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Application of Functional and Diffusion Tensor Mri for Early Detection of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia among neurodegenerative diseases. New advanced magnetic resonance imaging techniques, such as functional (fMRI) and diffusion tensor (DT-MRI) imaging, allow assessment of brain tissue changes in AD at microstructural and functional levels and can be used in the diagnosis of this pathological process at early stages of cognitive impairment.

Key words: literature review; dementia; Alzheimer's disease; magnetic resonance imaging.

Introduction.

The development of modern medicine has led to an increase in the life expectancy of the world's population. However, along with this, there has been an increase in the incidence and prevalence of dementia in the population. Dementia is a syndrome caused by brain disease, usually chronic or progressive, in which there is impairment of many higher functions of the central nervous system, including memory, thinking, comprehension, speech, orientation, ability to count, cognition and reasoning. In dementia, there is no clouding of consciousness. Usually, this pathology is characterized by deterioration of emotional control, degradation of social behavior or changes in motivation for actions. All this is often combined with cognitive function disorders. According to the World Health Organization, in 2010 there were approximately 36 million people worldwide suffering from dementia. Every 20 years their number will practically double and will reach 115 million by 2050. This syndrome is detected in a large number of diseases causing primary or secondary brain damage [1].

Alzheimer's disease (AD) is the most common form of dementia, accounting for at least 35-40% of cases in the overall structure of dementias. Other common diseases similar to AD are vascular dementia, dementia with Lewy bodies, frontotemporal dementia, etc. [2]. The widespread prevalence of AD and the associated economic costs for patients' families, caregivers, and the community as a whole have stimulated the study of various methods for diagnosing this disease.

Today, there is no diagnostic test other than postmortem morphological examination that can reliably establish a

lifetime diagnosis of AD. The diagnosis of this disease is based on the priority of clinical criteria, including collection of complaints and medical history, neurological examination and neuropsychological testing with subsequent identification of disease biomarkers to confirm the diagnosis. Instrumental diagnosis of AD includes laboratory and neuroimaging methods. The latter include techniques for structural (magnetic resonance imaging - MRI, computed tomography - CT) and functional (positron emission tomography - PET-CT, single photon emission computed tomography - SPECT) assessment of the brain. MRI and PET-CT proved to be the most informative.

It has been established that new MRI techniques, such as functional MRI (fMRI) and diffusion tensor MRI (DT-MRI), can provide significant information about neuronal connections and microstructural changes in the brain in AD at early stages, when they are not yet detected by routine examination. In addition, new MRI techniques make it possible to predict the probability and dynamics of disease progression.

Functional MRI. Functional MRI is a method of functional brain mapping based on changes in hemodynamic parameters during activation of individual areas of the cerebral cortex in response to stimulus exposure (Task-fMRI) or at rest (Resting state fMRI). Compared to other functional neuroimaging methods in neurodegenerative diseases, fMRI has several advantages: the method is non-invasive, not associated with ionizing radiation exposure, dynamic examination and use in longitudinal studies is possible, has high spatial-temporal resolution, provides information about the integrity of functional neuronal networks.

Images in fMRI obtained based on gradient echo or T2* sequences represent recorded signals of the so-called BOLD contrast from voxels (blood oxygenation level dependent) depending on the percentage of deoxyhemoglobin. When groups of neurons are activated, their metabolism increases and, accordingly, oxygen consumption, as a result of which deoxyhemoglobin is washed out of tissues and the influx of oxygenated blood increases. Such a change in the ratio of oxyhemoglobin and deoxyhemoglobin is the basis of the BOLD contrast signal [3, 4].

A feature of the clinical picture of the early stage of Alzheimer's disease is a decrease in the ability to form stable working memory. In most fMRI studies in patients with AD and mild cognitive impairment (MCI), tasks and paradigms were aimed at activating working, semantic memory, in some cases associative and even emotional memory, to assess the degree of activation of the hippocampus, parahippocampal areas and medial temporal regions.

In scientific studies using fMRI in patients with AD, a consistent decrease or absence of activation of the medial temporal regions and hippocampus was detected compared to a control group of elderly subjects without cognitive impairment [5, 6]. In several studies in patients with AD, neuronal activation of the ventral lateral prefrontal cortex was noted in combination with low activity of the medial temporal regions, indicating a possible compensatory mechanism of cognitive functions [7, 8].

Regarding patients with mild cognitive impairment, fMRI results varied from hypo- to hyperactivation. There are several viewpoints on this issue. It should be noted that such variability in results is explained by the fact that many studies used different patient selection criteria, with different clinical symptoms, degrees of hippocampal and parahippocampal atrophy, and different activation paradigms were used, which complicates the analysis of results from numerous studies.

A common feature of studies reporting increased activity of the hippocampus and medial temporal regions is that these studies mainly included patients who could perform stimulation tasks and paradigms quite effectively [9-11]. However, longitudinal studies noted that hippocampal hyperactivation may indicate further rapid decline in cognitive functions and development of Alzheimer's disease. The potential mechanisms of hyperactivation of the medial temporal regions and hippocampus remain unclear and may include changes in synaptic transmission, cholinergic and other neurotransmitter transmission [7].

Given the need to perform specific tasks and paradigms during fMRI (task fMRI), there are several limitations for patients with AD and mild cognitive impairment, primarily due to difficult contact with such patients. In connection with this, in the last decade, the method of resting-state functional MRI (rs-fMRI) has become increasingly widespread among researchers studying functional connections in neurodegenerative diseases.

