Relationship of Clinical and Cognitive Variables with Brain Morphometric Abnormalities in Alzheimer’s Disease: a Voxel Based Morphometric Study Using 3-Tesla MRI

Bhavani S. Bagepally, John P. John, Mathew Varghese, Harsha N. Halahalli, Lakshminarayanan Kota, Palanimuthu T. Sivakumar, Srikala Bharath, Sanjeev Jain

1Department of Psychiatry, 2Department of Clinical Neuroscience, Geriatric Psychiatry Unit, 3Multimodal Brain Image Analysis Laboratory (MBIAL) & 4Molecular Genetics Laboratory, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India
5Current affiliation: Department of Physiology, KS Hegde Medical Academy, Nitte University, Mangalore 575018, India.

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ABSTRACT: Alzheimer’s disease (AD) is associated with widespread structural and functional brain alterations. The current study examined the gray matter (GM) voxel-based morphometric (VBM) correlates of cognitive and clinical severity scores in patients with AD. The study included 34 patients with AD according to NINCDS/ADRDA AD criteria and 28 matched elderly controls. All subjects were clinically evaluated using Hindi Mental Status Examination (HMSE), Everyday Abilities Scale for India (EASI) and the Clinical Dementia Rating (CDR) scale. The structural Magnetic Resonance Imaging (MRI) data were acquired using a 3 Tesla MRI scanner and VBM analysis was performed using VBM5.1 toolbox. The patients with AD had significantly lower GM volume, white matter volume and total brain volume as compared to controls. The HMSE scores were positively correlated (p=0.009) and EASI (p=0.04) & CDR (p=0.0004) were negatively correlated with the total GM volumes in patients with AD. The VBM analysis revealed diffuse GM atrophy in patients with AD. Frontal & temporal GM volumes were positively correlated with the HMSE scores. Thus the results of the study replicate the previous observations of generalized GM atrophy, in an Indian sample with AD. The cognitive decline, clinical dementia severity and impairment in activities of daily living were correlated whole brain GM and WM volumes as well as with specific brain regional atrophy in AD. However further studies with larger samples & with more detailed cognitive evaluation are required for confirmation & validation of the relationship between regional morphometric abnormalities and cognitive deficits in AD.

Key words: VBM, Cognitive decline, India

Alzheimer’s dementia (AD) is associated with widespread structural and functional brain alterations. Structural Magnetic Resonance images (MRI) allows in vivo visualization of brain structure in 3-dimension (3D). MRI also helps in early diagnosis, differential diagnosis, as well as predicting the severity and progression of Alzheimer’s disease (AD) [1]. A number of unbiased and objective techniques are available for better understanding of diseased brain structures. Voxel-based morphometry (VBM) is a method for examining brain morphometry using structural MRI. VBM is a statistical approach using 3D T1-weighted MRI, for automated detection of gray-matter (GM) volume loss in various disorders on a voxel-by-voxel basis after anatomic standardization [2, 3]. There are also good arguments that cortical GM deficits are proportional to the extent of cognitive dysfunction [4].

*Correspondence should be addressed to: John P. John, M.D., National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India 560 029. Email: jjpjnimhans@gmail.com
The GM loss in AD has been reported in many areas that mediate functional, goal-oriented activities of daily living which include temporal, frontal, occipital, and limbic regions [5, 6]. GM atrophy is reported to be better correlated with cognitive decline than with white matter (WM) lesions [7, 8]. Some of the commonly used cognitive assessment tools in AD, like Alzheimer’s disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Mini mental status examination (MMSE) have shown that cognitive decline is related with regional GM degeneration in the left temporal lobe [9]. It has also been suggested that the ADAS-Cog and MMSE may reflect different aspects of the underlying brain changes observed in AD with ADAS-Cog being better correlated with GM integrity and MMSE with a more global reduction in both GM and WM [9]. However, studies that have linked cognitive deficits as assessed by regionally validated cognitive assessment tools with structural brain changes in AD are limited. Moreover, neuroimaging studies on dementia from Indian subcontinent are surprisingly sparse, despite India being the second most populous country in the world, with a growing elderly population [10]. The present study aimed at examining structural brain alterations in AD in comparison to matched healthy elderly using VBM analysis, a hypothesis-free voxel-based whole brain morphometric method. The study also aimed at linking cognitive decline with structural brain alterations in these patients.

