



Naming impairment in Alzheimer's disease is associated with left anterior temporal lobe atrophy

Kimiko Domoto-Reilly ^{a,b,*}, Daisy Sapolsky ^{a,c,d}, Michael Brickhouse ^{a,c}, Bradford C. Dickerson ^{a,b,c,e,f} and for the Alzheimer's Disease Neuroimaging Initiative ¹

^a Frontotemporal Dementia Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^b Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^c Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^d Department of Speech and Language Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^e Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

^f Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:

Accepted 13 June 2012

Available online 21 June 2012

Keywords:

Magnetic resonance imaging

Cerebral cortex

Alzheimer's disease

Language

Anterior temporal lobe

Semantic memory

ABSTRACT

There is considerable debate about the neuroanatomic localization of semantic memory, the knowledge of culturally shared elements such as objects, concepts, and people. Two recent meta-analyses of functional imaging studies (fMRI and PET) sought to identify cortical regions involved in semantic processing. Binder and colleagues (Binder et al., 2009) identified several regions of interest, widely distributed throughout the frontal, parietal, and temporal cortices. In contrast, Lambon Ralph and colleagues (2010) focused on the anterior temporal lobe, and found that when the potential for signal loss is accounted for (due, for example, to distortion artifact or field of view restriction), significant regional activation is detected. We set out to determine whether the anterior temporal lobe plays a significant role in picture naming, a task which relies on semantic memory. We examined a relatively large sample of patients with early Alzheimer's disease (N = 145), a multifocal disease process typically characterized in the early stages by problems with episodic memory and executive function. Hypothesis-driven analyses based on regions of interest derived from the meta-analyses as well as exploratory analyses across the entire cerebral cortex demonstrated a highly specific correlation between cortical thinning of the left anterior temporal lobe and impaired naming performance. These findings lend further support to theories that include a prominent role for the anterior temporal lobe in tasks that rely on semantic memory.

© 2012 Elsevier Inc. All rights reserved.

Introduction

Semantic memory is a form of declarative memory, distinct from working and episodic memory, that supports factual knowledge about elements of the world. A major debate between investigators studying semantic memory hinges upon the neuroanatomic localization of brain regions contributing to this ability. One school of thought proposes that semantic memory is subserved by a distributed set of brain regions organized around the sensory and motor areas that support the perception of specific sensory properties of objects and execution of actions (Martin, 2007), with certain critical nodes in heteromodal

association cortex that integrate this information through convergence zones (Damasio, 1989, 1990; Tranel et al., 1997). An alternative view postulates that there is a hub localized in the anterior temporal lobes (ATL) that serves a central integrating function for information processed in the distributed set of sensory, motor, and linguistic zones (Patterson et al., 2007).

Each of these views is supported by evidence from both functional neuroimaging studies of healthy subjects and investigations of patients with brain lesions (Chertkow et al., 2008; Lambon Ralph et al., 2010a; Tranel, 2009). Two recent meta-analyses of functional neuroimaging data deserve particular mention. Binder and colleagues analyzed 120 functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies carefully chosen to include only those with tasks and contrasts that specifically differentiate semantic processing from other linguistic or cognitive processes (Binder et al., 2009). These authors identified seven regions that were consistently and specifically engaged during semantic processing: posterior inferior parietal lobule (angular gyrus), middle temporal gyrus, fusiform and parahippocampal gyri, dorsomedial prefrontal cortex, inferior frontal gyrus, ventromedial prefrontal cortex, and posterior cingulate gyrus. Although the involvement

* Corresponding author at: MGH Frontotemporal Disorders Unit, 149 13th St., Suite 2691, Charlestown, MA 02129, USA. Fax: +1 617 726 5760.

E-mail address: kdomoto-reilly@partners.org (K. Domoto-Reilly).

¹ Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

of the middle temporal gyrus extended rostrally toward the temporal pole, the ATL itself was not formally identified in this analysis nor did the authors include an ATL region in their proposed model of the large-scale semantic network (see Fig. 7 of Binder et al., 2009). In contrast, Lambon Ralph and colleagues performed a meta-analysis of 164 fMRI and PET studies, specifically focusing on the ATL, and concluded that semantic processing engaged the ATL without regard to the specific type of stimulus or task, supporting its role as an amodal “hub” of the semantic memory system (Visser et al., 2010). Their study highlighted the imperative for a careful analysis of ATL activation in functional neuroimaging experiments: if this region is not included in the field of view, or distortion artifact is not accounted for, the activation is easily missed.

In the present investigation, we sought to contribute to this debate by studying patients with Alzheimer’s disease (AD). AD is generally thought of as a disease affecting episodic memory, executive function, and multiple other cognitive domains; it is also well-known for producing a deficit in semantic memory (Appell et al., 1982; Chertkow and Bub, 1990; Kertesz et al., 1986; Martin and Fedio, 1983), although in the early stages of the illness this deficit is typically subtle (Joubert et al., 2008). Here we examined, within a large sample of patients with very mild and mild AD, the anatomic localization of cortical atrophy correlating with semantic impairment. We hypothesized that, if semantic memory is subserved primarily by a large-scale set of brain regions distributed throughout temporal, parietal, and frontal cortices, the degree of semantic impairment in AD would be predicted by the amount of atrophy throughout these brain regions. Conversely, if access to semantic memory requires the presence of a hub in the ATL, AD patients with relatively greater semantic impairment would be predicted to have the most significant atrophy in this region.

Material and methods

Overview

To address these questions, we performed two sets of analyses using imaging and neuropsychological data from the Alzheimer’s Disease Neuroimaging Initiative dataset (described below). We studied subjects with very mild or mild AD dementia, performing both hypothesis-driven and exploratory analyses of regional cortical atrophy in relation to the degree of semantic impairment. In the hypothesis-driven analysis, we chose regions of interest (ROIs) from prior analyses of functional neuroimaging data (Binder et al., 2009; Visser et al., 2010) to determine which ROIs better accounted for the relationship between degree of atrophy and level of semantic impairment. We also performed an exploratory analysis across the entire cortex to localize regions in which degree of atrophy correlated with level of semantic impairment.

