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3D mapping of language networks in clinical and pre-clinical Alzheimer's disease

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Abstract

We investigated the associations between Boston naming and the animal fluency tests and cortical atrophy in 19 probable AD and 5 multiple domain amnestic mild cognitive impairment patients who later converted to AD. We applied a surface-based computational anatomy technique to MRI scans of the brain and then used linear regression models to detect associations between animal fluency and Boston Naming Test (BNT) performance and cortical atrophy. The global permutation-corrected significance for the maps associating BNT performance with cortical atrophy was $p = .0124$ for the left and $p = .0196$ for the right hemisphere and for the animal fluency maps $p = .055$ for the left and $p = .073$ for the right hemisphere. The degree of language impairment correlated with cortical atrophy in the left temporal and parietal lobes (BA 20, 21, 37, 39, 40, and 7), bilateral frontal lobes (BA 8, 9, and 44) and the right temporal pole (BA 38). Using a novel 3D mapping technique, we demonstrated that in AD language abilities are strongly influenced by the integrity of the perisylvian cortical regions.

Keywords: Language; Alzheimer's disease; Mild cognitive impairment; Animal fluency; Boston Naming Test; Cortical atrophy; Gray matter atrophy; Brain atrophy

1. Introduction

Contemporary neuroimaging research on brain–behavior correlations focuses almost exclusively on the young healthy human brain, often using functional neuroimaging techniques. Relatively few researchers have attempted to identify anatomically specific correlations between cognition and brain structure in neurodegenerative diseases. Alzheimer's disease (AD) is the most common cause of cognitive decline among people age 65 and older. The underlying pathology consists of intracellular deposits of hyperphosphorylated tau protein and extracellular deposits of amyloid. The most pervasive sign of AD is declarative memory loss. Another frequent early complaint is anomia. As the disease progresses, semantic impairment becomes more noticeable and frequently a transcortical sensory aphasia ensues, with relatively preserved syntax and phonologic abilities (Pasquier, 1999). The increasingly studied intermediate cognitive state of mild cognitive impairment (MCI) is also associated with AD-type pathologic changes, and is of interest as those with MCI transition to AD at a rate of 12–15% per year (Bennett, Schneider, Bienias, Evans, & Wilson, 2005; Jicha et al., 2006).

From a neuroanatomical perspective, language processing involves many different systems that have more or less selective roles in language processing. It is thought that the areas processing phonological and semantic representations lie in the posterior left hemisphere (temporal and parietal cortices). Tasks such as phoneme monitoring seem

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to involve the frontal cortices while retrieval of phonological word forms involves the left posterior middle and inferior temporal regions. Anomic deficits result from anterior or inferior temporal lobe lesions suggesting that these areas house the semantic representations. The anterior left inferior frontal gyrus participates in lexical categorization, semantic generation and semantic judgment; the posterior left inferior frontal gyrus participates in phonemic monitoring (Bookheimer, 2002; Martin, 2003).

The linguistic correlates in AD have been almost exclusively examined with functional neuroimaging. The ^{18}[F]fluorodeoxyglucose positron emission tomography (FDG-PET) study by Zahn et al. (Zahn et al., 2004) investigated the correlation between regional cortical hypometabolism and impaired performance on verbal and non-verbal semantic tasks from the Consortium to Establish a Registry for AD (CERAD) battery. While investigating the relationship between the CERAD language tests and FDG-PET metabolism in AD Teipel et al. found the Animal fluency test to be associated with left temporo-parietal and left prefrontal metabolism, while the abbreviated 15-item Boston Naming Test (BNT) version linked to left middle temporal, left superior parietal and fusiform metabolism. (Teipel et al., 2006) Impaired verbal and non-verbal semantic performance correlated with hypometabolism in the left anterior temporal (Brodmann areas, BA 21 and 38), posterior inferior temporal (BA 37), inferior parietal (supramarginal gyrus, BA 40) and medial occipital cortex (Zahn et al., 2004). Another FDG-PET study by Hirono et al. described correlations between animal fluency and the left superior and inferior frontal, bilateral anterior cingulate and left inferior temporal metabolism, and naming performance was found to correlate with left middle and inferior temporal metabolism (Hirono et al., 2001). A third FDG-PET study reported that animal fluency correlated with left frontal, left temporal and left more than right parietal lobe hypometabolism (Welsh, Hoffman, Earl, & Hanson, 1994). One structural neuroimaging AD study reported a correlation between performance on the Aachen aphasia battery and the left temporal lobe volume (Pantel, Schonknecht, Essig, & Sc hroder, 2004). Boston Naming Test (BNT) and animal fluency performance correlated with temporal and frontal lobe volumes in another AD study using the magnetization transfer technique (van der Flier et al., 2002).

