fMRI and Voxel-based Morphometry in Detection of Early Stages of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia in older adults. Loss of memory is the usual first symptom and different brain regions are involved to this pathological process. The aim of the study was to investigate the organization of cortical areas responsible for visual memory and determine correlation between memory impairment and atrophy of memory specific brain regions in early stages of AD. Voxel-based MR-morphometry was used to evaluate brain atrophy and functional MRI was used to detect specific brain regions responsible to visual memory task in patients with Alzheimer's disease and in control group. FMRI was performed on Siemens Magnetom Symphony (1.5 T) with the use of Blood Oxygenation Level Dependent technique (BOLD), based on distinctions of magnetic properties of hemoglobin. For test stimuli we used blocks of 12 not related images for "Baseline" and 12 images with 6 presented before for "Active". Stimuli were presented 3 times with reduction of repeated images to 4 and 2. For functional and morthometric data post-processing we used SPM8. Patients with Alzheimer's disease showed less activation in hippocampal formation (HF) region and parahippocampal gyrus then the control group ($p<0.05$). The study also showed reduced activation in posterior cingulate cortex ($p<0.001$). Voxel-based morphometry showed significant atrophy of grey matter in Alzheimer's disease patients, especially of both temporal lobes (fusiform and parahippocampal gyri); frontal lobes (posterior cingulate and superior frontal gyri). The study showed correlation between memory impairment and atrophy of memory specific brain regions of frontal and medial temporal lobes. Reduced activation in hippocampal formation and parahippocampal gyri, in posterior cingulate gyrus in patients with Alzheimer's disease correlates to significant atrophy of these regions, detected by voxel-based morphometry. The use of functional MRI and voxel-based morphometry provides the way to find alterations in brain function on early stages of AD before the development of significant irreversible structural damage.

1 INTRODUCTION

Cognitive impairment is one of the most common neurological disorders. Especially high prevalence of neurological disease with clinical cognitive impairment is among the senior people. 10-15% of elderly people have severe cognitive impairment – dementia. Dementia significantly reduces the quality of life of patient and his family. Dementia causes additional difficulties in the diagnosis and treatment of opportunistic disease, and doctors have difficulties in collecting anamnesis, assessment of patient complaints. Alzheimer's disease (AD) is the most common form of dementia. Enormous number of publications are devoted to cognitive disorders research, based on the results of imaging studies. Functional MRI (fMRI) and voxel-based morphometry (VBM) open up new opportunities in study of AD pathogenesis (Vasconcelos, L.G., 2011; Odinak, M.M., 2011).

Different brain regions are involved to the pathological process in AD irregularly. Primary neuronal damage in the early stages of disease was noted in the mediobasal parts of the frontal lobes of the brain. Morphological changes are also defined in the hippocampus, deep and posterior parts of temporal and parietal lobes of the brain. The

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preferential involvement of mediobasal structures of the temporal lobe in the pathological process have been confirmed by numerous MRI studies, which demonstrates significant hippocampus gray matter atrophy in patients with Alzheimer's disease (Frisoni G.B., 2008; Karas G.B., 2004; Zhang N., 2011). More informative is to assess atrophy progression in dynamics, and therefore morphometry of various brain structures is used (Lobzin, V.Yu., 2013).

Alzheimer's disease is characterized by progressive decline in memory. Functional MRI allows to investigate alterations in brain function before development of significant structural damage (Bassett, S.S., 2006). Golby A. et al. (2005) examined the functional competency of certain brain regions and their relationship with specific behavioural memory deficit in Alzheimer's disease. Results of fMRI resting state studies have so far relatively consistently pointed to the early involvement of posteromedial grey matter, such as the posterior cingulum and precuneus (Pihlajamaki M., 2008).

The purpose of this study was to evaluate brain activation by visual memory task in patients with Alzheimer's disease and to determine correlation between memory impairment and atrophy of memory specific brain regions of frontal and medial temporal lobes.

2 MATERIALS AND METHODS

2.1 Participants

We studied 27 patients with Alzheimer's disease (mean age 69,6±8,9 years), 22 matched by age (68,8±4,3 years) volunteers without evidence of brain lesions for VBM, and 20 healthy volunteers (35±5,1 years) for fMRI as a control group. Young volunteers were chosen as a control group for fMRI due to the absence of significant differences in healthy individuals of different ages according to our previous study (Odinak M.M. et al, 2011). Patients with Alzheimer's disease underwent a course of medical treatment in the neurological department of Military Medical Academy. Their evaluation included physical and neurological examination, brain imaging (MRI), blood analysis, including markers of inflammation, hormones, cholesterol and APOE. All of them underwent neuropsychological assessment to determine memory impairment, attention, thinking, speech and visual-spatial functions, using the following methods: Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR), Clock Drawing Test, Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT), Digit-span task (forward and backward), Luria´s Memory Words test (10 words), Digit Symbol Substitution Test. The study included patients with mild cognitive impairment or mild dementia. The diagnosis of Alzheimer's disease was established according to the NIA criteria (2011).