** MATERIALS AND METHODS **

** Sample **

Thirty-four patients with probable AD according to NINCDS/ADRDA AD criteria [11] were prospectively recruited for the study from January 2009 to December 2010 from patients who attended the Geriatric Clinic at the National Institute of Mental Health And Neurosciences (NIMHANS), Bangalore, India. All the patients with AD were on less than 2 months of treatment with anti-cholinesterase inhibitors (predominantly Donepezil) at the time of MRI scanning. Twenty eight healthy control subjects who were age and gender-matched to the patient sample were recruited after excluding history of previous neurological or psychiatric illness or history of dementia in first degree relatives. All subjects were right handed as tested by Edinburgh handedness inventory [12]. Among subjects 7 AD patients and 5 controls, reported of having diabetes mellitus, and 11 AD patients and 4 controls reported of having hypertension. Also a family history of dementia was noted in first/second degree of 7 of the AD subjects. Detailed informed consent was taken from the participants and/or their accompanying relatives; the study was approved by the institutional ethics committee.

** Assessments **

Hindi Mental Status Examination (HMSE) [13] was used for assessment of overall cognitive abilities. It is a validated Indian modification of the Mini Mental Status Examination (MMSE), consisting of 23 questions with a maximum score of 31. Everyday Abilities Scale for India (EASI) [14], a 12 item scale was used for measurement of activities of daily living. The Clinical Dementia Rating (CDR) [15] was used for staging the severity of dementia.

** MRI Scanning Protocol **

The MRI data was acquired using Phillips Archieva 3 Tesla MRI Machine, according to the following scanning protocol: Orientation-sagittal; FOV-256 x 256 x 155 mm; voxel size- 1mm x 1mm x 1mm; slice thickness=1 mm; acquisition matrix-256 x 256; TR=8.1 ms; TE=3.7 ms; flip angle=8 degree; sense factor=3.5; total scan time= 7 min 41 sec with 165 sagittal slices.

** Image processing: Voxel Based Morphometry (VBM) **

VBM compares different brains on a voxel-by-voxel basis after the deformation fields have been used to spatially normalize the MRI images thus providing greater sensitivity for localizing small scale, regional differences in GM or WM [3]. It has been used in many brain disorders including dementia [16-20]. The current study used VBM image processing using Christian Gaser’s VBM5 toolbox within the Statistical Parametric Mapping 5 software (SPM5). SPM5 has improved bias correction component for better segmentation of brain in diseased conditions (Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm). The VBM5 toolbox enables spatial normalisation of MRI images and provides more accurate results by combining tissue classification, bias correction and nonlinear warping into the same generative forward model. The VBM-5’s segmentation algorithm in SPM5 additionally warps the prior images to the data and tries to minimize the impact of the template and the prior images [21]. Therefore, the segmentation can be used without the modifications made for previous version-SPM2, known as optimized VBM procedure. Chris Rorden’s dcm2gui
toolbox (www.cabiatl.com/mricro/mricron/index.html) was used for conversion of image formats.

