Neuroradiology (2016) 58:59–67
DOI 10.1007/s00234-015-1596-3

FUNCTIONAL NEURORADIOLOGY

The neural correlates of anomia in the conversion from mild cognitive impairment to Alzheimer's disease

Emanuele Pravatà[1,2] · Joshua Tavernier[1] · Ryan Parker[3] · Hrvoje Vavro[4] · Jacobo E. Mintzer[5] · Maria Vittoria Spampinato[1]

Received: 19 May 2015 / Accepted: 14 September 2015 / Published online: 23 September 2015

Abstract
Introduction Language impairment is frequently observed in patients with Alzheimer's disease (AD): in this study, we investigated the extent and distribution of brain atrophy in subjects with conversion from mild cognitive impairment (MCI) to AD with and without naming difficulties.
Methods This study was approved by the institutional review board and was HIPAA compliant. All subjects or their legal representatives gave informed consent for participation. Ninety-one subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with (N=51) and without (N=40) naming impairment as per the Boston Naming Test (BNT), underwent brain magnetic resonance (MR) imaging 12 months before, at AD diagnosis, and 12 months after. Structural MR images were processed using voxel-based morphometry. Cross-sectional comparisons and mixed ANOVA models for assessing regional gray matter (GM) volume differences were performed.
Results As from 12 months prior to AD diagnosis, patients with naming difficulties showed distinct areas of greater GM loss in the left fusiform gyrus (Brodmann area 20) than patients without naming difficulties. Differences in the GM atrophy extended to the left hemisphere in the subsequent 12 months.
Conclusion This study provided evidence of distinct patterns and dynamics of brain atrophy in AD patients with naming difficulties when compared to those with intact language, as early as 12 months prior to AD diagnosis and in the subsequent 12 months.

Keywords Alzheimer's disease · Magnetic resonance imaging · Language · Voxel-based morphometry · Anomia

Introduction

Alzheimer's disease (AD) patients exhibit impairment in several neuropsychological domains, with episodic memory and executive functions being the most affected. However, language difficulties are also frequently observed in AD, most commonly word retrieval, object naming, and semantic categorization difficulties [1–5]. Neuropathological correlates of language impairment in AD have been previously investigated. Harasty et al. [6] showed postmortem pathological evidence of bilateral selective atrophy of language-associated temporal and parietal regions in AD patients with language impairment, and Gefen et al. [7] demonstrated a definite left-lateralized distribution of AD neurofibrillary tangles in a small group of aphasic AD patients. In addition, in vivo MR voxel-based morphometry (VBM) studies showed patterns of left temporal cortical atrophy in patients with diagnosis of definite AD, and in those with mild cognitive impairment (MCI) with lexical and naming impairment [8–11]. These pathological and structural imaging findings are also supported by previous FDG-PET studies showing a correlation between language performance in AD patients and either left or bilateral temporal lobe metabolism [12, 13]. Altogether, these findings

✉ Emanuele Pravatà
emanuele.pravata@gmail.com

1 Department of Radiology and Radiological Sciences, Medical University of South Carolina, Charleston, SC, USA

2 Department of Neuroradiology, Neurocenter of Southern Switzerland, Ospedale Regionale di Lugano, Via Tesserete 46, 6900 Lugano, Switzerland

3 Department of Anesthesiology, Vanderbilt University, Nashville, TN, USA

4 University Hospital Dubrava, Zagreb, Croatia

5 Clinical Biotechnology Research Institute, Roper Hospital, Charleston, SC, USA

indicate that AD pathology may have an asymmetrical distribution and target language network regions. However, up to now, differences in the dynamics of brain atrophy progression between language-impaired and non-impaired populations converting from MCI to AD have not been specifically assessed. The knowledge of these modifications over time may prove useful in the design of structural imaging biomarkers for the early detection of AD and may provide information about different trajectories of AD progression in language-impaired clinical subgroups.

Our goal was to investigate the structural correlates of word retrieval deficits in the earliest stage of AD, and in the subsequent 12 months, by evaluating regional gray matter (GM) volume loss patterns in patients with and without naming difficulties converting from MCI to AD. Based on prior studies [8–11, 14], our hypothesis was that the patterns of GM volume loss in brain regions involved in language processing occur with different spatial distributions over time between AD subjects with and without naming deficits during the conversion from MCI to AD, and in the subsequent 12 months.

Patients and methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute of 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 MCI and early 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 USA 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).

The diagnosis of AD was made by a multidisciplinary team that conducted extensive neuropsychological and neuroimaging assessments on the basis of established criteria [15]. Biological markers supportive of AD diagnosis at baseline were also obtained from the ADNI database [16], whenever available: the β-amyloid ($A\beta_{1-42}$) concentration in the cerebro-spinal fluid (CSF); the 18-fluoro-deoxy-glucose (FDG)-PET cerebral metabolic rate of glucose consumption (CMRglc) in the frontal, parietal, and temporal cortices normalized to pons was used as measure of cerebral metabolism; the normalized hippocampal volumes [generated by using Freesurfer (http://surfer.nmr.mgh.harvard.edu/) and normalized by brain size].

Once enrolled in ADNI, subjects with MCI and AD in the ADNI study undergo serial clinical and imaging evaluation for the following 5 years. All subjects or their legal representatives gave informed consent for participation. Data collection for the purpose of this retrospective study was conducted between November 2010 and January 2011. This study was approved by the local Institutional Review Board and was compliant with Health Insurance Portability and Accountability Act regulations.