Each participant gave written informed consent to participate in the study. The study was approved by Ethics Committee of Military Medical Academy.

2.2 fMRI and VBM Data Acquisition

To investigate the organization of memory and localize cortical areas activated by visual memory task we used functional magnetic resonance imaging and to evaluate brain atrophy of patients with Alzheimer's disease voxel-based MRI morphometry was performed. Conventional T1- and T2-weighted images in three orthogonal planes were obtained also.

fMRI was performed on 1.5 T MR-scanner (Magnetom Symphony) with BOLD (Blood Oxygenation Level Dependent) technique, that is based on distinctions of magnetic properties of haemoglobin. Functional MR images were acquired using echo-planar imaging (EPI) with repetition time (TR) = 3700 ms, echo time (TE) = 50 ms, flip angle = 90º, field of view (FOV) = 230 mm and matrix size 128*128. For test stimuli we used series of 12 not related images for "baseline" and 12 images with for "active". 6 images in "active" period have been already presented in "baseline". Stimuli were presented 3 times with reduction of repeated images to 4 and 2. A finger switch response system was used to collect patient responses.

To obtain high resolution images of whole brain for Talairach coregistration and reslicing along different planes, we used 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) – T1-sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 4,38 ms, flip angle = 10º, field of view (FOV) = 250 mm, 160 slices and matrix size 256*256.

2.3 fMRI and VBM Data Post-processing

For functional data post-processing we used SPM8 (Welcome Department of Imaging Neuroscience, University College, London, UK) software package

running under MATLAB R2010a (The Mathworks, Sherborn, MA, USA) programming. For voxel-based morphometry we used VBM toolbox of SPM8. Template space was defined by standard EPI template data in SPM (MNI coordinates - Montreal neurologic Institute, McGill University, Montreal, Canada).

VBM data were visualized with MRICron (http://www.mccauslandcenter.sc.edu/mricro/mricron/), using Talairach atlas masks (Talairach and Tournoux, 1988).

3 RESULTS

Examining each group separately, we found that group of healthy volunteers showed activation of cingulated gyrus ($p<0.001$). Cingulate gyrus plays an essential role in memory formation and provide intercommunications between brain regions. Controls also showed statistically significant activation in hippocampal formation (HF) and parahippocampal gyrus and Broadman area 6 (BA6). The function of BA6 is to organize complex motor response while carrying out the instructions, in particular the definition of "right" or "wrong" stimulus. 80% of controls showed activation of BA40, which plays the role in recognition of visual images.

Group comparison analysis allows to identify certain brain regions with different activation patterns. Patients with Alzheimer's disease showed less activation in hippocampal formation (HF) and parahippocampal gyri comparing to healthy controls group ($p<0.05$). The study also showed reduced activation in posterior cingulate gyrus ($p<0.001$).

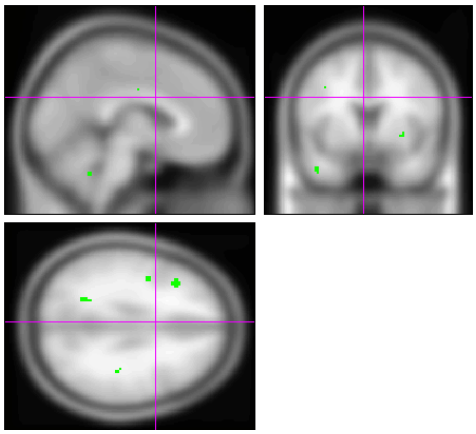

Figure 1: Reduced activation in posterior cingulated gyrus and in hippocampal formation region in AD patients ($p<0.001$).

The results demonstrate that a lot of different brain regions participating in the differentiation of the stimuli are involved. This corresponds to the opinion, that the morphological substratum of higher cortical functions is a set of combined functional centers (Luria A., 1962), thereby confirming the concept of dynamic functional localization.

