisions about ANIMALS and more activated voxels in left lateral frontal, left striatal-thalamus and right medial frontal regions for IMPLEMENTS.

Direct contrasts of activation patterns in healthy seniors and Alzheimer’s disease patients for each category of knowledge are summarized in Table 6 and illustrated in Fig. 2. For the category of ANIMALS, Fig. 2A shows that Alzheimer’s disease patients activated left posterolateral temporal-inferior parietal cortex less than healthy seniors in a modest manner. By comparison, Alzheimer’s disease patients

### Table 3 Mean (standard deviation) pleasantness judgements and latencies for pleasantness judgements in implement and animal categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Healthy seniors</th>
<th>Alzheimer’s disease patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPLEMENTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Judgements (% judged pleasant)</td>
<td>89.9 (14.7)</td>
<td>81.8 (24.3)</td>
</tr>
<tr>
<td>Latencies (ms)</td>
<td>1158.7 (211.3)</td>
<td>1374.4 (327.6)</td>
</tr>
<tr>
<td>ANIMALS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Judgements (% judged pleasant)</td>
<td>79.7 (17.2)</td>
<td>73.1 (28.1)</td>
</tr>
<tr>
<td>Latencies (ms)</td>
<td>1235.2 (205.7)</td>
<td>1279.2 (307.6)</td>
</tr>
</tbody>
</table>
showed significantly greater activation than healthy seniors during ANIMAL judgements in a left ventral temporal distribution (Fig. 2B). For the category of IMPLEMENTS, we again saw less recruitment of the left posterolateral temporal-parietal cortex in Alzheimer’s disease patients compared with healthy seniors (Fig. 2C). Alzheimer’s disease patients showed relatively greater activation than healthy seniors in left lateral frontal cortex, left striatum-thalamus and right medial frontal cortex during pleasantness judgements of IMPLEMENTS (Fig. 2D).

Direct contrasts of activation patterns for ANIMALS and IMPLEMENTS within each group of subjects are summarized in Table 7 and illustrated in Fig. 3. For healthy seniors, we saw activation of left ventral temporal cortex for the contrast of ANIMALS minus IMPLEMENTS (Fig. 3A), but we did not see significant activation differences for the contrast of IMPLEMENTS minus ANIMALS in healthy seniors. For Alzheimer’s patients, Fig. 3B shows greater activation of the left ventral temporal cortex for the contrast of ANIMALS minus IMPLEMENTS that was more posterior than the activation seen in healthy seniors for the same contrast. The contrast of IMPLEMENTS minus ANIMALS in Alzheimer’s patients (Fig. 3C) shows relative activation of the right medial frontal cortex and right caudate.

**Discussion**

The main effects of the factorial analysis indicate that Alzheimer’s disease patients had reduced activation of left posterolateral temporal-inferior parietal and left lateral frontal regions relative to healthy seniors. Alzheimer’s disease patients also showed relatively reduced left posterolateral temporal-inferior parietal activation for each category of knowledge. Limited activation of these heteromodal association areas across several categories of knowledge in Alzheimer’s disease appears to be consistent with difficulty implementing a category-neutral process that is important for semantic memory. We also found distinct recruitment patterns for each category of knowledge in Alzheimer’s disease that differ from the activation profiles seen for the corresponding categories in healthy seniors. These findings are consistent with our two-component model of semantic memory, and with the hypothesis that the neural substrate for semantic memory is compromised at several levels in Alzheimer’s disease. Thus, Alzheimer’s disease patients may have difficulty with processes involving the integration of feature knowledge represented in multiple brain regions that is necessary for understanding any concept, and category-specific changes that may be concerned with the neural representation of knowledge contributing to individual concepts. We discuss below the processes important for integrating features into a coherent concept and the neural representation of feature knowledge.