In the present study, we analyzed 1.5 T structural magnetic resonance imaging (MRI) data using a novel cortical pattern matching technique to control for inter-subject anatomical variability. The technique employs sulcal-based cortical alignment to better localize disease-specific cortical atrophy and has been further developed to analyze structure–function correlations. It has been well validated in several neurodegenerative (Apostolova et al., in press; Ballmaier et al., 2004; Ballmaier et al., 2004; Thompson et al., 2003; Thompson et al., 2004), psychiatric (Ballmaier et al., 2004; Sowell et al., 2003; Thompson et al., 2004) and developmental (Sowell et al., 2003; Sowell, Thompson, Tessner, & Toga, 2001) imaging studies.

The language impairments observed in patients with AD are complex. Some have postulated that the word-finding difficulty is the direct result of general impairments in explicit memory while visuoperceptual deficits have also been proposed as a potential contributor to naming breakdown (Cromier, Margi son, & Fisk, 1991). However, converging evidence have implicated the semantic and/or lexical systems as the primary source of the naming impairment commonly observed in AD. More specifically, early in the dementing process, the ability to consciously access of lexical information about a target word is impaired (Chenery, Murdoch, & Ingram, 1996), but as the disease progresses, it is likely that degradation of the semantic system occurs resulting in impaired naming in structured tasks as well as in spontaneous conversation (Chenery et al., 1996; Huff, Corkin, & Growdon, 1986; Nicholas, Obler, Au, & Albert, 1996; Shuttleworth & Huber, 1988). The BNT and animal fluency tests tap into lexical and semantic retrieval operations and were chosen to measure these specific aspects of language breakdown in AD.

2. Subjects and methods

2.1. Subjects

We enrolled 19 probable AD and 5 multiple domain amnestic MCI patients who later converted to probable AD. Their diagnoses were established based on the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS–ADRDA) criteria for AD (McKhann et al., 1984) and the Petersen criteria for amnestic MCI (Petersen et al., 2001). All five MCI subjects met the NINCDS–ADRDA criteria for probable AD during subsequent follow-up. Additional inclusion criteria were age 55–90 years, no evidence of a concurrent general medical condition of sufficient severity to impact cognition, no history of drug or alcohol abuse, no concurrent psychiatric or other neurological illness and a MMSE score above 18 for the mild AD group to assure their ability to perform adequately on the language instruments described below. We excluded subjects whose baseline images were acquired more than 6 months from the date of neuropsychological evaluation and those with conditions precluding safe performance of MRI. Demographic and neuropsychological data for the subjects in our study are provided in Table 1.

2.2. Neuropsychologic testing

We tested semantic fluency with the animal fluency test where subjects are asked to name as many animals as possible within 1 min (Benton & deS, 1989). The test taps into many functions—semantic knowledge, efficient planning, searching and retrieval strategies, set-shifting, intact working memory, and finally lexical retrieval of specific phono-

Table 1
Demographic and neuropsychological variables

Variable	AD		MCI	
	Mean	*SD*	Mean	*SD*
Age (years)	76	8.9	69.6	7.3
Education (years)	14.1	2.0	16.4	3.0
Gender (M:F)	10:9	N/A	4:1	N/A
Race (W:AA:A)	15:1:3	N/A	5:0:0	N/A
MMSE	23.6	3.90	28.8	0.84
BNT raw	39.1	13.0	51.8	2.2
BNT *Z* score	−3.78	3.1	−1.7	1.1
Animals raw	10.2	4.7	13.8	4.4
Animals *Z* score	−1.65	1.1	−0.9	1.0