In rs-fMRI, low-frequency temporal sequences of BOLD signal oscillations of spontaneous neuronal activity of various brain areas at rest are recorded. The subject receives no active tasks; they should be maximally relaxed and not think about anything specific. The low-frequency oscillations detected in such examination reflect basal neuronal activity of the brain and are not artifacts of respiratory movements or heartbeat, which has been proven in several studies [13].

Systematic processing of rs-fMRI data using various analysis methods provides information about so-called functional connectivity (FC) of the brain and allows identification of neuronal activations similar in temporal and frequency characteristics of anatomically distant brain areas - resting-state networks (RSNs).

Despite differences in data collection protocols and different post-processing methods, eight resting-state brain networks involved in maintaining and ensuring cognitive processes were consistently identified in conducted studies: primary motor, primary visual, extrastriate visual, insular-temporal, left and right hemispheric, parietal-frontal resting networks, frontal RSN and default mode network (DMN) [4].

The latter RSN, in turn, is associated with emotional, spontaneous thought processes and is mostly active when subjects are focused on introspective analysis. The default mode network is of great interest in studying patients suffering from Alzheimer's disease and mild cognitive impairment, as the functionally connected anatomical areas of gray matter of this network are the posterior and anterior cingulate cortex and precuneus, medial temporal regions, medial, lateral and inferior frontal and parietal regions.

There are various software methods for processing rs-fMRI data, such as independent component analysis, neuronal network analysis based on region of interest selection (seed-based analysis, ROI search), principal component analysis, analysis of amplitude of low-frequency fluctuations of BOLD signal and regional homogeneity (amplitude of low-frequency fluctuation, ALFF) [3]. Most works most often used independent component analysis and analysis based on region of interest selection.

Despite different statistical data processing methods, practically all works determined a decrease or absence of DMN formation, both in patients suffering from Alzheimer's disease and in patients with MCI, compared to the control group. Areas where neuronal connectivity disruption was found were the posterior cingulate cortex, precuneus and prefrontal cortex. In their work, C. Sorg et al. [6] noted bilateral connectivity disruption in the superior parietal lobes and inferior frontal gyri compared to the control group. W. Koch et al. [1,7] during rs-fMRI in patients with MCI observed decreased neuronal coactivation only in the anterior cingulate cortex and parietal lobe, while neuronal activity in patients with AD was decreased in all DMN areas.

In the study by J.R. Petrella et al. [2], it was suggested that DMN disruption in patients with MCI is a marker of further development of Alzheimer's disease within several years. In the study by L. Farràs-Permanyer et al. [9], an analysis of 79 scientific works devoted to fMRI research using activation tasks and at rest in patients with MCI and AD was conducted. Each work evaluated the purpose and type of study, types of tasks performed by subjects (including resting state mode), as well as programs and methods of statistical data analysis.

The purpose of most scientific works was to study functional neuronal connections in patients with AD and mild cognitive impairment compared to control groups, study the reliability and reproducibility of fMRI results using various data processing programs, as well as identification of possible prognostic biomarkers for Alzheimer's disease development. Almost every work analyzed changes in neuronal activity of the hippocampus, parahippocampal areas and medial temporal regions, as well as changes in functional connectivity of the brain's DMN.

L. Farràs-Permanyer et al. concluded that resting-state fMRI compared to fMRI using activation tasks and paradigms is the most informative method in longitudinal studies and in identifying brain functional connectivity changes characteristic of AD. As the degenerative process progresses and clinical symptoms severity increases, it becomes more difficult for patients with AD to perform tasks set by the researcher and maintain immobility throughout the entire study, although unfortunately, all fMRI methods are very sensitive to head movement, which significantly limits the application of this technique and is one of the factors that do not allow including it in a standardized protocol used when examining patients with AD.

Longitudinal fMRI studies are necessary to track changes in neuronal activation structures throughout the entire disease period - from healthy brain aging, preclinical AD stage, mild cognitive impairment to dementia. Also, combination of neuroimaging methods such as voxel-based morphometry, fMRI and PET-CT may contribute to further understanding of the relationship between AD markers and their relative value in tracking changes throughout the disease.

However, the main problem of fMRI is the absence of a reliable standardized statistical software method for data processing. In the meta-analysis by L. Farràs-Permanyer et al., several important aspects of resting-state fMRI were established:

- use of different statistical models for data analysis does not allow comparing results in a cumulative and integrated manner;
- complexity of each statistical model is associated with different phases and algorithms of data processing, in addition, this means that each statistical model represents brain functional connectivity differently; an attempt to group different statistical methods showed only inconsistency and lack of specificity of each individual data processing method;
- when studying patients with MCI, results depended on many different factors, such as clinical picture, degree

of hippocampal and parahippocampal atrophy, effective performance of tasks set by the researcher, etc.

Conclusions: Thus, fractional anisotropy and mean diffusivity indicators proved to be non-specific; the authors failed to identify a statistically significant difference in FA and mean diffusivity values that would allow confident judgment about the presence or absence of neurodegenerative disease in the examined subjects. Currently, the pathophysiological relationship between white matter and cortical damage in Alzheimer's disease remains unclear. Possibly, brain white matter damage is a secondary process developing due to gray matter neuronal degeneration, but concomitant vascular brain damage cannot be excluded [34].

In addition, the absence of a unified method for conducting and processing diffusion tensor MRI results does not allow including this technique in a standardized protocol for examining patients with neurodegenerative diseases, as different post-processing methods provide information differently and strongly depend on basic algorithms and methodological implementation of the process.

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