Subjects

Data used in this study were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco.

ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

For the current analysis, we selected right-handed native English speakers with an initial diagnosis of very mild or mild AD who underwent a baseline 1.5 T MRI scan of adequate quality to obtain the below described morphometric measures, and who had initial visit performance data on the Boston Naming Test (N = 175). Diagnosis of AD was made based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria (McKhann et al., 1984). All AD subjects in the cohort had a memory complaint corroborated by an informant, objective memory impairment on the Logical Memory II test, a Mini Mental State Examination (MMSE) score of 20 to 26 (inclusive), and a Clinical Dementia Rating (CDR) scale score of 0.5 or 1.0 (Morris, 1993) (see Table 1). Thus, these individuals all exhibited the most common form of AD dementia, which is an amnesic presentation; none exhibited a syndrome consistent with Primary Progressive Aphasia. Other inclusion and exclusion criteria for ADNI are described at: <http://www.adni-info.org/index.php>. The older controls (OC), all right-handed native English speakers with adequate baseline imaging and language measures, were also extracted from the ADNI dataset (N = 210).

Semantic memory assessment

In the ADNI version of the Boston Naming Test (BNT), subjects are asked to name 30 black and white line drawings, each of a single object. The subject is given up to 20 s to respond, and if the initial response is determined to be an error based on visuoperceptual misinterpretation, a semantic cue is offered. A phonemic cue is offered for all incorrect or non-responses, regardless of whether there was a visuoperceptual error. The test is discontinued if there are 6 consecutive failures, inclusive of responses to semantic cueing. The subject receives an initial “spontaneous” score based on the first response (or lack thereof); the total score is the sum of the initial correct responses plus additional correct responses after a semantic prompt (if given). A separate score of correct responses to phonemic cues is recorded but not included in the total score. The number of semantic and phonemic cues given is also recorded.

Although the test is supposed to be discontinued after 6 consecutive errors, there were multiple instances in which the entire battery of 30 pictures was administered despite, for example, a total score of 5. However, presentation of all 30 stimuli was of greatest interest to our analysis, as it provided the most complete assessment of semantic memory integrity as determined by naming ability. We therefore

Table 1
Subject demographics and behavioral measures.

	Older controls	AD subjects
N [F]	183 [90]	145 [64]
Age, years	75.8 (5.1)	75.7 (7.4)
Education, years	16.1 (2.8)	14.8 (3.0)*
MMSE (/30)	29.1 (1.0)	23.4 (2.0)*
CDR 0/0.5/1.0	183/0/0	0/77/68
CDR-SB	0.03 (0.1)	4.2 (1.6)*
BNT sum score (/30)	29.5 (1.0)	26.5 (5.0)*
BNT sum Z score	0.0 (1.0)	− 3.0 (5.0)

AD = Alzheimer’s disease; F = female; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating scale; CDR-SB = Clinical Dementia Rating scale Sum of Boxes; BNT = Boston Naming Test; unless otherwise indicated, values are mean (standard deviation).

* $p < 0.05$.

excluded subjects who had not been presented all 30 items. Subjects were also excluded if they did not receive cueing for all of the items that they failed to name. This left 183 OC subjects and 145 AD subjects who had been presented with 30 items and who had also received phonemic cueing for all items that were not named correctly either spontaneously or after a semantic cue. We calculated a summary score (“BNT sum score”) consisting of the total of spontaneous correct responses and any additional correct responses following semantic and phonemic cueing. BNT sum Z scores were calculated for the AD subjects using the Older Control group as the normative sample. This measure served as our primary behavioral variable. For completeness sake, we also analyzed spontaneous BNT scores as well as BNT scores with semantic cues only (and not phonemic cues). Because these measures were highly correlated, they produced very similar results and therefore are not reported.

MRI data acquisition and analysis

MRI scans for ADNI were collected on a 1.5 T scanner using a standardized protocol across sites. For the present analysis, the MPRAGE sequence was used with the following characteristics: sagittal plane, TR/TE/TI, 2400/3/1000 ms, flip angle 8°, 24 cm FOV, 192 × 192 in-plane matrix, 1.2 mm slice thickness (Jack et al., 2008).

T1 image volumes were examined quantitatively by a cortical surface-based reconstruction and analysis of cortical thickness using FreeSurfer version 5.0 (<http://surfer.nmr.mgh.harvard.edu>). The general procedures for this processing method have been described in detail and applied and validated in a number of publications and presentations; the technical details can be found in select manuscripts (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999a,b, 2002, 2004). Cortical thickness measures were analyzed by both a hypothesis-driven and an exploratory approach.

For the hypothesis-driven approach, we first utilized ROIs defined from prior literature as follows. Using the map shown in Fig. 3 of the Binder et al. meta-analysis (Binder et al., 2009), we defined 15 ROIs: bilateral posterior inferior parietal lobule (angular gyrus), bilateral caudal supramarginal gyrus, left rostral supramarginal gyrus, left caudal superior temporal sulcus, right rostral superior temporal sulcus, right caudal superior temporal gyrus, bilateral caudal middle temporal gyrus, left parahippocampal gyrus, left dorsomedial, ventromedial, and ventrolateral prefrontal cortex, left caudal inferior frontal gyrus, left frontoinsula cortex, left superior frontal gyrus, and bilateral posterior cingulate gyrus. These ROIs were created by resampling the statistical map used to generate Fig. 3 (Binder et al., 2009) onto the cortical surface average template (Freesurfer's *fsaverage*, N = 40, version 5.0) and then thresholding the map to create approximately similarly sized ROIs on the cortical surface.