M, male; F, female; W, white; AA, African American; A, Asian; MMSE, mini-mental state examination.

logic entities. We tested naming with the Boston Naming Test (BNT) where subjects are asked to name 60 line drawings of objects and animals (Kaplan, Goodgalss, & We intraub, 1983). This test taps into semantic knowledge and lexical retrieval. Both tests also rely on intact perception, comprehension, motivation, and attention. Test scores for both measures were age- and education-adjusted.

2.3. Image acquisition and processing

All subjects underwent 3D brain MRI scanning with SPGR (spoiled gradient echo) acquisition parameters: repetition time (TR) 28 ms, time to echo (TE) 6 ms, field of view (FOV) 220 mm, 256 × 192 matrix, and slice thickness 1.5 mm. The raw data was scaled and spatially normalized to the International Consortium for Brain Mapping ICBM53 average brain imaging template with a nine-parameter linear transformation method (Collins, Neelin, Peters, & Evans, 1994). Magnetic susceptibility artifacts and image non-uniformities were reduced using a regularized tricubic B-spline approach (Shattuck, Sandor-Leahy, Schaper, Rottenberg, & Leahy, 2001). The skull and soft tissues were automatically removed and the results visually inspected and manually corrected as appropriate to correct mislabeling of brain and non-brain tissues. 3D hemispheric reconstructions were created and 38 sulci per hemisphere were manually traced following a detailed well-established and validated protocol, with previously reported inter-rater reliability (Sowell et al., 2000; Hayashi et al., 2002). The sulcal traces of all 24 subjects were then averaged in 3D space. The hemispheric surfaces were parameterized, flattened and warped so that the individual sulcal lines were transformed to explicitly match the average sulcal lines thus substantially controlling for inter-individual variability in gyral patterning and cortical shape. Gray matter volumes were extracted (Shattuck et al., 2001) and mapped onto the hemispheric models that were in precise spatial registration with them. We used a widely used regional gray matter volumetric measure known as gray matter density (GMD) for our analyses. GMD represents the proportion of tissue labeled as gray matter within a 10 mm radius of each surface point (Wright et al., 1995; Ashburner & Friston, 2000; Good et al., 2001; Good et al., 2001). The age- and education-corrected individual test scores were entered as covariates in a general linear model that predicted the 3D cortical GM density at each cortical point for each subject. The results of these correlation analyses were plotted as a map of correlation values on the cortex, with associated significance values at each cortical point. The significance map was corrected for multiple comparisons by permutation testing using a threshold of $p < .01$ to define a suprathreshold region. The area of this suprathreshold region was compared with a statistical null distribution of correlations that occurred by chance when test scores were randomly assigned to subjects, in 100,000 random simulations. These methods have been described in detail elsewhere and are somewhat standard (Thompson et al., 2003; Apostolova et al., in press).

To test whether the observed associations are language specific vs. non-specific (e.g., reflecting AD disease severity) we searched for an association between the test scores and MMSE. We first ran Pearson correlation coefficients searching for significant association between the BNT or animal fluency and MMSE scores. None of the tests were correlated with MMSE scores (BNT $r = .097$, $p = .65$; animal fluency $r = -.092$, $p = .67$). We then developed separate linear regression models with BNT and animal fluency scores as the dependent and MMSE the predictor variable. Based on these models, we were able to compute the residual BNT and animal fluency scores unaccounted for by MMSE. We used these residualized scores as dependent variables in the statistical analyses at each cortical surface point.

3. Results

The global permutation-corrected significance for the maps associating BNT performance and cortical atrophy was $p = .0124$ for the left and $p = .0196$ for the right hemisphere (Fig. 1) and for the animal fluency maps $p = .055$ for the left and $p = .073$ for the right hemisphere (Fig. 2). All 3D statistical and correlation maps showed strong left-sided lateralization, with greater effect sizes and more of the left hemisphere cortex showing atrophy that was statistically linked with language function.