Inclusion criteria were as follows: (1) mild cognitive impairment when recruited in the ADNI study (CDR sum of boxes= 0.5); (2) clinical conversion from MCI to AD during study participation. By the time of data collection (January 2011), 153/396 MCI subjects (38.6 %) had clinical progression to probable AD; (3) availability of brain MRI study obtained 12 months prior to AD diagnosis (i.e., at MCI stage), and at the time of AD diagnosis; (4) availability of serial clinical and neuropsychological data including AD diagnosis documentation, Clinical Dementia Rating scale, and naming performance assessment (see "Cognitive testing" section for details). We excluded all patients with other intervening neurological or systemic pathologies that may secondary affect the central nervous system and/or their cognitive status as reported in the ADNI database, and patients with technically inadequate MR scans due to image post-processing issues and/or extensive leukoencephalopathy.

After initial screening, subjects with MCI participating in the ADNI1 study underwent brain MRI and a comprehensive clinical evaluation every 6 months for the first 2 years and then after12 months. As a result, the date of conversion from MCI to AD is not precisely known because conversion could have happened during the 6-month interval between visits. However, in order to include AD patients at the same stage of the disease, we included in the early AD group only patients who converted from MCI to AD during the first 2 years of their participation to the ADNI project, when study visits were conducted every 6 months. As a result, 91 patients who progressed from MCI to probable AD during study participation were included in this study. Of those, 74/91 (81.3 %) had MRI and clinical data available 12 months after AD conversion.

Cognitive testing

The Clinical Dementia Rating (CDR) scale, a semistructured interview with the patient and caregiver, was used to provide

an index of global cognitive status [17]. The Clinical Dementia Rating has been extensively validated as a clinical tool to assess the severity of dementia [17–19]. By assigning a severity score for six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care), a score known as the CDR sum of boxes (SB) is obtained, ranging from 0 (normal) to 18 (severely impaired). Additional cognitive testing included the Category Fluency test with Animals (CF-A), a quick and easy to administrate test that proved to be useful in the diagnosis of mild AD, in which subjects are asked to name as many animals as they can in a minute [20]. Moreover, patients' visuospatial, memory and executive cognitive domains were specifically assessed by using the Clock Drawing - copy Test (CDT) [21], the Rey's Auditory Verbal Test (AVT) (trials 1–5 and delayed recall) [22], and the Trail Making Test (TMT) (parts A and B) [23], respectively.

The 30-item Boston Naming Test (BNT) was used to assess naming impairment. It is a confrontation naming test which is used to provide a measure of word retrieval performance and is sensitive to the word-finding difficulties occurring in the early stages of AD [1]. The BNT version used in the ADNI study ranges from 0 to 30, with 30 indicating a normal performance [24]. Based on previously published normative data adjusted for age, gender, and education level [25], a standard cutoff threshold of 26 was used in this study to stratify patients with naming impairment, so that patients with a score of ≤26 could be classified as impaired (Low-BNT) and those with a score of ≥27 as non-impaired (High-BNT). Corrected-BNT baseline z-scores accounting for age, gender, and years of education were also obtained.

VBM analysis

The ADNI database provides high-resolution 3D magnetization prepared rapid gradient echo (MPRAGE) T1 scans acquired according to optimized protocols and procedures previously described [26]. MPRAGE images were processed using VBM8 with statistical parametric mapping (SPM8, Welcome Dept. London) on Matlab v. 7.14. All volumes were manually translated and rotated into a plane passing through the anterior and posterior commissures. The VBM8 toolbox (developed by Christian Gaser, University of Jena) was used for data processing, and the built-in DARTEL algorithm [27] was used for non-linear, high-dimensional registration and normalization. After an initial realignment, the mean of the realigned images was calculated and used as reference image in a subsequent realignment; correction for signal inhomogeneity with respect to the mean image was followed by spatial normalization parameter estimation using the segmentations of the mean image; normalization parameters were then applied to the segmentations of the bias-corrected images; the resulting normalized segmentations were again realigned. In order to allow for between subjects GM volumes comparison, normalized data intensity was non-linearly modulated, correcting for individual brain sizes. Finally, images were smoothed with an 8-mm FWHM isotropic Gaussian kernel. Since our study population includes patients with significant brain atrophy, we estimated a customized GM mask and used it as an explicit mask in all statistical analyses. This mask was obtained by averaging all patients GM smoothed partitions, and by applying a signal intensity absolute lower threshold of 0.25.

Statistical analyses

Statistical analyses of clinical and neuropsychological data were conducted using SPSS (SPSS 16.0; SPSS, Chicago, IL). Differences between subjects with and without naming impairment were evaluated using the Pearson χ^2 test for gender, handedness, and ethnicity. Differences in age, years of education, CDR-SB, CDT, VAT, TMT, BNT, and BNT-corrected scores, as well as in the β-amyloid, tau/β-amyloid, 18FDG-PET, and hippocampal volumes biormarkers, were assessed by using ANOVA. Since Low-BNT patients were significantly older, and had significantly higher AVT (trials 1–5) scores, than High-BNT ones (see Table 1), all statistical comparisons of clinical and VBM measures were adjusted for age and AVT (trials 1–5) as appropriate. The general linear model repeated measures was performed to provide analysis of variance of repeated CDR-SB measurements (within-subjects factor) over time, stratifying patients based on the presence or absence of naming impairment. A P value of less than 0.05 indicated a significant difference.