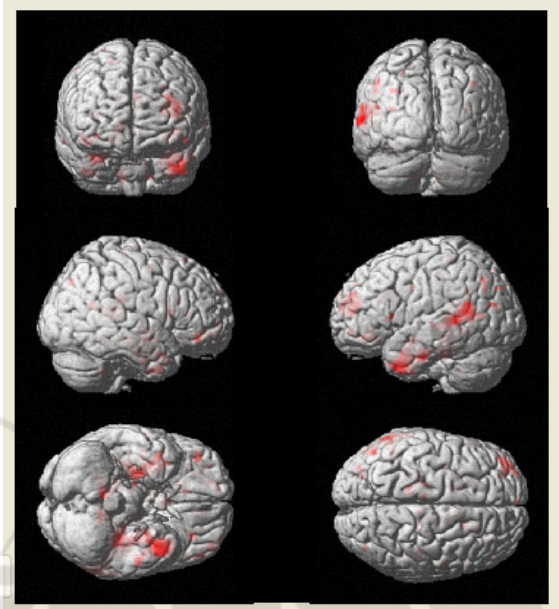

Figure 2: Differences in activation between AD group and healthy controls (three-dimensional volume-rendered display).

Voxel-based morphometry showed significant general atrophy of grey matter in AD patients, especially of both temporal lobes (fusiform and parahippocampal gyri), frontal lobes (and superior frontal gyri), parietal lobes and cingulate gyrus. However, the most significant changes were found in mediobasal temporal lobe (up to 3.6 cm^3 at $p<0,01$) and thalamuses (up to 4.5 cm^3 at $p = 0,02$).

Table 1: The values of volumes (cm^3) of different brain regions, based on MRICron analysis.

Cerebral Region	AD patients group	Control group	p-value
Frontal lobes	365,9±18,0	382,4±6,3	<0,01
Temporal lobes	217,4±3,9	225,7±3,2	<0,01
Parietal lobes	179,0±5,3	181,9±3,6	0,03
Hippocampal region	3,6±0,5	3,9±0,1	<0,01

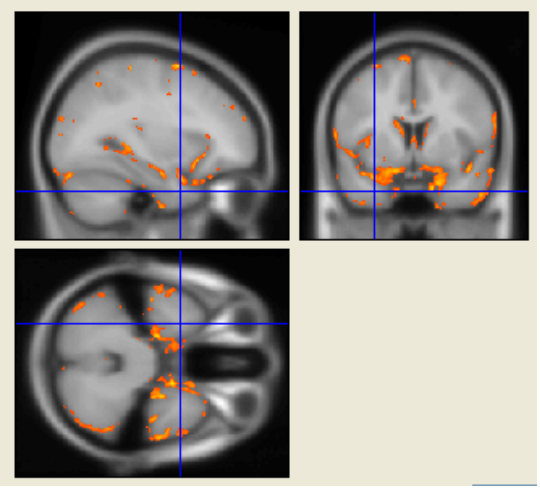

Figure 3: Brain atrophy in Alzheimer's disease patients comparing to the control group ($p<0.001$).

In this study we identified patterns of cognitive deficits of varying severity in accordance to the volume changes of certain brain structures. For this purpose, a correlation analysis was performed comparing the results of neuropsychological assessment and identified brain volumes. The most significant correlations are shown in Table 2.

Table 2: Correlations between brain atrophy and neuropsychological assessment.

Cerebral Region	Neuropsychological scale	Spearman's rank correlation coefficient (r), $p<0,05$
Total gray matter volume	MMSE orientation subtest	0,56
Temporal lobe	MMSE total, FCSRT-IR	0,57 0,56
Parietal lobe	MMSE Luria´s Memory Words test	0,44 0,53
Cingulate cortex	Luria´s Memory Words test, FCSRT-IR	0,85 0,86
Frontal lobe	MMSE total, categorical verbal fluency	0,51 0,43
Occipital lobe	TMT «A» TMT «B»	– 0,86 – 0,78
Hippocampal formation region	MMSE orientation subtest, FCSRT-IR	0,52 0,65
Thalamus	MMSE attention subtest,	0,70

According to the correlation analysis there is a decrease of certain brain structures volume accompanied by deterioration of specific cognitive functions. This was true for such intellectual-mental functions such as memory, attention and thinking. Atrophy of temporal and parietal lobes associated with a reduction of scale results: MMSE ($r = 0,57$ and $r = 0,54$, respectively, at $p <0,05$) and 5 words test ($r = 0,53$, $p <0,05$).

4 CONCLUSION

In summary, combined application of fMRI and VBM allows to assess brain atrophy along with functional component of memory impairment and can help to detect Alzheimer's disease related changes in early stages before they may be revealed by means of conventional MRI study. The study showed correlation between memory impairment and atrophy of memory specific brain regions of frontal and medial temporal lobes. Thus, reduced activation in hippocampal formation and parahippocampal gyri, in posterior cingulate gyrus in patients with Alzheimer's disease correlates to significant atrophy of these regions, detected by voxel-based morphometry, and to deterioration of specific cognitive functions. Obtained data correspond to comprehensive conceptions of pathogenesis and general clinical features of AD. Combined fMRI and voxel-based morphometry study can be used in clinical practice in patients with AD and cognitive disorders.

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