All the images were inspected and oriented to anterior commissure-posterior commissure (AC-PC) plane. The images were pre-processed using combined affine and nonlinear (SPM5 default) normalization for GM and WM segmentation with fixed HMRF weightage of 0.3 in VBM5 toolbox. Image pre-processing as integrated in VBM5 toolbox involves certain steps. The initial normalisation step involves spatial normalisation of the original T1 images to MNI template image [18] to generate optimally normalised whole brain T1 images. The next step is segmentation of normalised whole brain into GM, WM and Cerebrospinal fluid (CSF) images. This is followed by the modulation step which involves multiplying (or modulating) voxel values in the segmented images by the Jacobian determinants derived from spatial normalization step. This step was performed in order to preserve the volume of a particular tissue (GM or WM or CSF) within a voxel. In effect, analysis of modulated data tests for regional differences in amount (volume) of GM. As the previous modulation step itself involves some smoothening in its process [22] we used gaussian filter of 8mm Full Width Half Maximum (FWHM) for smoothening to make data less noisy. By smoothening, voxels are averaged with their neighbours. This normalised, segmented, modulated, and smooth GM images with a voxel size of 1 cumm were used for further statistical analysis. The total GM, WM and intracranial volume (ICV) were extracted from VBM5 toolbox analysis. The total brain volumes (TBV) were calculated as sum of GM and WM volumes.

**Statistical Analysis**

**Clinical variables**: The statistical analyses were performed using R Cran Statistical Package (www.R-project.org). Univariate comparisons of demographic characteristics between patients with and controls were performed used Pearson’s chi square test while continuous variables were analyzed using independent samples t-test. Correlation tests were performed using Pearson’s correlation analysis for continuous variables and Spearman rank based correlation test for ordinal variables. Statistical significance was noted at p < 0.05.

**Statistical parametric mapping (SPM):** optimized voxel based morphometry analyses, Group comparisons for cerebral GM morphometric differences were performed between patients with AD and controls with age, gender, CDR,ICV and TBV as covariates using Analysis of Covariance (ANCOVA) within the framework of general linear model (GLM) in SPM5. The corrections for multiple comparisons were done using false discovery rate (FDR) correction (p < 0.05) [23]. TBV was used as a covariate along with age, gender and CDR in comparing between patients with AD and controls to identify regions of atrophy after adjusting for global atrophy at p<0.05, FDR corrected.

| **Table 1. Socio-demographic and clinical characteristics of study samples** |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                           | **Alzheimer's Dementia (n=34)** |                           | **Controls (n=28)** |                           |
|                           | Males (n=16) | Females (n=18) | Males (n=13) | Females (n=15) |
| Age (years)                | 70.5 ± 8.3 | 67 ± 6.4 | 68.7 ± 5.9 | 66.3 ± 6.5 |
| Duration of illness (years)| 3.3 ± 2.2 | 3.1 ± 3.1 | - | - |
| HMSE *                     | 16.8 ± 7.6 | 9.9 ± 6.6 | 30.4 ± 0.8 | 30.6 ± 0.5 |
| EASI *                     | 7.1 ± 2.5 | 9.3 ± 2.4 | 0 | 0 |
| CDR                        | 1.75 ± 0.7 | 2.2 ± 0.7 | 0 | 0 |
| GMV (mm$^3$) *             | 488.8 ± 49 | 459.8 ± 149 | 532.3 ± 63 | 507.3 ± 24 |
| WMV(mm$^3$) *              | 371.3 ± 51 | 325.3 ± 39 | 404.1 ± 42 | 379.7 ± 56 |
| TBV (mm$^3$) *             | 860 ± 89 | 785.1 ± 125 | 936.4 ± 95 | 886.9 ± 73 |
| ICV(mm$^3$)                | 1418 ± 107 | 1386.3 ± 354 | 1392 ± 182 | 1280.9 ± 128 |

* Significant (p<0.05) differences between AD and control samples.
HMSE: Hindi Mental Status Examination; EASI: Everyday Abilities Scale for India; CDR: Clinical Dementia Rating Scale; GMV: Gray matter Volume; WMV: White matter volume; TBV: Total Brain Volume; ICV: Intra cranial volume.
To evaluate GM areas correlated with the cognitive decline, multiple regression models in SPM5 was used with HMSE score as regressor with age, gender, TBV as covariates. No voxels stand significant at \(p<0.05\) FDR corrected so we also report the results at \(p<0.001\) uncorrected. The coordinates of significant voxels are converted into Talairach space (http://imaging.mrc-cbu.cam.ac.uk/imaging/mnitalairach). The coordinates were mapped using Talairach client version 2.4.2 [24].