Voxel-wise cross-sectional comparisons of GM volume maps between Low-BNT and High-BNT subjects at MCI (12 months before AD diagnosis), at the time of AD diagnosis, and 12 months after, were conducted in SPM8 using independent sample t tests. In order to investigate the existence of differences in the patterns of longitudinal atrophy changes between the groups, we performed two separate age-corrected mixed ANOVA with the Low-BNT and High-BNT groups as the between factor: the first one with the (MCI stage)-(AD diagnosis) time points as the within factor; the second one with the (AD diagnosis)-(12 months after diagnosis) as the within factor. Voxel-wise statistics were carried out with the significance threshold was set at P value of <0.001 uncorrected, since in VBM a statistical threshold of $p<0.001$ not corrected for multiple comparisons can be used when an a priori hypothesis has been defined according to Ashburner et al. [28], with a minimum extent of $k=50$ voxels. Statistically significant clusters were submitted to MRIcron (v.11 http://www.mccauslandcenter.sc.edu/mricro/mricron/) software to display overlap and conjunctions plots of the statistical maps, and to estimate GM atrophy asymmetry indexes (AIs) by counting the number of voxels in each statistically significant region of a map in the left hemisphere

Table 1 Patients' main demographic and clinical characteristics stratified by naming performance

	Low-BNT (mean±SD)	High-BNT (mean±SD)
Age (years)*	78.7±5.7	75.1±7.6
Gender[a]	33/17	27/14
Handedness[b]	46/4	37/4
Education	15.4±3.2	16.3±2.9
CDR-SB		
MCI	2.2±1	2.2±1
AD conversion	3.8±1.4	3.9±1.5
12 months after AD conversion	5.25±2.1	5.29±2.2
TMT		
Part A	52±27	45.2±25.6
Part B	188.5±45.1	147.6±77.3
CDT (copy)	4.52±0.73	4.62±.78
AVT		
(Trials 1–5)*	24.1±5.3	27.7±7.1
Delayed	0.72±0.9	1.57±1.1
BNT		
MCI**	22.2±4.4	28.7±1
AD conversion**	20.9±4.7	27.9±1.9
12 months after AD conversion**	17.9±6	26.17±3.1
CF-A		
MCI**	13.6±5	17.4±7.7
AD conversion**	12±4.9	16.1±5.1
12 months after AD conversion**	8.7±3.8	13.82±6.1

*Statistically significant at $P<0.01$; **statistically significant at $P<0.005$

CDR-SB Clinical Dementia Ratings scale sum of boxes, *TMT* Trail Making Test, *CDT* Clock Drawing Test, *AVT* Rey's Auditory Verbal Test, *BNT* Boston Naming Test, *CF-A* Category Fluency test with Animals, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

[a] Males/females

[b] Right-handed/left-handed patients

(LH) and right hemisphere (RH). AIs were subsequently calculated according to the formula: AI=LH voxels−RH voxels/LH voxel+RH voxels. A negative AI indicates a left-lateralized asymmetry.

In order to assess the relationships between naming impairment-related neurostrucutral and clinical findings, the modulated GM signal intensity values of the statistically significant clusters obtained from the contrasts described above were extracted by using MarsBaR v0.44 toolbox for SPM (http://marsbar.sourceforge.net/). Values were correlated with the BNT scores with Spearman's rho test and considered statistically significant at a P value of <0.05, and adjusting for multiple comparisons.

MR image post-processing and statistical analyses were conducted by two neuroradiologists (M.V.S. and E.P.) with, respectively, 10 and 5 years of experience with brain MR post-processing with statistical parametric mapping.

Results

Clincal data

Table 1 summarizes demographic and clinical data of patients stratified by naming performance. The Low-BNT group included 50 patients with an abnormal [25] BNT score ≤26 (mean±SD=22.2±4.4) and the High-BNT group included 41 patients with BNT score ≥27 (mean±SD=28.7±1). Analysis of demographic characteristics and neuropsychological tests (Table 1) revealed no statistically significant differences between Low-BNT and High-BNT groups with respect to gender ($P=0.53$), racial distribution ($P=0.33$), handedness ($P=0.53$), years of education ($P=0.17$), CDR-SB ($P=0.44$), TMT (A and B) ($P=0.25$ and 0.12, respectively), CDT ($P=0.56$), and AVT-Delayed ($P=0.13$); however, Low-BNT patients were significantly older than High-BNT patients, and presented significantly higher scores at the AVT (trials 1–5) (see Table 1). A statistically significant difference in the BNT performance between the Low-BNT and High-BNT groups was confirmed, also when age-, gender-, and education-corrected scores were compared [mean (±SD)=−1.76±1.4 and 0.31±0.5, respectively; $P<0.0001$].

At 12 months after AD conversion, clinical and MRI data were available for 35 patients in the Low-BNT group and 36 patients in the High-BNT group (Table 1). Cognitive status and language performances as measured using the CDR-SB, BNT, and CF-A, declined over time in both groups (Fig. 1), without a significant interaction between degree of cognitive decline and presence or absence of naming impairment ($P=0.15$). As expected, BNT and CF-A scores were significantly different between the two groups at all of the three time points (Table 1).