**Activation patterns common to several categories of knowledge**

One factor potentially contributing to the semantic memory impairment in Alzheimer’s disease is a limitation in a category-neutral process that contributes to word comprehension. In our model of semantic memory, this refers to the
implementation of processes, such as feature integration and semantic categorization, that play a role in word meaning independently of the specific category of knowledge. Alzheimer’s disease patients appear to be impaired in rule-based semantic categorization (Grossman et al., 2001; Koenig et al., 2001). We hypothesize that the rule-based difficulty integrating features and categorizing objects in Alzheimer’s disease is related in part to executive limitations that mediate several processes important for semantic memory. These include identifying diagnostic features contributing to semantic category membership, inhibiting consideration of features that do not play an important role in semantic categorization, keeping track of these features in working memory, and allowing the flexible application of these criteria to the variety of exemplars of a semantic category. Executive resources such as working memory, selective attention and inhibitory control are limited in Alzheimer’s disease (Fisher et al., 1990; Morris, 1994; LaFleche and Albert, 1995; Cherry et al., 1996; Patterson et al., 1996; Perry and Hodges, 1999). Evidence consistent with our hypothesis comes from the observation of a rule-based semantic categorization deficit in Alzheimer’s disease that correlates with performance on measures of executive functioning (Rhee et al., 2001; Koenig et al., 2001). We and others also find some difficulty assessing the overall similarity between a test stimulus and a prototype or a remembered exemplar of a category in Alzheimer’s disease, whereby patients’ comprehension appears to be more dependent on highly representative exemplars of a category than less representative exemplars (Bozoki et al., 2001).

We hypothesize that the reciprocal connectivity pattern between heteromodal cortical association regions and modality-specific association cortices (Mesulam, 1985; Mesulam et al., 1977) supports category-neutral semantic processes such as these. More direct evidence consistent with this claim comes from fMRI observations of healthy adults showing recruitment of heteromodal association cortices during challenges dependent on semantic categorization. For example, we find relatively increased inferior parietal-posterior temporal activation during similarity-based semantic categorization (Rhee et al., 2001; Koenig et al., 2001). We and others also find some difficulty assessing the overall similarity between a test stimulus and a prototype or a remembered exemplar of a semantic category in Alzheimer’s disease, whereby patients’ comprehension appears to be more dependent on highly representative exemplars of a category than less representative exemplars (Bozoki et al., 2001).

### Table 5

<table>
<thead>
<tr>
<th>Contrast and region (Brodmann area)</th>
<th>Healthy seniors</th>
<th>Alzheimer’s disease patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease &lt; seniors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left posterolateral temporal (22, 39)</td>
<td>11.7 (5.5)</td>
<td>7.4 (4.2)</td>
</tr>
<tr>
<td>Left lateral frontal (44, 46)</td>
<td>18.2 (6.7)</td>
<td>2.6 (1.3)</td>
</tr>
<tr>
<td>Left occipital (17, 18)</td>
<td>11.7 (3.8)</td>
<td>4.4 (1.9)</td>
</tr>
<tr>
<td>Right ventral temporal (22, 20)</td>
<td>11.1 (4.0)</td>
<td>4.6 (1.7)</td>
</tr>
<tr>
<td>Alzheimer’s disease &gt; seniors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior temporal (19, 37)</td>
<td>16.2 (5.9)</td>
<td>25.3 (9.5)</td>
</tr>
<tr>
<td><strong>ANIMALS &gt; IMPLEMENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventral temporal (28, 34)</td>
<td>12.0 (3.2)</td>
<td>9.6 (4.2)</td>
</tr>
<tr>
<td><strong>IMPLEMENTS &gt; ANIMALS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right medial frontal (32, 24)</td>
<td>12.3 (3.0)</td>
<td>14.6 (5.3)</td>
</tr>
<tr>
<td><strong>Group differences within each category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANIMALS: Alzheimer’s disease &lt; seniors</td>
<td>4.7 (3.5)</td>
<td>3.3 (2.1)</td>
</tr>
<tr>
<td>ANIMALS: Alzheimer’s disease &gt; seniors</td>
<td>11.8 (6.3)</td>
<td>30.5 (8.1)</td>
</tr>
<tr>
<td>IMPLEMENTS: Alzheimer’s disease &lt; seniors</td>
<td>19.0 (4.0)</td>
<td>4.1 (1.6)</td>
</tr>
<tr>
<td>IMPLEMENTS: Alzheimer’s disease &gt; seniors</td>
<td>2.8 (1.3)</td>
<td>17.6 (7.9)</td>
</tr>
<tr>
<td>Left lateral frontal (44, 46)</td>
<td>3.0 (1.7)</td>
<td>11.3 (4.9)</td>
</tr>
<tr>
<td>Right striatum-thalamus</td>
<td>5.7 (2.3)</td>
<td>10.2 (4.7)</td>
</tr>
</tbody>
</table>