RESULTS

The patients with AD had significantly lower HMSE scores \((p<0.001)\) and higher EASI scores \((p<0.001)\), when compared to control subjects. The total GM volume \((p < 0.03)\) as well as total WM volume \((p <0.001)\) were significantly lower in patients with AD as compared to control subjects. Also TBV of patients with AD was significantly lower than control subjects \((p<0.0008)\). However, ICV was not significantly different \((p <0.21)\) between controls and patients with AD (Table 1). HMSE scores were positively correlated \((p=0.009)\) while EASI \((p=0.04)\) and CDR \((p=0.0004)\) scores were negatively correlated with the total GM volume when all subjects were pooled together.

In patients with AD, the HMSE scores were positively correlated with total GM volume \((\text{Pearson’s } r =0.36, \ p= 0.009)\) (Figure 1A) & also with TBV \((\text{Pearson’s } r = 0.52, \ p = 0.00006)\) as shown in Figure 1B. The EASI scores in patients with AD were negatively correlated with GM volume \((\text{Pearson’s } r = -0.28, \ p = 0.04)\) (Figure 1D) and also with TBV \((\text{Pearson’s } r = -0.46, \ p = 0.0004)\) as shown in Figure 1E. The CDR scores in patients with AD were negatively correlated with GM volume \((\text{spearman’s rho} = -0.502, \ p\text{-value} = <0.001)\) & also with TBV \((\text{spearman’s rho} = -0.50, \ p<0.0001)\). The HMSE scores \((p= 0.916)\), EASI scores \((p = 0.78)\) and CDR scores \((p = 0.75)\) were not correlated with ICV (Figure 1C and 1F).

Figure 1. Gray matter, Total brain and Intra-cranial volume changes with HMSE & EASI. Scatter plots showing that correlation of Hindi Mental Status Examination (HMSE) and Everyday Abilities Scale for India (EASI) among AD patients with gray matter (GMV), total brain (TBV) & intracranial volumes (ICV) with corresponding Box plots at the side of each graph.
VBM comparisons between AD and healthy control subjects with age, gender and ICV as co-variates revealed generalized cerebral atrophy with predominance in temporal and parietal lobe, in patients with AD (p<0.05, FDR corrected) (Fig 2 A-B), the respective coordinates and labels of voxel clusters that showed significant volumetric reductions in AD at various brain regions namely bilateral parahippocampal gyrus, bilateral cingulate gyrus, bilateral temporal fusiform gyrus, middle, and inferior temporal gyrus, right transverse temporal gyrus, bilateral inferior parietal lobule, bilateral superior, inferior, medial & middle frontal gyrus, bilateral insular region, bilateral cuneus & precuneus and right uncus regions; which were predominantly in temporal, parietal, frontal and limbic regions. On using TBV instead of ICV as covariate in VBM statistical analysis to evaluate whether the atrophy in a given local region is above and beyond the degree of global atrophy, the significant regions of atrophy were observed mainly in bilateral medial temporal lobe and hippocampal region (p<0.05, FDR corrected) (Figure 2 C-D).

Figure 2. VBM comparison between AD and controls. Statistical Parametric map rendered on the template image showing the result of 2 sample t-test between AD patients and matched controls at threshold of 0.2, and P_{FDR\ corrected}\ p<0.05 with 2A: age, gender, and intracranial volume as covariates, and 2B: corresponding design matrix, 2C: with age, gender and total brain volume as covariates, 2D: corresponding design matrix.
Prefrontal and temporal cortical volumes that were positively correlated with HMSE scores (Figure 3) in patients with AD (p<0.001, uncorrected), and their respective coordinates are given in Table 2.