Biological markers

CSF data were available in 25 (50 %) of Low-BNT patients and 24 (58.5 %) of High-BNT patients. $A\beta_{1-42}$ was abnormal (<192 pg/ml) [16] in 22/25 (88 %) of Low-BNT patients and in 20/24 (83.3 %) of High-BNT patients. The L and R average normalized hippocampal volume was 1.79 (SD=0.28) in the Low-BNT group and 1.80 (SD=0.29) in the High-BNT group. 18FDG-PET data were available in 17/50 (34 %) of Low-BNT patients and 20/41 (48.8 %) of High-BNT patients. The average CMRglc was 1.22 (SD=0.1) for the Low-BNT group and 1.21 (SD=0.1) for the High-BNT group. No statistically significant differences were detected in the average measures of these biomarkers between Low-BNT and High-BNT groups [P ($A\beta_{1-42}$)=0.47; P (hippocampal)=0.87; P (CMRglc)=0.75].

GM atrophy VBM analysis

Voxel-wise cross-sectional comparisons were performed between Low-BNT and High-BNT MCI subjects 12 months

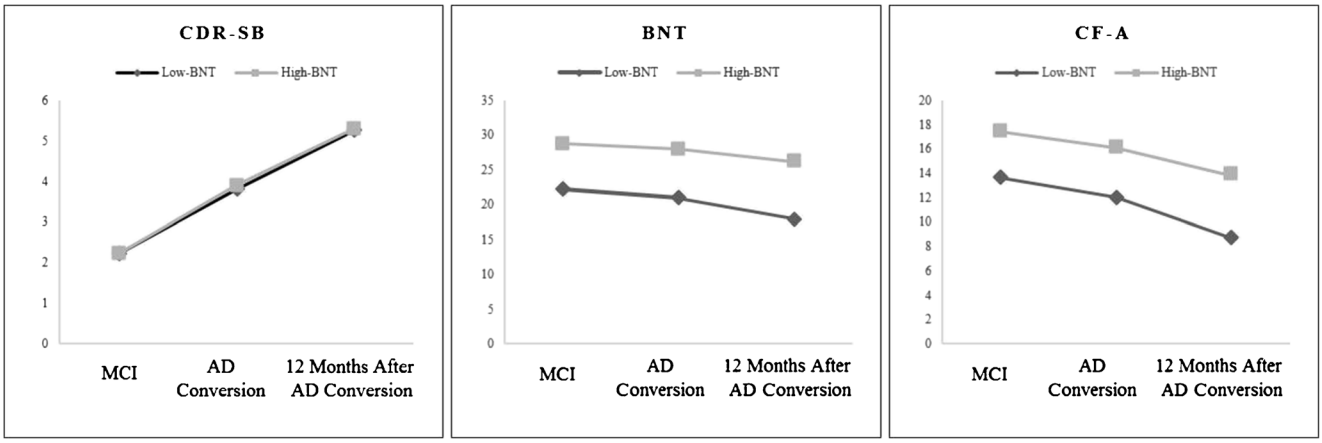

Fig. 1 Trajectories of neurocognitive and language performance decline over time in Low-BNT and High-BNT patients, as measured with the CDR-SB (**a**), BNT (**b**), and CF-A (**c**) scores. Seventy-one out of 91 patients were evaluated at 12 months after AD conversion. *CDR-SB* Clinical Dementia Ratings scale sum of boxes, *BNT* Boston Naming Test, *CF-A* Category Fluency test with Animals, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

before AD diagnosis (MCI stage), at AD diagnosis, and 12 months after AD diagnosis [only 71 out of 91 patients (81.3 %) were available at this time]. Given the significant difference in age and AVT (trials 1–5) between groups, age and the AVT (trials 1–5) scores were included in the models as nuisance variables. The Low-BNT group showed a circumscribed area of greater atrophy in the left anterior fusiform gyrus extending into the adjacent inferior temporal gyrus [within Brodmann area 20 (BA20)] at each of the three time points (Fig. 2, Table 2). No significant group-by-time interactions were detected between the (MCI)-(AD diagnosis) time points. At 12 months after AD diagnosis, additional areas of reduced GM volume distributed in the frontal, temporal, and parietal lobes, developed in the Low-BNT compared to the High-BNT group (Table 2), with a definite asymmetric left-lateralized pattern (AI=−0.78). Within these areas, a cluster of significant group-by-time interaction (F=12.55) was detected in the L middle frontal gyrus (MNI coordinates −48, 32, 33; BA44) between the (AD diagnosis)-(12 months after diagnosis) time points (Fig. 2). There was no area of statistically significantly greater atrophy in the High-BNT group than Low-BNT group at each time point. Taken together, these results indicate that Low-BNT patients, compared to the High-BNT ones, presented reduced volumes in the L BA20