Tight regions were drawn around the significantly activated clusters of each group-wise contrast on each transaxial image of a normalized brain, and these regions were transferred in a user-independent manner to each corresponding slice for each activation of each subject’s normalized brain image. All voxels exceeding a statistical threshold set at a $P < 0.05$ level of significance were tabulated. We calculated the number of significantly activated voxels in each healthy senior and each Alzheimer’s disease patient as a percentage of the total number of voxels in each region, and multiplied this by 100. *Regions illustrated in Fig. 1 were analysed in healthy seniors and Alzheimer’s disease patients; †regions illustrated in Fig. 2 were analysed in healthy seniors and Alzheimer’s disease patients.
semantic categorization compared with rule-based semantic categorization (Koenig et al., 2002; Grossman et al., 2002b). These fMRI studies also demonstrate greater activation in dorsolateral prefrontal and dorsal inferior frontal regions during rule-based semantic categorization relative to similarity-based semantic categorization. Less direct evidence comes from multiple neuroimaging studies of healthy subjects showing that posterolateral temporal-inferior parietal and prefrontal/inferior frontal regions are recruited during semantic memory challenges regardless of the domain of knowledge or the nature of the task (Frith et al., 1991; Martin et al., 1995, 1996; Fiez et al., 1996; Warburton et al., 1996; Price et al., 1997; Mummery et al., 1998; Chao et al., 1999; Kellenbach et al., 2001; Tyler and Moss, 2001; Devlin et al., 2002; Grossman et al., 2002a; Whatmough et al., 2002).

Consider in this context the areas of changed activation that we observed in Alzheimer’s disease patients compared with healthy seniors in the factorial analysis across both categories.

Table 6 Direct contrasts of healthy seniors and Alzheimer’s disease patients during pleasantness judgements of animals and implements

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Activation locus (Brodmann area)</th>
<th>Co-ordinates</th>
<th>Activation extent (no. of voxels)</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANIMALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease &lt; seniors</td>
<td>Left posterolateral temporal-parietal (22, 40)</td>
<td>−52, −32, 24</td>
<td>58</td>
<td>2.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Alzheimer’s disease &gt; seniors</td>
<td>Left ventral temporal (19, 37)</td>
<td>−28, −40, −4</td>
<td>110</td>
<td>3.70</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>IMPLEMENTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease &lt; seniors</td>
<td>Left posterolateral temporal-parietal (22, 39)</td>
<td>−56, −40, 12</td>
<td>808</td>
<td>3.28</td>
<td>0.001</td>
</tr>
<tr>
<td>Alzheimer’s disease &gt; seniors</td>
<td>Left lateral frontal (44, 46)</td>
<td>−52, 4, 20</td>
<td>106</td>
<td>3.37</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Right medial frontal (32, 24)</td>
<td>20, 32, 16</td>
<td>60</td>
<td>3.21</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Left striatum–thalamus</td>
<td>−20, −12, 0</td>
<td>113</td>
<td>3.21</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 2 Direct contrasts of activation patterns in healthy seniors compared with Alzheimer’s disease patients during pleasantness judgements of ANIMALS and IMPLEMENTS. (A) Alzheimer’s disease patients showing less activation than healthy seniors for ANIMALS (Z = +16). (B) Alzheimer’s disease patients showing greater activation than healthy seniors for ANIMALS (Z = 0). (C) Alzheimer’s disease patients showing less activation than healthy seniors for IMPLEMENTS (Z = +16). (D) Alzheimer’s disease patients showing greater activation than healthy seniors for IMPLEMENTS (Z = +16).
of knowledge. Alzheimer’s disease patients showed less activation than healthy seniors in left posterolateral temporal-inferior parietal cortex for both ANIMALS and IMPLEMENTS. The reduced activation in this anatomical distribution in Alzheimer’s disease relative to healthy seniors was evident in direct group comparisons for each category of knowledge as well. We also found reduced activation of this brain region in Alzheimer’s disease relative to healthy seniors during pleasantness judgements of verbs (M. Grossman, P. Koenig, C. DeVita, G. Glosser, P. Moore, J. Gee, J. Detre and D. Alsop, unpublished results). Left posterolateral temporal-inferior parietal cortex has been implicated in semantic processing on the basis of structural imaging studies of patients with insult to this region (Hart and Gordon, 1990; Chertkow et al., 1997; Hillis et al., 2001), and correlations of performance on semantic tasks with functional neuroimaging studies obtained at rest in Alzheimer’s disease patients (Grossman et al., 1997; Desgranges et al., 1998). We also found less activation in left lateral frontal regions in Alzheimer’s disease compared with healthy seniors. These heteromodal areas show significant histopathological abnormalities in Alzheimer’s disease (Arnold et al., 1991; Braak and Braak, 1991). We hypothesize that these cortical regions are important for the semantic processes implicated in integrating the features contributing to a concept that are represented throughout modality-specific association cortices. Reduced activation in temporal-parietal and lateral frontal distributions during semantic judgements in Alzheimer’s disease thus may contribute to the semantic impairment that limits their word comprehension for multiple categories of knowledge.