**Table 2.** VBM results of correlation analysis on GM morphometry with HMSE scores among combined sample (AD + control) at significance level of p<0.001 (uncorrected) and adjusted for age, gender and ICV.

| X coor  | Y coor  | Z coor  | Brain regions                                      | Brodmann areas          |
|---------|---------|---------|----------------------------------------------------|--------------------------|
| -46.53  | 27.80   | -7.28   | Left Inferior Frontal Gyrus                       | Brodmann area 47         |
| 4.95    | 55.39   | -18.75  | Right Medial Frontal Gyrus                        | Brodmann area 11         |
| -17.82  | -32.60  | -10.98  | Left Limbic Lobe Parahippocampal Gyrus            | Brodmann area 35         |
| -28.71  | -4.93   | -20.78  | Left Limbic Lobe Parahippocampal Gyrus            | Amygdala                 |
| -27.72  | 10.91   | -34.19  | Left Superior Temporal Gyrus                      | Brodmann area 38         |
| -19.80  | -29.86  | -14.49  | Left Cerebellum Anterior Lobe Culmen              | -                        |
| 33.66   | 52.13   | 13.05   | Right Superior Frontal Gyrus                      | Brodmann area 10         |
| 5.94    | 53.42   | 0.09    | Right Medial Frontal Gyrus                        | -                        |
| -4.95   | 11.66   | 58.37   | Left Superior Frontal Gyrus                       | Brodmann area 6          |
DISCUSSION

The present study illustrates the pattern of diffuse morphometric abnormalities in a sample of patients with Alzheimer’s disease from India using images acquired on a 3 Tesla MRI scanner and analyzed using VBM. Further, results of study highlight, the relationship between cognitive deficits and overall clinical severity indices (CDR and EASI) in AD with whole brain (Figure 1) as well as regional (Figure 3) brain morphometric abnormalities. Patients with AD significantly differed in cognitive functions with healthy elderly as tested by HMSE, and were having significant impairment in activities of daily living as evaluated by EASI. The observation of GM volume loss, especially involving temporal lobe, limbic & parahippocampal regions, as well as fronto-parietal regions is similar to results of previous MRI studies [19, 20, 22, 25]. Interestingly, on evaluation of GM morphometry using TBV as covariate (instead of ICV), predominant volume reductions of medial temporal lobe and hippocampal structures was noted. This finding suggests the medial temporal cortex suffers preferential atrophic damage, over and above the diffuse brain atrophy in AD. Whole brain volumetric measures like total GM, total WM and total brain (TBV) volumes were significantly correlated positively with cognitive functioning as assessed using HMSE (Figure 1). This indicates that there is a significant overall reduction in gray, white and total brain volumes associated with worsening cognitive dysfunction in AD. Moreover, decline in activities of daily living as well as clinical dementia rating severity were significantly correlated with the decline of GMV, WMV and TBV (Figure 1). These results suggest an association between clinical severity and structural brain atrophy.

The specific brain regions that showed a significant positive correlation with cognitive status using VBM include Brodmann’s areas 6, 10, 11 47 in frontal lobe apart from left parahippocampal gyrus (BA 35), left amygdala, left superior temporal gyrus (BA 38) and left cerebellum (Figure 3). Brodmann area 10 or the rostral prefrontal cortex has been consistently reported to have a role in event-based prospective memory & time-based prospective memory and also believed to play a part in strategic processes involved in memory retrieval and executive function [26]. Moreover, a previous VBM study has reported atrophy of medial temporal region that correlated closely with episodic memory performance [27]. There is also extensive evidence of involvement of amygdala in affectively influenced memory [28]. The results of the present study are similar to those of Baxter et al. that linked volumetric reductions in various brain regions associated with reduction in MMSE scores [9]. Furthermore, the results of the study indicate involvement of specific regions in frontal and temporal lobes that might underlie specific cognitive deficits in AD. However studies with larger sample sizes and more comprehensive neuropsychological assessments are needed to delineate the role of regional morphometric deficits associated with various cognitive deficits in AD. Nevertheless, the results of regional volumetric deficits associated with overall cognitive deficits should be interpreted with caution, in view of the lower statistical significance threshold (p<0.001, uncorrected) used in the present study.

