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ScienceDirect
Brain and Language 104 (2008) 33–41
Brain and Language
www.elsevier.com/locate/b&l

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

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Accepted 27 March 2007
Available online 7 May 2007

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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doi:10.1016/j.bandl.2007.03.008

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, & Schroder, 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, Margison, & Fisk, 1991). However, converging evidence has 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 & Hamsher, 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