Strong positive correlations ($r > .37$) between BNT performance and gray matter atrophy were seen in the posterior middle and inferior temporal gyri (BA 21 and 37), temporo-occipital (BA 37 and 19) and parieto-occipital (BA 39 and 19) association cortices. In the frontal lobes, relationships were seen in the posterior halves of the middle and superior frontal gyri bilaterally (BA 8 and 9) as well as in BA 46, 10, and 44, on the right. BNT performance also correlated strongly with gray matter atrophy in the left inferior sensorimotor strips (BA 1–4), parts of the posterior left inferior frontal gyrus (BA 44), the left fusiform gyrus (BA 20) and the right temporal pole (mostly BA 38). Strong correlations were seen in the bilateral entorhinal

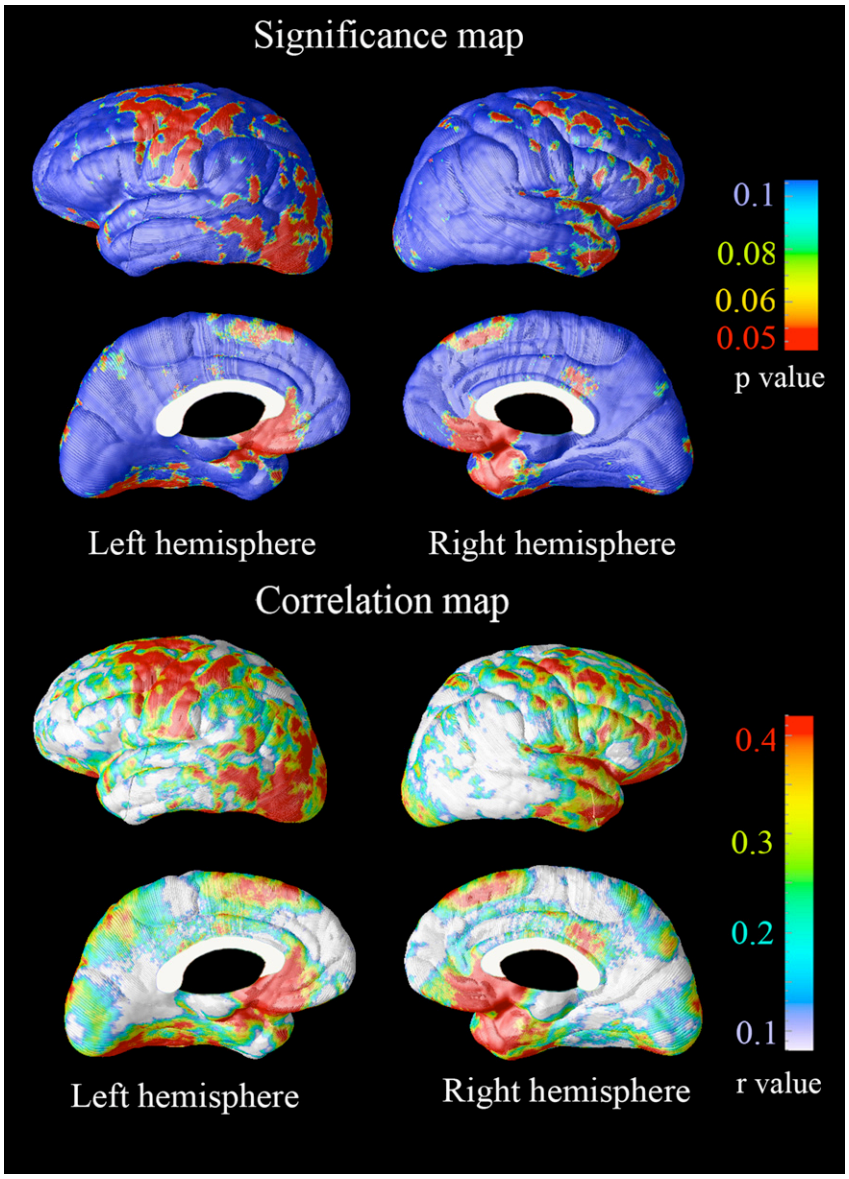

Fig. 1. Statistical (top) and correlation maps (bottom) demonstrating the association between the Boston Naming Test score and gray matter density in subjects with clinical and pre-clinical Alzheimer's disease.