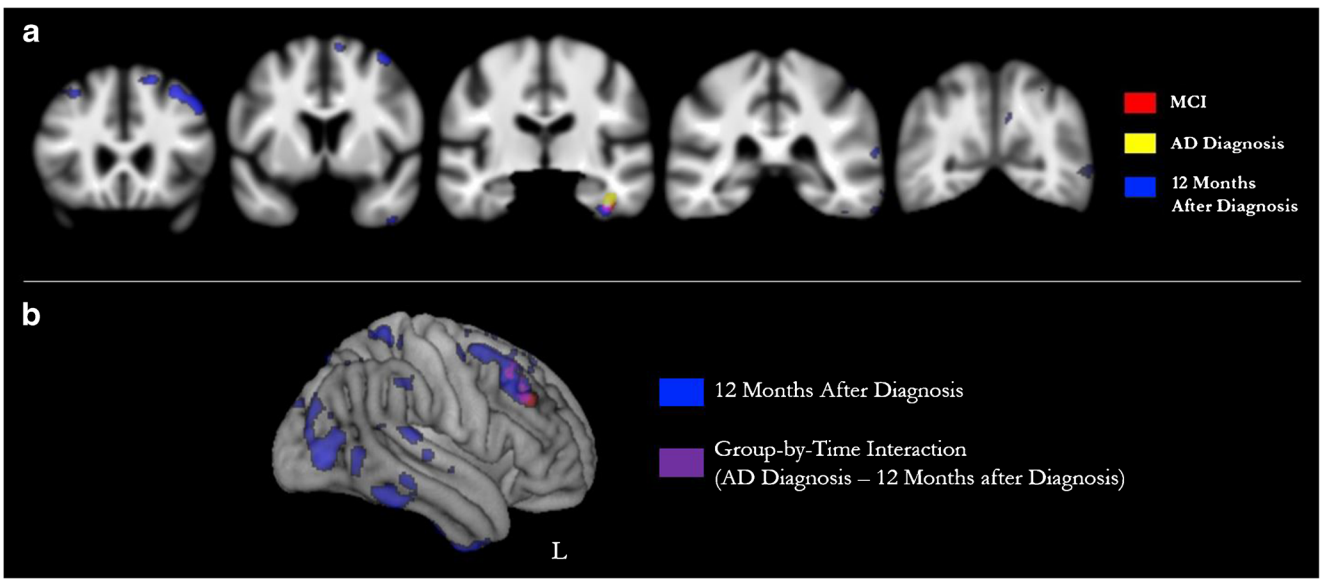

Fig. 2 **a** Progression of GM atrophy in Low-BNT compared to High-BNT AD patients at the MCI stage (red clusters), at AD diagnosis (*yellow clusters*) and 12 months after AD diagnosis (*blue clusters*). Statistical maps are presented in radiological convention, with a significance threshold of P=0.001 (extent threshold=50 voxels, uncorrected), and overlaid on patients' average anatomical template coronal slices. **b** Shows in *purple* the overlapping clusters of significant group-by-time interaction between the Low-BNT and High-BNT groups, and the (AD diagnosis)-(12 months after diagnosis) time points (ANOVA). These clusters indicate a more severe atrophy progression between the two-time points in Low-BNT patients at the level of the L middle frontal gyrus (BA44)

Table 2 Areas of greater gray matter volume in High-BNT compared to Low-BNT patients at the MCI stage, at the time of AD diagnosis, and 12 months after AD diagnosis

	X[a]	Y[a]	Z[a]	BA[b]	T-score*
MCI					
L Inferior temporal gyrus	−40	−20	−29	20	4.48
AD diagnosis					
L fusiform gyrus	−40	−21	−26	20	4.93
12 Months after AD conversion					
L inferior temporal gyrus	−40	−20	−29	20	4.36
L middle frontal gyrus	−38	15	45	9	4.34
L insula	−39	−15	−35	13	4.19
L superior parietal lobule	−28	−43	66	2	4.32
R middle frontal gyrus	36	20	49	9	4.17
L middle temporal gyrus	−66	−7	−11	21	4.12
L superior frontal gyrus	−16	24	54	8	4.09
L superior frontal gyrus	−10	2	63	6	4.06
L superior temporal gyrus	−64	−31	13	22	4.04
R superior frontal gyrus	16	10	60	6	3.95
L supramarginal gyrus	−57	−27	42	2	3.55
L lingual gyrus	−9	−60	34	18	3.65
L superior occipital gyrus	−22	−82	33	19	3.64

*P value=0.001 (uncorrected)

[a] X-Y-Z indicate anatomical coordinates based on the Montreal Neurological Institute standard brain template by describing the distance from a point at midline and 4 mm below the anterior commissure. The X,Y,Z dimensions refer to left-right, posterior-anterior, and inferior-superior, respectively. By convention, the right hemisphere has positive X values, the anterior brain has positive Y values, and the superior brain has positive Z values

[b] Corresponding Brodmann area

as from the MCI stage and over the subsequent 24 months. In addition, following AD conversion, Low-BNT patients tended to develop a relatively more severe atrophy progression in the left hemisphere, which reached a statistically significant group-by-time interaction at the level of the L BA44. Significant correlations were found at each time point between the GM amount in the L BA20 and the BNT scores, and at 12 months after diagnosis between the GM amount in the L BA44 and the BNT scores, so that patients with reduced GM volumes presented lower BNT scores (Fig. 3).

In order to investigate how the naming impairment-related structural findings was dependent on the AD course, we correlated patients' variations (expressed as delta between the 12 months after diagnosis and the MCI time-points) of the BNT scores and the L BA20 volumes, with that of the normalized L and R hippocampal volumes (representing relatively independent AD biomarkers from naming performance). Moderate, but statistically significant correlations, were obtained for the BNT and both L and R hippocampal volumes delta (rho=0.33; P=0.007 and rho=0.32; P=0.012, respectively), whereas only the R hippocampal volume delta presented a statistically significant correlation with the L BA20 volume delta (rho=0.28; P=0.02).