Based on the Visser et al. meta-analysis (Visser et al., 2010), we defined 4 ROIs in the anterior temporal and frontal cortex: left medial temporal pole, left rostral superior temporal sulcus, right temporal pole, and left caudal orbitofrontal cortex. The maps in Fig. 3B-1 of the manuscript were visually inspected and each of the ATL clusters were localized in MNI template space and then mapped to the cortical surface average template; an ROI was created around the point by manually tracing a surface-based sphere.

We therefore had two sets of ROIs on the Freesurfer *fsaverage* cortical surface template: a “distributed” set based on the Binder et al. meta-analysis, and a “hub” set based on the Visser et al. meta-analysis (see Fig. 1). Each ROI was then mapped to each individual subject's cortical surface reconstruction using the spherical coordinate system. The average thickness of the cortex within each ROI was extracted for statistical analysis. For each subject, the individual ROIs from each of these two sets were averaged to compute a single composite measure for each set. A Z score of each composite measure was then calculated using the OC group as the normative sample as previously described

(Bakkour et al., 2009; Dickerson et al., 2011b). These measures were then used in the hypothesis-driven statistical analyses described below.

Statistical analysis

Analyses of demographic and behavioral data, as well as hypothesis-driven ROI analyses, were performed using standard methods in SPSS 16.0 (Chicago, IL). Pearson correlations between composite ROI (distributed or hub) cortical thickness Z score and BNT sum Z scores were calculated within the AD patient group (N = 145), after controlling for the effects of age, education, gender, MMSE score, and CDR sum of boxes (CDR-SB) on naming performance. In addition, one-way ANOVA analyses were performed of AD patients with impaired BNT performance (2.0 or more S.D. below that of controls) vs. those with BNT performance within normal limits (less than 2.0 S.D. below that of controls). The alpha value was set at 0.05 for all tests and for the hypothesis-driven ROI analysis it was Bonferroni-corrected for 2 comparisons (2 composite ROI measures).

For the exploratory analysis, general linear models were implemented in Freesurfer using the *mri-glmfit* command with BNT sum Z score as the independent variable of interest, cortical thickness values as the dependent variable, and age, education, gender, MMSE score, and CDR-SB as covariates. This analysis was run in the group of AD patients (N = 145). The results of this analysis were inspected via maps of the statistical significance at each surface point overlaid on the average cortical surface template. For these exploratory analyses, an arbitrary uncorrected statistical threshold of $p < 10^{-3}$ was used.

We also performed a Freesurfer analysis of regional cortical thinning across the entire cortical surface in the group of AD patients as compared to older controls (N = 183), controlling for age, as has been previously described (Bakkour et al., 2009; Dickerson et al., 2009).

Results

Demographic data

183 older control subjects (90 females) and 145 AD subjects (64 females) with very mild (CDR 0.5, 77 subjects) or mild (CDR 1.0, 68 subjects) were included in the analyses (see Table 1). As expected, the older control and AD groups differed MMSE and CDR-SB scores ($p < 0.05$). In addition, the AD subjects performed – as a group – worse on the naming task than the controls, but there was a considerable range in naming ability with 59% of the AD patients scoring within the normal range. There was a statistically significant but small (1 year) difference between the years of education for each group.

Hypothesis-driven ROI measures in relation to naming impairment in AD

Cortical thickness of the distributed set of ROIs did not correlate with BNT performance ($R = 0.122$, $p = 0.145$; see Fig. 2). In contrast, a correlation was found between cortical thickness of the hub ROIs and BNT performance ($R = 0.316$, $p = 0.0001^{**}$). To further examine these variables, we ran a multiple linear regression model with BNT (adjusted for covariates) as the dependent variable and the ROIs as independent variables; hub ROIs entered the model as expected but the distributed ROIs did not explain any additional variance in BNT performance and did not enter the model (R squared change = 0.01, $p = 0.17$).

In addition to this analysis, we compared the ROI measures using ANOVA between the AD patients who demonstrated impairment on the BNT sum score as defined above to those who performed within normal limits on this score. This analysis demonstrated that the hub ROIs were substantially smaller in the AD patient group with impaired naming than in the group with preserved naming performance ($F = 22.3$, $p < 0.00001$; Cohen's *d* effect size = 0.79). However, the distributed ROIs showed a smaller trend-level similar effect ($F = 3.4$,

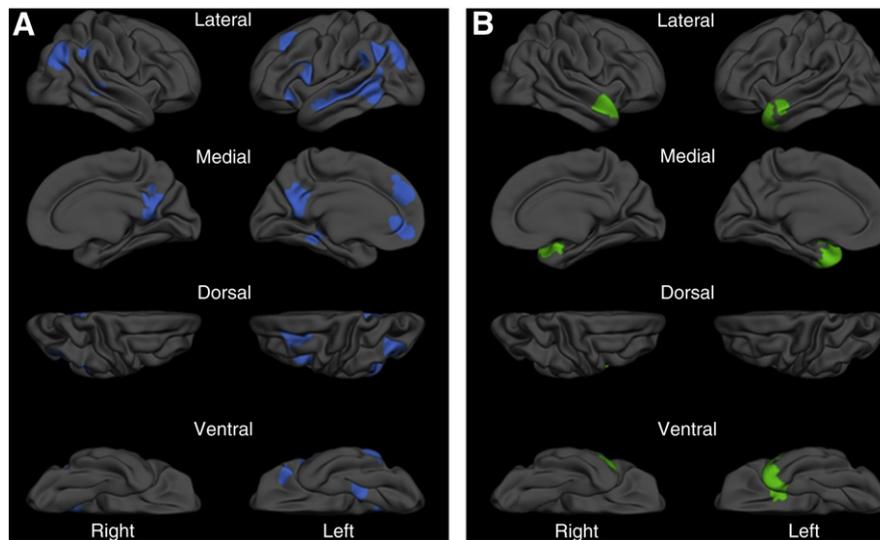


Fig. 1. The composite ROI sets used for hypothesis-driven analyses. The “distributed” ROI set (A) is based on the Binder et al. (2009) meta-analysis of functional neuroimaging data, and the “hub” ROI set (B) on the Visser et al. meta-analysis (2010), as described in the text.