(BA 28), anterior cingulate (BA 32) and mesial orbitofrontal cortex (BA 12 and 25; Fig. 1).

Animal fluency showed a different regional correlation pattern (Fig. 3). While it also associated with atrophy in the posterior superior and middle frontal gyri, the somatomotor cortex (SMA) the anterior cingulate and the posterior left temporal lobe association areas, it did not correlate with structural differential in the right temporal pole. Parietal association cortical atrophy correlated more strongly and extensively with performance on the animal fluency test relative to the BNT. Correlations with visual association cortices such as the inferior temporal and the occipital association areas appeared stronger for BNT as opposed to animal fluency.

In addition, Fig. 3 shows the MMSE significance map for our patient cohort displaying the regional correlations between the MMSE score and cortical atrophy. MMSE performance was associated with atrophy in bilateral entorhinal, parahippocampal, precuneal, inferior, and lateral temporal and lateral parietal areas as we previously reported (Apostolova et al., 2006). Only few areas of overlap between the MMSE map and the BNT and animal fluency maps (Figs. 2 and 3) can be appreciated—the right temporal pole and left posterior temporal cortices for BNT, and the left lateral parietal and lateral posterior temporal and left precuneal cortices for animal fluency. These findings further support the reported weak correlation between the language tests and the MMSE score.

4. Discussion

The neuroanatomical correlates of lexical and semantic retrieval deficits often seen in AD have been almost