Discussion

Language impairment in AD is mostly characterized by naming, sentence comprehension, repetition, and semantic categorization impairment, while speech fluency and phonological skills are usually relatively preserved [1–5]. The neuropsychological correlates of these deficits are thought to reside in the deterioration of the general knowledge about facts, concepts, and the meanings of words underlying semantic processes [2]. The underlying neuroanatomical substrates are very complex and still debated: language areas related to semantic memory, previously described in functional studies, display a widespread distribution in the temporal, parietal and frontal lobes (see [29] for a review). Moreover, naming impairment is a heterogeneous spectrum of disorders that may be selective for different living or non-living semantic categories and may accordingly segregate in different anatomical regions [30]. On the other hand, studies on neurodegenerative diseases including AD [8–11, 14] and lesion-mapping analyses [31, 32] highlighted the critical role of various regions localized in the temporal lobes for the preservation of naming functions. No previous study, however, focused on the patterns of progression of anomia-related brain damage in AD.

In our early AD population, Low-BNT and High-BNT patients were comparable with respect to the degree of global dementia, education level, and disease biomarker signatures, and experienced similar trajectories of cognitive decline over time. However, they also exhibited significant differences in naming performance that were maintained over time. We showed that these differences were paralleled by a greater GM atrophy of the left fusiform and inferior temporal gyri, specifically in BA20, as early as 12 months prior to AD diagnosis and in the subsequent 12 months. Furthermore, between-group differences increased after AD conversion with a more widespread atrophy progression in the left hemisphere, particularly at the level of the L middle frontal gyrus. Despite the L frontal lobe, in contrast to the temporal, was less frequently associated with naming deficits, it is known to play a role in the retrieval aspect of semantic processing [29]. Since the volume loss in this area was noted only in a later phase (12 months after AD conversion) in our naming-impaired patients, we speculate that atrophy development in the L frontal lobe might be a secondary degenerative process related to previous disruption of the main semantic network nodes in the temporal love.

Our findings are consistent with previous observations which linked atrophy of the left anterior and inferior ATL to naming deficits in AD patients [8–12, 14] and confirm the