We also found reduced activation in a right temporal distribution in Alzheimer’s disease compared with healthy seniors. There is considerable evidence that right hemisphere regions contribute to lexical comprehension, particularly for the concrete nouns that we used as stimuli in the present study (Zaidel, 1978; Chiarello et al., 1987; Kounios and Holcomb, 1994). Evidence to support the claim that the right ventral temporal cortex contributes to semantic decisions comes from a cognitive and computational modelling study in which patients with semantic dementia who had a semantic deficit also had atrophy involving the right temporal region (Lambon

**Table 7** Locus and extent of peak activations in brain regions during comparisons of pleasantness judgements for ANIMALS and IMPLEMENTS within each group

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Activation locus (Brodmann area)</th>
<th>Co-ordinates</th>
<th>Activation extent (no. of voxels)</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy seniors</td>
<td>ANIMALS &gt; IMPLEMENTS</td>
<td>Left ventral temporal (28, 34)</td>
<td>–20, –4, –8</td>
<td>201</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>IMPLEMENTS &gt; ANIMALS</td>
<td>No significant differences</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease patients</td>
<td>ANIMALS &gt; IMPLEMENTS</td>
<td>Left ventral temporal (19, 37)</td>
<td>–24, –40, –4</td>
<td>125</td>
<td>3.18</td>
</tr>
<tr>
<td></td>
<td>IMPLEMENTS &gt; ANIMALS</td>
<td>Right medial frontal (24, 32)</td>
<td>16, 32, 16</td>
<td>141*</td>
<td>3.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right caudate</td>
<td>4, 12, 8</td>
<td>141*</td>
<td>3.13</td>
</tr>
</tbody>
</table>

*These regions are part of the same cluster.
Ralph et al., 2001). However, this study does not provide precise anatomical information about the locus of atrophy in the semantic dementia patients. We found modest right temporal activation during pleasantness judgements in healthy seniors when compared with a pseudoword baseline, and other work investigating semantic memory reports activation in this anatomical distribution (Martin et al., 1996; Chao et al., 1999; Moore and Price, 1999). fMRI activation studies with other materials may be necessary to demonstrate more clearly the role of the right ventral temporal cortex in semantic memory.

Our findings suggest an area of increased activation for both categories of knowledge in Alzheimer’s disease relative to healthy seniors as well. Specifically, we found relatively increased activation in left inferior temporal cortex in Alzheimer’s disease. This is in an anatomical distribution that is adjacent to the left lateral temporal activation seen in healthy seniors compared with Alzheimer’s disease patients. We found a similar distribution of relatively increased activation during comprehension of verbs in Alzheimer’s disease (M. Grossman, P. Koenig, C. DeVita, G. Glosser, P. Moore, J. Gee, J. Detre and D. Alsop, unpublished results). While Alzheimer’s disease patients do not equal healthy seniors in their single-word comprehension accuracy, we hypothesize that mechanisms associated with upregulation play a compensatory role in mild or moderate Alzheimer’s disease that allows these patients to maintain some understanding of single-word meaning. This observation of local cortical reorganization must be interpreted cautiously because of the limited spatial resolution of MRI, the spatial smoothing that we used to minimize individual differences in gyral anatomy, and the atrophy that can occur in the brains of Alzheimer’s disease patients. The need for caution is further emphasized by the largely venous source of the BOLD signal, which may not correspond precisely to the locus of neural activity at the magnet strength of 1.5 T that we used for this study. Upregulation of a cortical region in Alzheimer’s disease that is adjacent to the area activated by healthy seniors nevertheless may reflect compensatory cortical reorganization following injury to the CNS that parallels some of the changes observed in patients recovering successfully from stroke-induced aphasia (Heiss et al., 1999; Rosen et al., 2000). Increased activation in Alzheimer’s disease relative to healthy seniors in the present study is paralleled by previous demonstrations showing upregulation during functional neuroimaging assessments in Alzheimer’s disease (Becker et al., 1996; Woodard et al., 1998; Saykin et al., 1999; Grady et al., 2001). The biological basis for this compensatory activation may be the axonal sprouting and biochemical changes associated with cortical reorganization that are described in Alzheimer’s disease (Scheibel and Tomiyasu, 1978; Geddes et al., 1985; Kowall and McKee, 1993). Regardless of the basis for these observations, increases in activation in Alzheimer’s disease compared with healthy seniors emphasize that areas of limited activation in Alzheimer’s disease are not due to something like a general or non-specific reduction in activation.