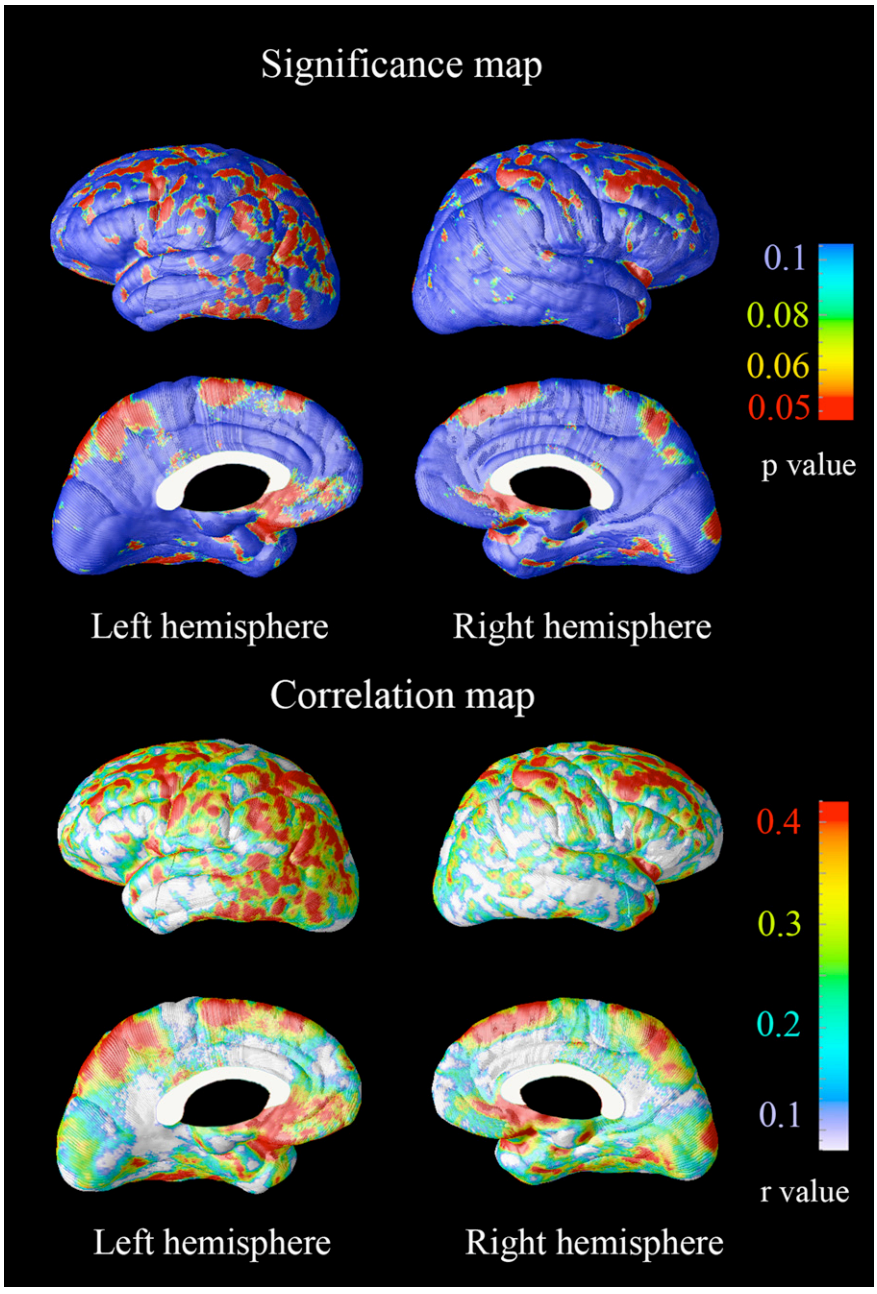

Fig. 2. Statistical (top) and correlation maps (bottom) demonstrating the association between the Animal Fluency Test score and gray matter density in subjects with clinical and pre-clinical Alzheimer's disease.

exclusively examined with functional neuroimaging. Only few studies have attempted to define the linkage between language impairment and cortical atrophy in AD (Pantel et al., 2004; van der Flier et al., 2002; Teipel et al., 2006).

In the current study, we tested the correlation between cortical atrophy in AD, and each of two language tests (i.e., verbal semantic fluency and naming). Both tests require intact semantic and phonologic processing and are probably supported by structures in both hemispheres with left-sided predominance.

4.1. Correlations between language test performance and the left hemisphere

We found that impairment on either test was associated with cortical atrophy in the left posterior temporal and temporo-occipital, and parietal and parieto-occipital association cortices. These cortical areas have been linked to semantic and phonologic processing (Gold & Buckner, 2002; McGraw, Mathews, Wang, & Phillips, 2001; Pantel et al., 2004). Greater activation has been reported in the lateral temporal neocortex (BA 21) in semantic tasks rela-

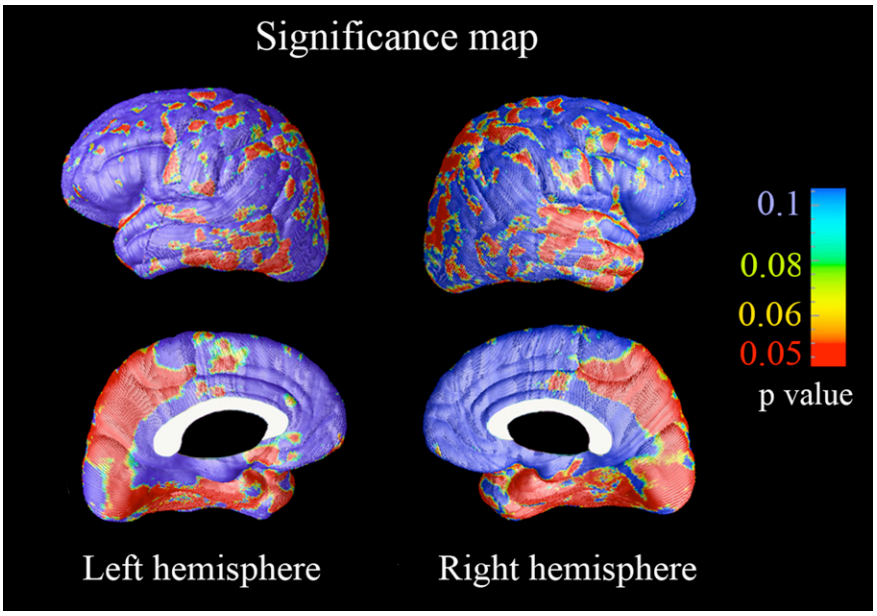

Fig. 3. Statistical map demonstrating the association between the MMSE score and gray matter density in subjects with clinical and pre-clinical Alzheimer's disease.

tive to phonologic tasks and the opposite dichotomy has been observed for the parietal neocortex (BA 40) (Gold & Buckner, 2002).