We acknowledge the inherent limitations of the VBM technique with respect to making inferences regarding regional morphometric abnormalities in the atrophied brain as is the case in AD [29]. However, it must be noted that the method has been applied and validated in many studies involving various neurodegenerative disorders [3]. Moreover, the present study has several strengths: we used a 3.0 Tesla MRI scanner for image acquisition, which provides improved signal-to-noise ratio and spatial resolution, resulting in anatomically more detailed images, more accurate spatial representation, better structural depiction (e.g., contrast between white and GM) [30] and increased sensitivity for detecting subtle abnormalities. To assess the relationship between brain volumetric deficits and clinical severity, we adopted an unbiased image analysis using VBM methodology in which both cortical damage and severity of illness was assessed in a graded manner [31]. This was achieved by correlating the continuous intensity value for each voxel with suitably continuous clinical severity data (HMSE scores) thereby increasing both the sensitivity and statistical power of the analyses. We used culturally validated tools for cognitive (HMSE) as well functional assessment (EASI) in order to account for the influence of culture and education [32] in acquisition of cognitive skills as well as cognitive performance.

In summary, the present study replicates the previous findings of generalized GM atrophy in AD in an Indian cohort. Specifically, the results of the study confirm the relationship between diffuse as well as regional brain morphometric reductions in AD with the cognitive deficits as well as disease severity indices. The novelty of the study is demonstration of neuro-anatomical correlates of culturally/regionally validated tools for assessment of cognitive functions (Viz HMSE), activities of daily living (Viz EASI) in Alzheimer’s dementia from Indian sample. However, larger samples with comprehensive neuropsychological assessments are needed to specifically link brain regional volumetric deficits with specific cognitive deficits in AD.
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References