**Activation patterns for category-specific knowledge**

We also found some activation changes in Alzheimer’s disease compared with healthy seniors that were category-specific since they were associated either with ANIMALS or with IMPLEMENTS. fMRI activation in young adults shows distinct recruitment patterns for ANIMAL and IMPLEMENT categories of knowledge using the pleasantness judgement technique of this study as well as other kinds of semantic challenges (Martin et al., 1996; Moore and Price, 1999; Grossman et al., 2002a). In our study, for example, healthy subjects recruited left ventral temporal cortex for ANIMALS; for IMPLEMENTS, lateral temporal and prefrontal portions of the left hemisphere were activated. Some attribute category-specific recruitment patterns such as these to the privileged role that particular features may play in specific categories of knowledge, such as the hypothesized importance of visual–perceptual feature knowledge for the mental representation of natural kinds like ANIMALS, or the importance of visual–motion and motor–action features for IMPLEMENTS (Perani et al., 1995; Damasio et al., 1996; Martin et al., 1996; Cappa et al., 1998b; Grabowski et al., 1998; Chao et al., 1999; Smith et al., 2001). Several investigators question the claim that category-specific semantic memory effects can be explained entirely by the role of feature knowledge in a specific semantic category (McRae et al., 1997; Caramazza and Shelton, 1998; Tyler and Moss, 2001). Similarly, inconsistent patterns of neural activation associated with a category, possibly due to the assessment of different subcategories, tasks and baselines across studies, raise doubts about the meaningfulness of associating a specific set of features with activation for a particular category of knowledge (Farah and Aguirre, 1999; Joseph, 2001). Additional evidence inconsistent with the claim that left frontal and temporal activation is related exclusively to sensory–motor feature knowledge comes from the finding that ABSTRACT nouns impoverished in their sensory–motor features also activate the same brain regions as IMPLEMENTS (Beaufregard et al., 1997; Kiehl et al., 1999; Grossman et al., 2002a; Noppeney and Price, 2002).

An alternative approach to the neural representation of category-specific knowledge focuses on the different patterns of overlapping and shared features associated with each category (Tyler and Moss, 2001; Devlin et al., 2002). While fMRI studies from this perspective often minimize category-specific activation patterns, our model takes into account the observation of distinct anatomical distributions of activation that are reported for categories such as these (Martin et al., 1996; Moore and Price, 1999; Grossman et al., 2002a; J. Kounios, P. Koenig, G. Glosser, C. DeVita, K. Dennis, P. Moore and M. Grossmann, unpublished results). In particular,
we find significantly greater activation in the left medial temporal lobe (MTL) for IMPLEMENTS but not ANIMALS in young adults compared with healthy seniors (J. Kounios, P. Koenig, G. Glosser, C. DeVita, K. Dennis, P. Moore and M. Grossmann, unpublished results). The MTL is associated with consolidation in long-term memory in several studies of brain-damaged patients (Lambon Ralph et al., 1998a; Westmacott et al., 2001; Holdstock et al., 2002) and fMRI experiments in young adults (Maguire et al., 2000; Ryan et al., 2000; Haist et al., 2001). The acquisition of knowledge about ANIMALS may be relatively complete at a young age and thus equally consolidated in young adults and healthy seniors, facilitated in part by the greater overlapping of shared features across exemplars of this category. We speculate that this reliable overlapping of shared perceptual features may also lead to the neural representation of knowledge associated with ANIMALS relatively early in the visual processing stream, as we and others find (Martin et al., 1995, 2000; Chao et al., 1999; Thompson-Schill et al., 1999; Wiggs et al., 1999; Kellenbach et al., 2001). By comparison, knowledge of IMPLEMENTS may continue to be acquired and consolidated in young adults relative to healthy seniors because of limited overlapping features across exemplars of this category. The age-related difference in MTL activation only for IMPLEMENTS may reflect the sparser distributional pattern of features for this category. The neural representation of knowledge about a category like IMPLEMENTS thus may depend on the complex relationships between multidimensional features represented in long-term memory. From this perspective, posterolateral temporal cortex may need to be recruited to help integrate this sparsely distributed feature knowledge.