$p = 0.068$; Cohen's d effect size = 0.31), further supporting the localization of this naming deficit to the anterior temporal lobe. See Fig. 3 for an illustration of these results.

Exploratory cortical thickness correlates of naming impairment in AD

The analysis exploring cortical thickness in relation to naming impairment across the entire cortical mantle demonstrated that, in subjects with very mild to mild AD, naming impairment is specifically correlated with cortical thinning of the left temporal pole and nearby ventrolateral temporal regions (Fig. 4). Specific regions of cortical thinning in the left hemisphere are: temporal pole, the anterior two thirds of the middle temporal gyrus, the anterior two thirds of the inferior temporal gyrus, the majority of the parahippocampal gyrus including the perirhinal cortex, and the mid-fusiform gyrus. The strongest correlation was present in the dorsal temporal pole ($R = 0.342$, $p < 0.00001$).

Exploratory analysis of regional cortical thinning in AD

Finally, we performed an analysis across the entire cortical mantle to determine the regions of cortical thinning in this group of AD patients as compared to the group of older controls (Fig. 5). As expected,

the multiple foci of thinning are distributed symmetrically throughout both hemispheres, in a pattern corresponding closely to the set of ROIs our group has previously defined as being affected in early AD (Bakkour et al., 2009; Dickerson et al., 2009, 2011a). Thus, the “anatomic” lesion of cortical thinning in this group of mild AD patients (Fig. 5) is distinct from the “functional” lesion of cortical thinning that predicts poor naming performance (Fig. 4).

Discussion

The localization of neural substrates of semantic memory continues to be debated. In this study, we set out to investigate two of the leading models: one describing a widely “distributed” set of multimodal regions versus an alternative model with the anterior temporal lobe (ATL) serving as a “hub” to integrate the multimodal information (“distributed plus hub” model). We analyzed cued naming performance as a means of assessing semantic memory integrity in a large group of patients with very mild to mild AD dementia. Although AD is a widely distributed multifocal neurodegenerative disease process, and is not typically characterized by prominent early impairment of semantic memory, we found here that cued naming impairment in mild AD is correlated specifically with cortical thinning

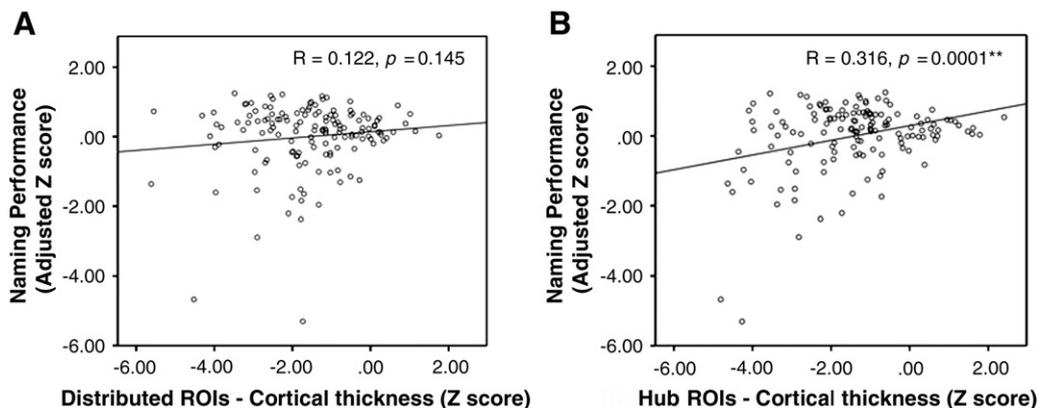


Fig. 2. Hypothesis-driven analysis in patients with AD dementia showed that naming impairment is correlated with cortical thinning in hub ROIs (B) but not in distributed ROIs (A). These ROIs were generated from previous meta-analyses of fMRI studies of semantic function as described in the Materials and methods section and as shown in Fig. 1. The x axis depicts Z scores for each ROI measure, derived from comparison with the control group. The graphs illustrate the results of partial correlation analyses after the naming measure was adjusted for covariates and standardized as described in the text; thus, the y axis depicts deviation of the naming measure from the mean of the AD patient group after these adjustments.

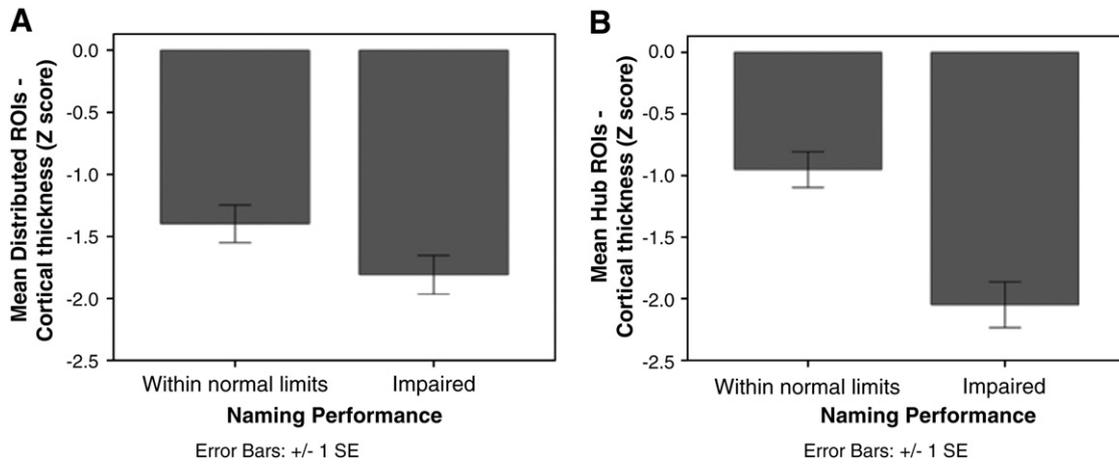


Fig. 3. Hypothesis-driven analysis showed that, compared to those who performed within normal limits on the naming task, AD patients with naming impairment have more prominent cortical thinning in hub ROIs (B) than in distributed ROIs (A). These graphs illustrate raw naming score without adjustment for covariates as was done in Fig. 2.

of the left ATL. The localization of this brain–behavior relationship is strikingly focal, clearly distinct from the medial and lateral temporal and posterior cingulate atrophy correlations with episodic memory impairment in the same sample (Wolk and Dickerson, 2011).