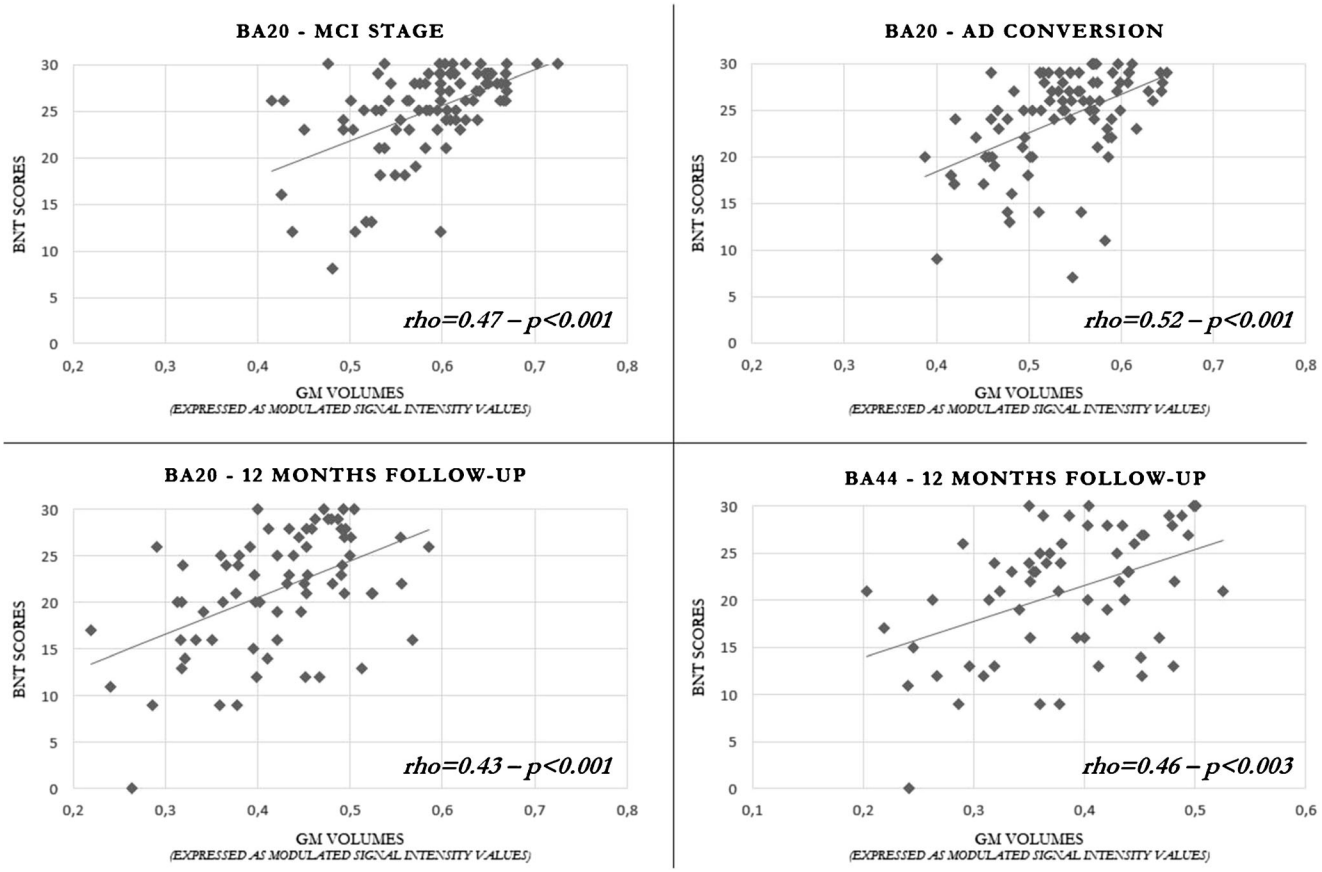

Fig. 3 Scatterplots, and corresponding Spearman's rho correlation values, of patients' GM volumes in the areas with increased atrophy in the Low-BNT (compared to High-BNT) group, and the relative BNT scores. Distribution linear regression fits are also provided. *P* values are statistically significant at the 0.012 Bonferroni-corrected threshold. *BA* Brodmann area, *BNT* Boston Naming Test, *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *GM* gray matter

critical role of BA20 in accounting for word finding difficulties in early AD. Notably, by performing a lesion-mapping analysis on patients with left anterior temporal lobectomy or left posterior circulation strokes, Antonucci et al. [31] found that patients with equivalent amounts of damage to the inferior temporal cortex, including BA20, showed a similar degree of semantic memory impairment. On the other hand, several previous structural and functional studies in AD and non-AD demented patients [8–12, 14], healthy subjects [33, 34], and also deaf sign-language subjects [35] found the inferior temporal lobe to be involved in naming functions. Similarities with canonical forms of primary progressive aphasias are also of particular interest. The left inferior temporal cortex, in fact, is known to be typically targeted in semantic dementia [10, 36], which is characterized by semantic memory rather than episodic memory impairment [37]. Interestingly, Joseph et al. evaluated a small number of subjects with aphasic phenotypes of AD and semantic dementia and found in both groups an atrophy of the left inferior temporal gyrus compared to age-matched healthy subjects [37]. Accordingly, evidence of left-lateralized development of cortical damage in AD has been provided by previous pathology studies [7]. Moreover, in our study group, statistically significant correlations were noted between BNT performance decline, BA20 atrophy progression, and hippocampal atrophy progression, which is an AD structural biomarker relatively independent from selective naming deficits.

This study has several limitations. First, it focuses on a relatively narrow but critical phase of the natural history of AD. Future studies should investigate the relationship between GM loss patterns and naming impairment in the transition from normal aging to MCI, in order to investigate the existence of potential early atrophy markers occurring before clinical symptoms development. A second limitation is the age and short-term memory performance (AVT trials 1–5) difference between language-impaired and language-intact patients. However, we minimized its influence by adjusting for age and AVT trials 1–5 scores our statistical comparisons. Third, the specificity of our findings relative to AD pathology itself may not be unequivocally proved, until similar findings are confirmed also when comparing with MCI patients who do not convert to AD. Such a comparison may be carried out in future investigations to address this issue. Finally, this work lacks of specific functional and neuropathological correlations

to be related to our structural findings. Atrophy, in fact, is preceded by cytotoxic events that may impair functionality [7], and the neuropathological substrates underlying language dysfunctions need further comprehensive investigation.

Conclusions

This study showed that patients with AD and naming performance impairment present a relatively greater regional damage to BA20 detectable as early as 1 year prior to the clinical diagnosis, and that this alteration is followed by an involvement of the left frontal lobe in the subsequent 1 year.

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 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.; IXICO Ltd.; 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 Rev March 26, 2012 Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129 and K01 AG030514.

Ethical standards and patient consent We declare that all human and animal studies have been approved by the local Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu).

Conflict of interest We declare that we have no conflict of interest.