Consider in this context the category-specific changes in activation seen in Alzheimer’s disease relative to healthy seniors. As in some studies of healthy seniors and young adults, Alzheimer’s disease patients activated ventral temporal portions of the left hemisphere centred in the lingual gyrus for the category of ANIMALS. Regardless of the specific explanation for this anatomical distribution, this observation suggests that Alzheimer’s disease patients are able to access at least some of the knowledge associated with ANIMALS. However, the distribution of peak activation associated with the contrast of ANIMALS minus IMPLEMENTS in Alzheimer’s disease (Table 7 and Fig. 3B) was displaced by ~30 mm from the activation peak noted for the contrast of ANIMALS minus IMPLEMENTS in healthy seniors (Table 7 and Fig. 3A). In a direct contrast of groups, Alzheimer’s disease patients recruited left ventral temporal cortex for ANIMALS in a more posterior distribution (Table 6 and Fig. 2B) than the main effect for ANIMALS minus IMPLEMENTS (Table 4 and Fig. 1C). The limited spatial resolution of MRI, the spatial smoothing we used and the atrophy that can occur in the brains of Alzheimer’s disease patients are among the reasons for cautious interpretation of these results. Nevertheless, this amount of displacement is likely to be beyond the spatial extent that can be accommodated by these factors.

According to histopathological observations (Arnold et al., 1991; Braak and Braak, 1991), ventral temporal cortex is compromised in Alzheimer’s disease. This anatomical distribution of disease has been the basis for arguments that Alzheimer’s disease patients are particularly impaired in their comprehension and naming of natural kinds, such as ANIMALS (Garrard et al., 1998). The present study suggests that the disease process results in sufficient impairment of cortical functioning in this region that ventral temporal cortex is not recruited in Alzheimer’s disease as it is in healthy seniors. Instead, the upregulation of a cortical region in Alzheimer’s disease that is adjacent to the area activated by healthy seniors may reflect compensatory cortical reorganization of the neural representation of semantic feature knowledge in the face of Alzheimer’s disease. The pattern of cortical reorganization associated with neurodegenerative disease appears to resemble in part that observed in stroke patients recovering successfully from aphasia (Heiss et al., 1999; Rosen et al., 2000).

It is unclear whether a similar pattern of compensatory local cortical reorganization is evident in the activation pattern associated with IMPLEMENTS in Alzheimer’s disease as well. Alzheimer’s disease patients thus show relatively greater activation than healthy seniors for IMPLEMENTS in left lateral frontal cortex, left striatum–thalamus and right medial frontal cortex. Left frontal cortex is recruited in healthy adults for IMPLEMENTS in several studies (Perani et al., 1995; Martin et al., 1996; Grabowski et al., 1998; Grossman et al., 2002a). Even though a direct contrast of IMPLEMENTS minus ANIMALS in healthy seniors did not show frontal activation in the present study, we did see greater prefrontal activation in healthy seniors relative to Alzheimer’s disease patients in the main effect of the factorial analysis. Frontal cortex is compromised histopathologically in Alzheimer’s disease (Arnold et al., 1991; Braak and Braak, 1991), and there may also be category-specific displacement of activation in left frontal cortex in Alzheimer’s disease during the evaluation of IMPLEMENT terms. This will require additional evaluation.

We also found category-specific areas of activation for IMPLEMENTS that were not adjacent to recruitment in healthy seniors. For example, between-group contrasts demonstrated greater left caudate recruitment for IMPLEMENTS in Alzheimer’s disease compared with healthy seniors. Greater right caudate activation was seen in the contrast of IMPLEMENTS minus ANIMALS in Alzheimer’s disease as well. This may be a category-specific effect related to the motor component of IMPLEMENT knowledge, given the role of striatal structures in motor functioning. Alternately, caudate activation may reflect relatively increased working memory demands (Poldrack et al., 1999; Rypma et al., 1999). We also found greater left thalamic activation for IMPLEMENTS in Alzheimer’s disease compared with healthy seniors. Thalamic activation has been associated with selective attention...
Relatively greater left thalamic and caudate activation in Alzheimer’s disease for IMPLEMENTS thus may reflect an attempt to respond to the increased resource demands of the IMPLEMENTS category of knowledge, possibly due to the less overlapping network of shared features relative to ANIMALS. Subcortical structures may be activated because these are less compromised histopathologically in patients with relatively mild Alzheimer’s disease. Additional work is needed to establish the basis for these changes in Alzheimer’s disease relative to healthy seniors.