Many investigators agree that semantic processing is subserved by a widely distributed, “partly organized,” multimodal semantic network of cortical regions; the primary point of contention revolves around whether the interactions of the components of the semantic network are governed by an amodal “hub” (Patterson et al., 2007). Such a hub would facilitate efficient, accurate access to semantic knowledge, regardless of task modality (e.g., picture naming, spontaneous speech, reading or writing). Although we have focused on the distributed versus hub models in the present study, there are additional theories regarding

the role of the ATL in the brain systems subserving semantic memory. In a recent review, Gainotti builds upon prior ideas to propose that, while the temporal pole is critical to semantic processing, its function is not as an amodal hub but rather as a convergence zone between dorsal and ventral visual streams with lateralized hemispheric specialization (Gainotti, 2011a,b; also Butler et al., 2009; Mion et al., 2010). A series of studies have led Tranel and colleagues to propose that the ATLs play more specific roles in the retrieval of names of unique entities (Grabowski et al., 2001; Tranel, 2009). Finally, Martin and colleagues have proposed an alternative function for the ATLs rooted in the interaction of semantic and social cognition networks (Simmons and Martin, 2009; Simmons et al., 2010; see also Thompson et al., 2004). Although our results do not adjudicate between these views, they provide

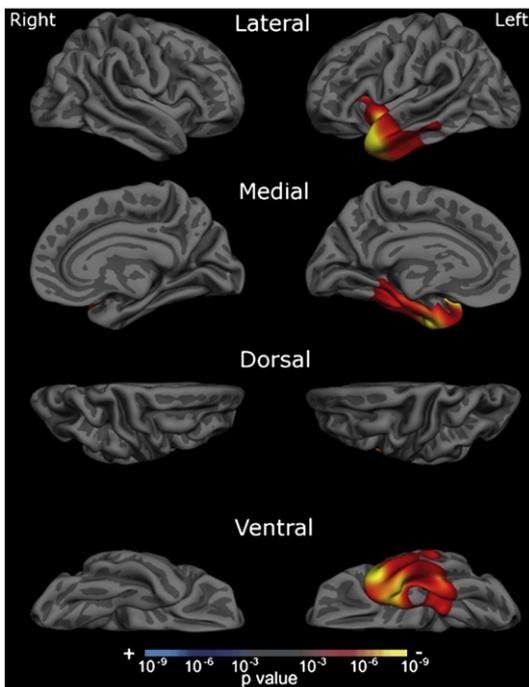


Fig. 4. AD patients with more prominent semantic impairment exhibit atrophy that localizes specifically to the left anterior temporal cortex. The map depicts the statistical significance of the general linear model correlating the BNT sum Z score with cortical thickness, adjusting for age, education, gender, MMSE, and CDR-SB (N = 145). This map is presented on the partially inflated surface of the Freesurfer *fsaverage* template with the color scale indicating the p value (10^{-3} – 10^{-9}) from this correlative general linear model.

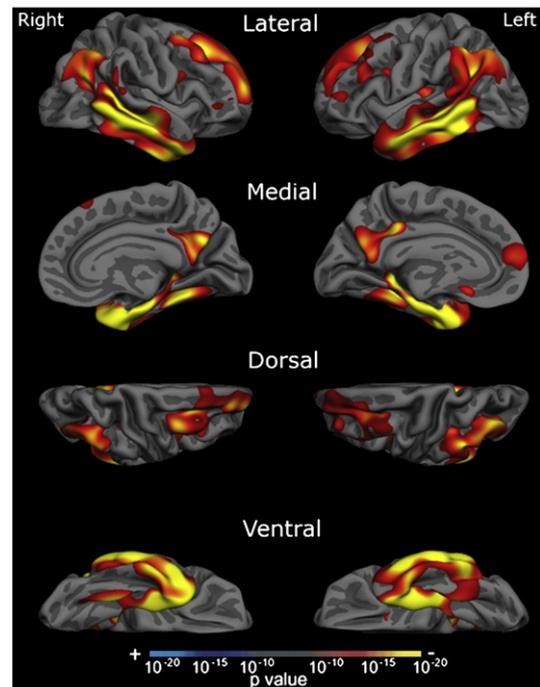


Fig. 5. The multifocal lesions of cortical thinning in AD patients (N = 145) as compared to the OC group (N = 183). This pattern of cortical thinning, distributed bilaterally throughout the cortex, is similar to the patterns identified in our previous studies and includes a relatively bilaterally symmetric set of temporal, parietal, cingulate, and prefrontal regions of thinning. This map is presented on the partially inflated surface of the Freesurfer *fsaverage* template with the color scale indicating the p value from this general linear model (10^{-10} – 10^{-20}) of group differences in thickness.

further strong support for the importance of the ATL in any model of semantic memory.

Behavioral analysis of patients with various forms of brain damage – typically strokes or other focal lesions – has been used to argue for each of the aforementioned viewpoints, and supports the hypothesis that distributed temporoparietal and inferior frontal damage may contribute to semantic deficits. Schwartz and colleagues recently performed a voxel-based lesion-symptom mapping study in post-stroke aphasia (Schwartz et al., 2009), analyzing the association between task performance and the localization of the lesion. They focused specifically on semantic errors incurred during picture naming, surveyed the entire brain, and controlled for lesion size. Lesions in the patients with semantic deficits were localized in the left ATL and to a lesser degree in the left lateral prefrontal cortex. The latter is considered to be primarily involved in controlled semantic retrieval mechanisms (Jefferies and Lambon Ralph, 2006; Moss et al., 2005), and this prefrontal finding was eliminated when the analysis was controlled for voxels associated with tasks designed to assess conceptual discrimination difficulties. The authors concluded that damage to the left ATL produces semantic naming errors by destroying fine-grained mapping between semantic memory and the lexical system.