The left fusiform and lingual gyri (BA 20) showed relatively stronger correlation to naming of line drawings (BNT) in our study while animal fluency performance showed bilateral correlations with inferior temporal atrophy. Ventral temporal activation has been reported in naming visually presented animals and other stimuli (Grabowski & Damasio, 2000).

The parts of the left frontal lobe implicated in language processing were the left premotor areas (BA 6 and 44), inferior frontal gyrus (BA 44, 45, and 47) and the supplementary motor cortex (SMA; BA 8 and 9) (Bookheimer, 2002; Gold & Buckner, 2002; Grabowski & Damasio, 2000). BA 44 has been consistently implicated in semantic processing (Bookheimer, 2002; Gold & Buckner, 2002; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), but some consider BA 6 to have a predominantly phonologic (Gold & Buckner, 2002) and others predominantly semantic function (Thompson-Schill et al., 1997). The left premotor cortex (BA 6 and 44) is also important for retrieval of responses associated with specific sensory stimuli (Geschwind & Iacoboni, 1999). In our study we found associations between naming and verbal fluency performance and BA 6 and 44. We did not see strong effects in the classically defined Broca's area (BA 44, 45, and 47). This could stem from the relatively small sample of our study, lesser atrophy or greater gray matter variance of this area, or to the fact that these tests truly have no association with Broca's area.

One model of the functional anatomy of language divides the left hemisphere language-related cortical areas into two subgroups—the language-implementation (the receptive and articulatory language centers) and the language-mediation areas (the higher order centers linking concepts and language) (Grabowski & Damasio, 2000). The language-implementation areas that show linkage to successful naming and semantic fluency performance in our study were the lower portions of the sensorimotor cortices, the SMA and the supramarginal and angular gyri (BA 39–40). The language-mediation areas were the left premotor/prefrontal cortex (BA 6 and 44) and the middle and inferior temporal gyri (BA 21, 20, and 37).

A recent study employing the diffusion tensor MRI tractography technique identified two parallel pathways connecting the perisylvian cortical areas (Catani, Jones, & ffytche, 2005). In addition to the arcuate fasciculus, Catani et al. identified an indirect pathway connecting the posterior frontal lobe (e.g., the classical Broca's area, the middle frontal and inferior precentral gyri) and the supramarginal and angular gyri with a second limb connecting the supramarginal and angular gyri and the posterior temporal and temporo-occipital regions (Catani et al., 2005). The areas served by this indirect pathway are strikingly similar to the ones we found associated with poor BNT and animal fluency performance in the present study. These two parallel pathways may therefore interconnect the language-implementation and language-mediation areas (Grabowski & Damasio, 2000).

4.2. Correlations between language tests performance and the right hemisphere

Language performance in AD correlated with GM atrophy in the right frontal association cortices (BA 44, 45, 46, 9, 8, and 6) and the right temporal pole (BA 38). There is evidence that the right frontal lobe participates in two lin-

guistic processes—verbal episodic memory (BA 8, 9, and 10) and semantic retrieval (BA 8, 9, and 10); it also supports working memory (BA 9 and 10) and attention (BA 8) (Grady, 1999). There is sparse and somewhat circumstantial evidence that the right temporal pole may subserve a linguistic function. One study showed PET activation of the right temporal pole (BA 38) in a semantic decision-making task (Perani et al., 1999). Semantic dementia, a neurodegenerative disorder from the fronto-temporal dementia spectrum that presents with progressive semantic language impairment, is associated with significant atrophy of both temporal poles albeit with a left-sided predilection (Mummery et al., 2000; Gorno-Tempini et al., 2004). Thus it seems plausible that the right temporal pole may participate in semantic processing. However, the lack of association of either language test with left temporopolar cortical atrophy was unexpected. It may result from regional variability of AD pathology in our sample that could contribute to lesser atrophy or greater gray matter variance of this area or from magnetic susceptibility artifacts.