Between-group comparisons also showed that right medial frontal activation was greater in Alzheimer’s disease patients than healthy seniors during judgements of IMPLEMENTS. This area was also activated for IMPLEMENTS relative to ANIMALS in Alzheimer’s disease. Pleasantness judgements in healthy young adults was associated with recruitment of medial frontal cortex in one study (Gusnard et al., 2001). The investigators suggest that this reflects the integration of cognitive and affective processing. The category-specific nature of this relative activation in Alzheimer’s disease indicates that this is not a general property of the pleasantness judgement task in the present study. However, it is possible that the relatively complex nature of IMPLEMENTS encourages Alzheimer’s disease patients to focus more on pleasantness per se than healthy seniors. Additional work is needed to determine the basis for this distribution of activation in Alzheimer’s disease.

We did not observe category-specific differences in the cognitive performance of the Alzheimer’s disease patients participating in this study. This may be due in part to the relatively mild level of disease severity in these patients. A distributed model of category-specific knowledge hypothesizes different rates of decline for ANIMALS and IMPLEMENTS as the disease progresses (Gonnerman et al., 1997; Devlin et al., 1998; Tyler et al., 2000). Decline in ANIMAL knowledge may be modest early in the disease process, for example, because the massively interconnected networks that support converging and shared features across natural kinds resist degradation in the face of a progressive neurodegenerative disease. Artefacts have fewer shared features, according to this theory, and Alzheimer’s disease patients thus may lose knowledge of IMPLEMENTS in an insidiously progressive manner as critical individual features are lost in proportion to disease progression. From a neural perspective, we find displaced activations for both categories of knowledge in Alzheimer’s disease, and the disease process may need to be more advanced for behavioural differences to emerge. Longitudinal neuroimaging studies of Alzheimer’s disease will be necessary to assess this possibility.

Conclusion
In the present study, we find changed activation patterns in Alzheimer’s disease patients relative to healthy seniors during a semantic challenge. The results are consistent with a neurocognitive model of semantic memory that hypothesizes two components: a category-neutral component contributing to feature integration processes such as semantic categorization; and a category-specific component that concerns the representation of feature knowledge peculiar to each semantic category. Alzheimer’s disease patients appear to be impaired in both components of this model. Category-neutral semantic processes appear to be related in part to heteromodal association cortices in posterolateral temporal-inferior parietal and lateral frontal regions of the left hemisphere. This may explain the frequent implication of these areas in a wide range of semantic studies, including neuroimaging activation studies of healthy subjects and correlational studies in patients with CNS disease. The hypothesized integrative function of these regions is consistent with their neuroanatomical connectivity pattern, involving reciprocal projections between heteromodal and modality-specific association cortices. Reduced activation of heteromodal regions in Alzheimer’s disease for both categories of knowledge suggests a limitation in the category-neutral processes involved in feature integration and categorization that are important for semantic memory. Upregulation of an adjacent area in the left temporal cortex in Alzheimer’s disease suggests an attempt to compensate for semantic categorization processes that appear to be compromised. We also see distinct patterns of changed activation in Alzheimer’s disease for each specific category of knowledge. Category-specific areas of increased recruitment for ANIMALS and IMPLEMENTS in Alzheimer’s disease may allow these patients to recruit partial representations of each category.

Acknowledgement
A portion of this work was presented at the 54th annual meeting of the American Academy of Neurology in Denver, April, 2002, and the Academy of Aphasia in New York, October, 2002. This work was supported in part by grants from the US Public Health Service (AG15116, AG17586, NS35867).

References
Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of...


Kiehl KA, Liddle PF, Smith AM, Mendrek A, Forster BB, Hare RD. Neural pathways involved in the processing of concrete and abstract words. Hum Brain Mapp 1999; 7: 225–33.


Perani D, Cappa SF, Bettinardi V, Bressi S, Gorno-Tempini M,


Whatmough C, Chertkow H, Murtha S, Hanratty K. Dissociable


Received September 4, 2002.
Accepted September 8, 2002