Undoubtedly some degree of cortical reorganization takes place after ischemic injury; the mean interval between injury and testing in the Schwartz et al. paper (Schwartz et al., 2009) was 68 months, but included at least one individual assessed 381 months out. Similar compensatory reorganization has been proposed to explain the sometimes surprisingly mild semantic impairments exhibited by post-surgical temporal lobe epilepsy and tumor patients (Lambon Ralph et al., 2010b; Warren et al., 2009). In contrast, Hillis and colleagues have focused on the acute stroke population. In a 2007 study, seven cortical areas were identified as contributing to various aspects of picture naming (written and oral), distributed across frontal, parietal, and temporal cortex, and including the left ATL (DeLeon et al., 2007). More recently, this group performed a focused analysis of the temporal pole (Tsapkini et al., 2011) with results leading them to question whether unilateral temporal pole damage is sufficient to cause naming and comprehension deficits. Nevertheless, the ATL was considered to be an integral component of a left-lateralized distributed semantic network.

Patient populations with relentlessly progressive neurologic impairment have also been studied. The central clinical feature of semantic dementia, or the semantic variant of Primary Progressive Aphasia (PPA-semantic), is a progressive, multimodal loss of semantic memory (Grossman, 2010; Hodges and Patterson, 2007; Snowden et al., 1989). Patients with PPA-semantic typically have strikingly asymmetric atrophy lateralized to the dominant ATL, although most patients have bilateral involvement if examined carefully (Rosen et al., 2002). The consistency of this atrophy pattern is such that it has been incorporated into the new diagnostic criteria (Gorno-Tempini et al., 2011). The selectivity of this cognitive and neuroanatomic phenotype have been cited as evidence of the prominent role for the ATL in semantic memory (e.g., Galton et al., 2001; Gorno-Tempini et al., 2004; Nestor et al., 2006).

In contrast, the atrophy pattern of mild AD dementia is typically multifocal with prominent foci in the medial temporal lobe, lateral temporoparietal cortex, posterior cingulate/precuneus, and dorsolateral prefrontal cortex (Dickerson et al., 2009). While the neural substrates of episodic memory deficits in AD have been extensively studied, remarkably little work has been done on the neuroanatomic basis of semantic memory impairments in AD. Apostolova et al. (2008) performed an analysis of spontaneous naming on the BNT in relation to cortical atrophy. This analysis demonstrated a relatively diffuse set of left lateralized regions in the caudal prefrontal cortex, precentral gyrus, fusiform gyrus, posterior temporo-occipital cortex, and right temporal pole. While the sample of subjects was small (19 probable AD, 5 MCI with subsequent conversion to AD), close inspection of the resultant maps presented in Fig. 1 reveals a small region of correlation in the left ATL, although other regions showed stronger effects.

Joubert and colleagues recently investigated the naming abilities and semantic memory of subjects with amnesic mild cognitive impairment compared to subjects with early AD (Joubert et al., 2010). They demonstrated that both subject groups have multimodal (visual and verbal) impairment of semantic memory. Furthermore, the voxel-based morphometric analysis of the neuroanatomic correlates of impaired semantic processing revealed clusters within the left inferior frontal gyrus and the left ATL with a localization very similar to our findings. Another similar report was recently published in MCI and AD (Frings et al., 2011). The focality of the brain-behavior relationship identified in the present and these prior studies are especially powerful given that AD is a widely distributed multifocal neurodegenerative disease, as illustrated by our cortical thickness analysis of the AD patient group (Fig. 4). Indeed, the focal “functional” lesion illustrated in Fig. 3 is impressively similar to the neuroanatomic lesion observed in the semantic variant of Primary Progressive Aphasia (Sapolsky et al., 2010).

Despite the power offered by the sizeable ADNI repository, there are limitations to this study. Most importantly, the naming responses are recorded in the database as simple binary scores which do not enable further insight into the nature of the error (e.g., no response versus erroneous response). Moreover, although successful naming requires access to semantic memory, we cannot definitively determine whether the naming difficulties encountered by this patient cohort are due to a deficit of lexical access or semantic memory stores. That is, semantic impairment in AD may be due to diminished stores of semantic information, impaired access to relatively intact stores of semantic representations, or a combination thereof (Chertkow and Bub, 1990; Chertkow et al., 1989; Giffard et al., 2002; Martin and Fedio, 1983; Nebes, 1989; Parasuraman and Martin, 1994; Reilly et al., 2011). Recent data suggest that intentional access to semantic information may be impaired as early as the MCI stage of AD (Duong et al., 2006). The cognitive assessment battery employed in ADNI does not include tests that provide further information on semantic memory abilities in patients with naming impairment on the BNT. Although we interpret our findings as supporting the ATL as a key hub-like node in the semantic memory network, it is also possible that semantic memory impairment could be observed in the setting of an intact hub which is either disconnected from the remainder of the network, or which is connected to other degraded nodes (de Zubicaray et al., 2011; Sonty et al., 2007). Further research will be required to address these issues more directly.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Amorfix Life Sciences Ltd.; AstraZeneca; Bayer HealthCare; Bioclinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30

AG010129, K01 AG030514, and the Dana Foundation. In addition, this work was supported by grants from the NIA R01-AG29411, R21-AG29840, P50-AG005134, and the Alzheimer's Association. The authors express special appreciation to Dr. Jeffrey Binder for sharing data with us.