4.3. Correlations between language tests performance and bilateral cortical regions

Atrophic changes of the left and right supplementary motor area (SMA, BA 8 and 9) and anterior cingulate gyrus were associated with poorer language test performance. The left SMA area has been linked with semantic judgment (Demonet et al., 1992) while the bilateral SMA/anterior cingulate gyrus have been implicated in task initiation, attention and volition (Kertesz, 1999).

The correlations of BNT performance and entorhinal atrophy are of interest. Such correlations were not detected for the semantic verbal fluency task. A large pathologic study investigating the association between neuropsychological test performance and amyloid plaque and neurofibrillary tangle counts reported a similar observation. (Kanne, Balota, Storandt, McKeel, & Morris, 1998) The authors found poorer performance on BNT but not on verbal fluency to correlate with higher neuritic plaque burden in the entorhinal cortex.

The correlations of the posterior middle and superior frontal gyri with language test performance were discussed separately for each hemisphere.

4.4. Correlations between MMSE and language test scores

The lack of correlation between the MMSE and language test performance is somewhat surprising as these tests are thought to concomitantly decline concomitantly with AD progression. However we confirmed our findings via formal correlation analyses, residualized BNT and animal fluency maps and by visualizing and comparing the MMSE and the language tests significance maps. There are two plausible explanations for this observation. The first explanation supported partly by the MMSE statistical map is that while all three tests correlate with dementia severity, MMSE associates mostly with atrophy in regions outside these that associate with BNT and animal fluency performance. A second explanation may be that the MMSE scale, being a brief cognitive instrument, does not represent a robust enough dementia severity index, and does not link with all the atrophy that is occurring.

4.5. Strengths and limitations of our study

Our findings replicate and build on the data from other AD structural and functional neuroimaging studies investigating the linkage between language performance and brain atrophy or cortical hypometabolism (Hirono et al., 2001; van der Flier et al., 2002; Welsh et al., 1994; Zahn et al., 2004). However, our study has some relative strengths and some limitations. Ours is one of a few studies that attempt to correlate cognitive decline with structural change in a disease state—e.g., AD. We employ a powerful localization technique that links corresponding cortical areas with the greatest precision possible and allows for 3D visualization of the associations. Additionally the technique visualizes cortical anatomy in 3D rather than a few pre-selected regions of interest. However, studying brain–behavior correlations in a disease state could be rather challenging as the cortical changes that correlate with the tasks may not be task-specific but rather disease-specific and thus any conclusions regarding the specificity of these correlations for a specific test may be erroneous. However, all regions that associated with the two language tests in our study have been linked to various linguistic functions in the literature. We also found no significant association between the language domain and one of the measures for disease severity—the MMSE score. Moreover, if the observed effects were not test-specific one should anticipate to see in addition to a significant overlap between the areas associated with language tests and the MMSE more evenly spread bilateral associations as AD does not favor one hemisphere over the other, and cortical atrophy is already relatively widespread in early AD. In this study as expected, we see strong left-sided lateralization, which conforms to the typical left hemispheric dominance for language function. Furthermore, if these associations were not test-specific, we should have observed entorhinal correlations both for the BNT and animal fluency tests. It is reassuring to find correlations between one of the most severely affected brain regions and BNT but not verbal fluency, as previously reported by Kanne et al. (Kanne et al., 1998). On the other hand studies in neurodegenerative disorders such as AD are advantageous as they can help to validate theoretical frameworks and aid in the understanding of linguistic networks. Our results show that language function correlates strongly with gray matter atrophy in language-mediation areas thought to process lexical phonologic and semantic representations, responsible for selection and retrieval of semantic and phonological knowledge, and in language-implementation areas concerned with the receptive and articulatory aspects of language.

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