[1] Dhenain M (2008). Preclinical MRI and NMR Biomarkers of Alzheimer’s disease: Concepts and Applications. Magnetic Resonance Insights, 2: 75-91.
[2] Ashburner J, Friston KJ (2001). COMMENTS AND CONTROVERSIES Why Voxel-Based Morphometry Should Be Used. Image (Rochester, N.Y.), 1243:1238-1243.
[3] Mechelli A., Price CJ, Friston KJ, Ashburner J (2005). Voxel-Based Morphometry of the Human Brain: Methods and Applications. Current Medical Imaging Reviews, 1:1-9.
[4] Vidoni ED, Honea RA, Burns JM (2010). Neural correlates of impaired functional independence in early Alzheimer’s disease. J. Alzheimers Dis., 19:517–27.
[5] Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, et al. (2003). Dynamics of gray matter loss in Alzheimer’s disease. J. Neurosci., 23:994–1005.
[6] Camarda R, Camarda C, Monastero R, Grimaldi S, Camarda LKC, Pipia C, et al (2007). Movements execution in amnestic mild cognitive impairment and Alzheimer’s disease. Behav Neurol, 18(3):135–42.
[7] Mouton PR, Martin LJ, Calhoun ME, Dal Forno G, Price DL (1998). Cognitive decline strongly correlates with cortical atrophy in Alzheimer’s dementia. Neurobiol. Aging, 19(5):371–77.
[8] Mungas D, Reed BR, Jagust WJ, DeCarli C, Mack WJ, Kramer JH, et al. (2002) Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. Neurology, 59(6):867–873.
[9] Baxter LC, Sparks DL, Johnson SC, Lenoski B, Lopez JE, Connor DJ, et al. (2006). Relationship of cognitive measures and gray and white matter in Alzheimer’s disease. J. Alzheimers Dis., 9(3):253–260.
[10] Shaji KS, Jotheeswaran AT, Girish N, Bharath S, Dias A., Pattabiraman M, Varghese M (2010). THE DEMENTIA INDIA REPORT 2010 Prevalence, impact, costs and services for dementia.; A report prepared for the Alzheimer’s and Related Disorders Society of India. 2010 (www.alzheimer.org.in/assets/dementia.pdf).
[11] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Emanuel 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.
[12] Oldfield R (1971). The assessment and analysis of Handedness: The Edinburgh inventory. Neuropsychologica, 9: 97-113.
[13] Ganguli, M, Chandra V, Sharma S, Gilby J, Pandav R, Belle S, et al. (1995). A Hindi Version of the MMSE: The Development of a Cognitive Screening Instrument for Largely Illiterate Rural Elderly Population in India. International Journal of Geriatric Psychiatry, 10:367-377.
[14] Fillenbaum GG, Chandra V, Ganguli M, Pandav R, Gilby J E, Seaberg EC, et al (1999). Development of activities of daily living scale to screen for dementia in an illiterate rural older population in India. Age and Ageing, 28: 161-168.
[15] Morris JC (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology, 43:2412-2414.
[16] Ashburner J, Friston KJ (2000). Voxel-Based Morphometry the Methods. NeuroImage 11:805-821.
[17] Good C, Johnsrude I, Ashburner J, Henson R, Friston K, Frackowiak R, et al (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage, 14:685–700.
[18] Good C, Johnsrude I, Ashburner J, Henson R, Friston K, Frackowiak R., et al (2001). Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. NeuroImage, 14:685–700.
[19] Boxer AL, Rankin KP, Miller BL, Schuff N, Weiner M, Gorno-Tempini M, et al (2003). Cinguloparietal Atrophy Distinguishes Alzheimer Disease From Semantic Dementia. Arch Neurol, 60:949-956.
[20] Burton EJ, McKeith IG, Burn DJ, Williams ED, Brien JT (2004). Cerebral atrophy in Parkinson’s disease with and without dementia: a comparison with Alzheimer’s disease, dementia with Lewy bodies and controls. Brain, 127:791–800.
[21] Ashburner J, Friston KJ (2005). Unified segmentation. NeuroImage, 26:839-851.
[22] Good C, Scähill R, Fox N, Ashburner J, Friston K, Chan D, et al. (2002). Automatic Differentiation of Anatomical Patterns in the Human Brain: Validation with Studies of Degenerative Dementias. Neuroimage 17:29-46.
[23] Genovese CR, Lazar NA, Nichols TE (2002). Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate. NeuroImage, 15: 870-878.
[24] Lancaster J, Woldorff M, Parsons L, Liotti M, Freitas C, et al. (2000). Automated Talairach Atlas labels for functional brain mapping. 10 (3):120-131.
[25] Smith C, Chebrolu H, Wekstein D, Schmitt F, Markesbery W (2007). Age and gender effects on human brain anatomy: a voxel-based morphometric study in healthy elderly. Neurobiol Aging, 28(7):1075-1087.
[26] Okuda J, Fujii T, Ohtake H, Tsukiura T, Yamadori A, Frith CD, et al (2007). Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10)
in time- and event-based prospective memory. Int J Psychophysiol, 64(3): 233-246.

[27] Leube DT, Weis S, Freymann K, Erb M, Jessen F, Heun R, Grodd W, Kircher TT (2008). Neural correlates of verbal episodic memory in patients with MCI and Alzheimer’s disease—a VBM study. Int J Geriatr Psychiatry, 23(11):1114-8.

[28] Mcgaugh J, Cahill L, Roozendaal B (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. Proc. Natl. Acad. Sci, 93:13508-13514

[29] Bookstein FL (2001). Voxel-Based Morphometry” Should Not Be Used with Imperfectly Registered Images. NeuroImage, 14: 1454-1462.

[30] Willinek W, Schild H (2008). Clinical advantages of 3.0 T MRI over 1.5 T. Eur J Radiol, 65: 2-14.

[31] Tyler L, Marslen-Wilson W, Stamatakis E (2004). Dissociating neuro-cognitive component processes: voxel-based correlational methodology. Neuropsychologia, 43:771–778.

[32] Ganguli M, Chandra V, Gilby JE, Ratcliffe G, Sharma SD, Pandav R, et al (1996). Cognitive Test Performance in a Community-Based Nondemented Elderly Sample in Rural India: The Indo-U.S. Cross-National Dementia Epidemiology Study. Int Psychogeriatr., 8(4):507-524.