References

- Apostolova, L.G., Lu, P., Rogers, S., Dutton, R.A., Hayashi, K.M., Toga, A.W., Cummings, J.L., Thompson, P.M., 2008. 3D mapping of language networks in clinical and pre-clinical Alzheimer's disease. *Brain Lang.* 104, 33–41.
- Appell, J., Kertesz, A., Fisman, M., 1982. A study of language functioning in Alzheimer patients. *Brain Lang.* 17, 73–91.
- Bakkour, A., Morris, J.C., Dickerson, B.C., 2009. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. *Neurology* 72, 1048–1055.
- Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–2796.
- Butler, C.R., Brambati, S.M., Miller, B.L., Gorno-Tempini, M.L., 2009. The neural correlates of verbal and nonverbal semantic processing deficits in neurodegenerative disease. *Cogn. Behav. Neurol.* 22, 73–80.
- Chertkow, H., Bub, D., 1990. Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? *Brain* 113 (Pt 2), 397–417.
- Chertkow, H., Bub, D., Seidenberg, M., 1989. Priming and semantic memory loss in Alzheimer's disease. *Brain Lang.* 36, 420–446.
- Chertkow, H., Whatmough, C., Saumier, D., Duong, A., 2008. Cognitive neuroscience studies of semantic memory in Alzheimer's disease. *Prog. Brain Res.* 169, 393–407.
- Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9, 179–194.
- Damasio, A.R., 1989. Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. *Cognition* 33, 25–62.
- Damasio, A.R., 1990. Category-related recognition defects as a clue to the neural substrates of knowledge. *Trends Neurosci.* 13, 95–98.
- de Zubicaray, G.I., Rose, S.E., McMahon, K.L., 2011. The structure and connectivity of semantic memory in the healthy older adult brain. *Neuroimage* 54, 1488–1494.
- DeLeon, J., Gottesman, R.F., Kleinman, J.T., Newhart, M., Davis, C., Heidler-Gary, J., Lee, A., Hillis, A.E., 2007. Neural regions essential for distinct cognitive processes underlying picture naming. *Brain* 130, 1408–1422.
- Dickerson, B.C., Bakkour, A., Salat, D.H., Feczko, E., Pacheco, J., Greve, D.N., Grodzstein, F., Wright, C.I., Blacker, D., Rosas, H.D., Sperling, R.A., Atri, A., Growdon, J.H., Hyman, B.T., Morris, J.C., Fischl, B., Buckner, R.L., 2009. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb. Cortex* 19, 497–510.
- Dickerson, B.C., Stoub, T.R., Shah, R.C., Sperling, R.A., Killiany, R.J., Albert, M.S., Hyman, B.T., Blacker, D., deToledo-Morrell, L., 2011a. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology* 76, 1395–1402.
- Dickerson, B.C., Wolk, D.A., Alzheimer's Disease Neuroimaging, I., 2011b. Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics. *J. Neurol. Neurosurg. Psychiatry* 82, 45–51.
- Duong, A., Whitehead, V., Hanratty, K., Chertkow, H., 2006. The nature of lexico-semantic processing deficits in mild cognitive impairment. *Neuropsychologia* 44, 1928–1935.
- Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11050–11055.
- Fischl, B., Sereno, M.I., Dale, A.M., 1999a. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9, 195–207.
- Fischl, B., Sereno, M.I., Tootell, R.B., Dale, A.M., 1999b. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum. Brain Mapp.* 8, 272–284.
- Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 33, 341–355.
- Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M., 2004. Automatically parcellating the human cerebral cortex. *Cereb. Cortex* 14, 11–22.
- Frings, L., Klöppel, S., Teipel, S., Peters, O., Frolich, L., Pantel, J., Schroder, J., Gertz, H.J., Aert, S., Heuser, I., Kornhuber, J., Wiltfang, J., Maier, W., Jessen, F., Hampel, H., Hull, M., 2011. Left anterior temporal lobe sustains naming in Alzheimer's dementia and mild cognitive impairment. *Curr. Alzheimer Res.* 8, 893–901.
- Gainotti, G., 2011a. The format of conceptual representations disrupted in semantic dementia: a position paper. *Cortex* 48, 521–529.
- Gainotti, G., 2011b. The organization and dissolution of semantic-conceptual knowledge: is the 'amodal hub' the only plausible model? *Brain Cogn.* 75, 299–309.
- Galton, C.J., Patterson, K., Graham, K., Lambon-Ralph, M.A., Williams, G., Antoun, N., Sahakian, B.J., Hodges, J.R., 2001. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 57, 216–225.
- Giffard, B., Desgranges, B., Nore-Mary, F., Lavee, C., Beaudouin, H., de la Sayette, V., Pasquier, F., Eustache, F., 2002. The dynamic time course of semantic memory impairment in Alzheimer's disease: clues from hyperpriming and hypoprimer effects. *Brain* 125, 2044–2057.
- Gorno-Tempini, M.L., Dronkers, N.F., Rankin, K.P., Ogar, J.M., Phengrasamy, L., Rosen, H.J., Johnson, J.K., Weiner, M.W., Miller, B.L., 2004. Cognition and anatomy in three variants of primary progressive aphasia. *Ann. Neurol.* 55, 335–346.
- Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. *Neurology* 76, 1006–1014.
- Grabowski, T.J., Damasio, H., Tranel, D., Ponto, L.L., Hichwa, R.D., Damasio, A.R., 2001. A role for left temporal pole in the retrieval of words for unique entities. *Hum. Brain Mapp.* 13, 199–212.
- Grossman, M., 2010. Primary progressive aphasia: clinicopathological correlations. *Nat. Rev. Neurol.* 6, 88–97.
- Hodges, J.R., Patterson, K., 2007. Semantic dementia: a unique clinicopathological syndrome. *Lancet Neurol.* 6, 1004–1014.