References

1. Becker JT, Huff FJ, Nebes RD et al (1988) Neuropsychological function in Alzheimer's disease. Pattern of impairment and rates of progression. Arch Neurol 45:263–268
2. Hodges JR, Patterson K (1995) Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. Neuropsychologia 33:441–459
3. Aronoff JM, Gonnerman LM, Almor A et al (2006) Information content versus relational knowledge: semantic deficits in patients with Alzheimer's disease. Neuropsychologia 44:21–35. doi:10.1016/j.neuropsychologia.2005.04.014
4. Blair M, Marczinski CA, Davis-Faroque N, Kertesz A (2007) A longitudinal study of language decline in Alzheimer's disease and frontotemporal dementia. J Int Neuropsychol Soc 13:237–245. doi:10.1017/S1355617707070269
5. Reilly J, Peelle JE, Antonucci SM, Grossman M (2011) Anomia as a marker of distinct semantic memory impairments in Alzheimer's disease and semantic dementia. Neuropsychology 25:413–426. doi:10.1037/a0022738
6. Harasty JA, Halliday GM, Kril JJ, Code C (1999) Specific temporoparietal gyral atrophy reflects the pattern of language dissolution in Alzheimer's disease. Brain 122(Pt 4):675–686
7. Gefen T, Gasho K, Rademaker A et al (2012) Clinically concordant variations of Alzheimer pathology in aphasic versus amnestic dementia. Brain 135:1554–1565. doi:10.1093/brain/aws076
8. Brambati SM, Myers D, Wilson A et al (2006) The anatomy of category-specific object naming in neurodegenerative diseases. J Cogn Neurosci 18:1644–1653. doi:10.1162/jocn.2006.18.10.1644
9. Balthazar ML, Yasuda CL, Pereira FR et al (2010) Coordinated and circumlocutory semantic naming errors are related to anterolateral temporal lobes in mild AD, amnestic mild cognitive impairment, and normal aging. J Int Neuropsychol Soc 16:1099–1107. doi:10.1017/S1355617710000998
10. Grossman M (2010) Primary progressive aphasia: clinicopathological correlations. Nat Rev Neurol 6:88–97. doi:10.1038/nrneurol.2009.216
11. Frings L, Kloppel S, Teipel S et al (2011) Left anterior temporal lobe sustains naming in Alzheimer's dementia and mild cognitive impairment. Curr Alzheimer Res 8:893–901
12. Teipel SJ, Willoch F, Ishii K et al (2006) Resting state glucose utilization and the CERAD cognitive battery in patients with Alzheimer's disease. Neurobiol Aging 27:681–690. doi:10.1016/j.neurobiolaging.2005.03.015
13. Melrose RJ, Campa OM, Harwood DG et al (2009) The neural correlates of naming and fluency deficits in Alzheimer's disease: an FDG-PET study. Int J Geriatr Psychiatry 24:885–893. doi:10.1002/gps.2229
14. Zahn R, Buechert M, Overmans J et al (2005) Mapping of temporal and parietal cortex in progressive nonfluent aphasia and Alzheimer's disease using chemical shift imaging, voxel-based morphometry and positron emission tomography. Psychiatry Res 140:115–131. doi:10.1016/j.pscychresns.2005.08.001
15. McKhann G, Drachman D, Folstein M et al (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 34:939–944
16. Shaw LM, Vanderstichele H, Knapik-czajka M et al (2009) Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 65:403–413. doi:10.1002/ana.21610. Cerebrospinal
17. Berg L, Miller JP, Baty J et al (1992) Mild senile dementia of the Alzheimer type. 4. Evaluation of intervention. Ann Neurol 31:242–249. doi:10.1002/ana.410310303
18. Juva K, Sulkava R, Erkinjuntti T et al (1995) Usefulness of the Clinical Dementia Rating scale in screening for dementia. Int Psychogeriatr 7:17–24
19. Morris JC (1997) Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 9(Suppl 1):173–178

20. Canning SJ, Leach L, Stuss D et al (2004) Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. Neurology 62:556–562
21. Rouleau I, Salmon DP, Butters N et al (1992) Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. Brain Cogn 18:70–87. doi:10.1016/0278-2626(92)90112-Y
22. Vakil E, Blachstein H (1993) Rey auditory-verbal learning test—structure analysis. J Clin Psychol 49:883–890. doi:10.1002/1097-4679(199311)49:6<883::AID-JCLP2270490616>3.0.CO;2-6
23. Reitan RM, Wolfson D (1994) A selective and critical-review of neuropsychological deficits and the frontal lobes. Neuropsychol Rev 4:161–198
24. Mack WJ, Freed DM, Williams BW, Henderson VW (1992) Boston naming test: shortened versions for use in Alzheimer's disease. J Gerontol 47:P154–P158
25. Jefferson AL, Wong S, Gracer TS et al (2007) Geriatric performance on an abbreviated version of the Boston naming test. Appl Neuropsychol 14:215–223. doi:10.1080/09084280701509166
26. Jack CR Jr, Bernstein MA, Fox NC et al (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging 27:685–691. doi:10.1002/jmri.21049
27. Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38:95–113. doi:10.1016/j.neuroimage.2007.07.007
28. Ashburner J, Csernansky JG, Davatzikos C et al (2003) Computer-assisted imaging to assess brain structure in healthy and diseased brains. Lancet Neurol 2:79–88
29. Binder JR, Desai RH, Graves WW, Conant LL (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 19:2767–2796. doi:10.1093/cercor/bhp055
30. Gainotti G (2000) What the locus of brain lesion tells us about the nature of the cognitive defect underlying category-specific disorders: a review. Cortex 36:539–559
31. Antonucci SM, Beeson PM, Labiner DM, Rapcsak SZ (2008) Lexical retrieval and semantic knowledge in patients with left inferior temporal lobe lesions. Aphasiology 22:281–304. doi:10.1080/02687030701294491
32. Lambon Ralph MA, Cipolotti L, Manes F, Patterson K (2010) Taking both sides: do unilateral anterior temporal lobe lesions disrupt semantic memory? Brain 133:3243–3255. doi:10.1093/brain/awq264
33. Buckner RL, Raichle ME, Miezin FM, Petersen SE (1996) Functional anatomic studies of memory retrieval for auditory words and visual pictures. J Neurosci 16:6219–6235
34. Damasio H, Grabowski TJ, Tranel D et al (1996) A neural basis for lexical retrieval. Nature 380:499–505. doi:10.1038/380499a0
35. Emmorey K, Grabowski T, McCullough S et al (2003) Neural systems underlying lexical retrieval for sign language. Neuropsychologia 41:85–95
36. Galton CJ, Patterson K, Graham K et al (2001) Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology 57:216–225
37. Josephs KA, Whitwell JL, Duffy JR et al (2008) Progressive aphasia secondary to Alzheimer disease vs FTLD pathology. Neurology 70:25–34. doi:10.1212/01.wnl.0000287073.12737.35