- Jack Jr., C.R., Bernstein, M.A., Fox, N.C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P.J., Whitwell, J.L., Ward, C., Dale, A.M., Felmlee, J.P., Gunter, J.L., Hill, D.L., Killiany, R., Schuff, N., Fox-Bosetti, S., Lin, C., Studholme, C., DeCarli, C.S., Krueger, G., Ward, H.A., Metzger, G.J., Scott, K.T., Mallozzi, R., Blezek, D., Levy, J., Debbins, J.P., Fleisher, A.S., Albert, M., Green, R., Bartzokis, G., Glover, G., Mugler, J., Weiner, M.W., 2008. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J. Magn. Reson. Imaging* 27, 685–691.
- Jefferies, E., Lambon Ralph, M.A., 2006. Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain* 129, 2132–2147.
- Joubert, S., Felician, O., Barbeau, E.J., Didic, M., Poncet, M., Ceccaldi, M., 2008. Patterns of semantic memory impairment in mild cognitive impairment. *Behav. Neurol.* 19, 35–40.
- Joubert, S., Brambati, S.M., Ansado, J., Barbeau, E.J., Felician, O., Didic, M., Lacombe, J., Goldstein, R., Chayer, C., Kergoat, M.J., 2010. The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia* 48, 978–988.
- Kertesz, A., Appell, J., Fisman, M., 1986. The dissolution of language in Alzheimer's disease. *Can. J. Neurol. Sci.* 13, 415–418.
- Lambon Ralph, M.A., Cipolletti, L., Manes, F., Patterson, K., 2010a. Taking both sides: do unilateral anterior temporal lobe lesions disrupt semantic memory? *Brain* 133, 3243–3255.
- Lambon Ralph, M.A., Sage, K., Jones, R.W., Mayberry, E.J., 2010b. Coherent concepts are computed in the anterior temporal lobes. *Proc. Natl. Acad. Sci. U. S. A.* 107, 2717–2722.
- Martin, A., 2007. The representation of object concepts in the brain. *Annu. Rev. Psychol.* 58, 25–45.
- Martin, A., Fedio, P., 1983. Word production and comprehension in Alzheimer's disease: the breakdown of semantic knowledge. *Brain Lang.* 19, 124–141.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34, 285–297.
- Mion, M., Patterson, K., Acosta-Cabrero, J., Pengas, G., Izquierdo-Garcia, D., Hong, Y.T., Fryer, T.D., Williams, G.B., Hodges, J.R., Nestor, P.J., 2010. What the left and right anterior fusiform gyri tell us about semantic memory. *Brain* 133, 3256–3268.
- Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 43, 2412–2414.
- Moss, H.E., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., Tyler, L.K., 2005. Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. *Cereb. Cortex* 15, 1723–1735.
- Nebes, R.D., 1989. Semantic memory in Alzheimer's disease. *Psychol. Bull.* 106, 377–394.
- Nestor, P.J., Fryer, T.D., Hodges, J.R., 2006. Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage* 30, 1010–1020.
- Parasuraman, R., Martin, A., 1994. Cognition in Alzheimer's disease: disorders of attention and semantic knowledge. *Curr. Opin. Neurobiol.* 4, 237–244.
- Patterson, K., Nestor, P.J., Rogers, T.T., 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat. Rev. Neurosci.* 8, 976–987.
- Reilly, J., Peelle, J.E., Antonucci, S.M., Grossman, M., 2011. Anomia as a marker of distinct semantic memory impairments in Alzheimer's disease and semantic dementia. *Neuropsychologia* 25, 413–426.
- Rosen, H.J., Gorno-Tempini, M.L., Goldman, W.P., Perry, R.J., Schuff, N., Weiner, M., Feiwell, R., Kramer, J.H., Miller, B.L., 2002. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* 58, 198–208.
- Sapolsky, D., Bakkour, A., Negreira, A., Nalipinski, P., Weintraub, S., Mesulam, M.M., Caplan, D., Dickerson, B.C., 2010. Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology* 75, 358–366.
- Schwartz, M.F., Kimberg, D.Y., Walker, G.M., Faseyitan, O., Brecher, A., Dell, G.S., Coslett, H.B., 2009. Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. *Brain* 132, 3411–3427.
- Simmons, W.K., Martin, A., 2009. The anterior temporal lobes and the functional architecture of semantic memory. *J. Int. Neuropsychol. Soc.* 15, 645–649.
- Simmons, W.K., Reddish, M., Bellgowan, P.S., Martin, A., 2010. The selectivity and functional connectivity of the anterior temporal lobes. *Cereb. Cortex* 20, 813–825.
- Snowden, J.S., Goulding, P.J., Neary, D., 1989. Semantic dementia: a form of circumscribed cerebral atrophy. *Behav. Neurol.* 2, 167–182.
- Sonty, S.P., Mesulam, M.M., Weintraub, S., Johnson, N.A., Parrish, T.B., Gitelman, D.R., 2007. Altered effective connectivity within the language network in primary progressive aphasia. *J. Neurosci.* 27, 1334–1345.
- Thompson, S.A., Graham, K.S., Williams, G., Patterson, K., Kapur, N., Hodges, J.R., 2004. Dissociating person-specific from general semantic knowledge: roles of the left and right temporal lobes. *Neuropsychologia* 42, 359–370.

- Tranel, D., 2009. The left temporal pole is important for retrieving words for unique concrete entities. *Aphasiology* 23, 867.
- Tranel, D., Damasio, H., Damasio, A.R., 1997. A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia* 35, 1319–1327.
- Tsapkini, K., Frangakis, C.E., Hillis, A.E., 2011. The function of the left anterior temporal pole: evidence from acute stroke and infarct volume. *Brain* 134, 3094–3105.
- Visser, M., Jefferies, E., Lambon Ralph, M.A., 2010. Semantic processing in the anterior temporal lobes: a meta-analysis of the functional neuroimaging literature. *J. Cogn. Neurosci.* 22, 1083–1094.
- Warren, J.E., Crinion, J.T., Lambon Ralph, M.A., Wise, R.J., 2009. Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. *Brain* 132, 3428–3442.
- Wolk, D.A., Dickerson, B.C., 2011. Fractionating verbal episodic memory in Alzheimer's disease. *NeuroImage* 54, 1530–1539.