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Voxel-Based Morphometry in Frontotemporal Dementia

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Abstract—Frontotemporal dementia (FTD) is a clinically, genetically and pathologically heterogenous neurodegenerative disorder. FTD is characterized by a focal atrophy, which makes it a promising candidate for study using voxel-based morphometry (VBM). Visual assessment of magnetic resonance imaging of the brain is subjective and often depends on the researcher's experience, which reduces its diagnostic value. VBM, on the other hand, allows quantitative assessment of brain atrophy, which increases the accuracy and allows to identify the earliest stages of the neurodegenerative process. This review will cover the utility of VBM in the study of the neuroanatomical foundations of the disease, identify the atrophy patterns specific to each variants of FTD and analyze the role of VBM in diagnosis of clinical and preclinical stages of the disease.

Keywords: frontotemporal dementia, voxel-based morphometry, behavioral variant frontotemporal dementia, primary progressive aphasia

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INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by a focal atrophy, which predominantly involves frontal and temporal lobes of the brain. Onset is typically between 45 and 65 years, and FTD is considered the second most common early-onset dementia, second after Alzheimer's disease (AD) [2]. At the same time, some studies show that the socioeconomic burden of FTD can be up to two times higher than in AD [3].

FTD is further divided into three main clinical subtypes—behavioral variant FTD (bvFTD), semantic and non-fluent variants of primary progressive aphasia (svPPA and nfvPPA, respectively), their diagnosis is established in accordance with the current international diagnostic criteria [4, 5]. Less commonly, FTD can manifest itself as logopenic variant PPA (lvPPA), which is most commonly viewed as an atypical variant of AD [6–8]. The most common variant is bvFTD, which is characterized by the development of a whole spectrum of behavioral, cognitive and affective disturbances. Its key symptoms are early loss of empathy and sympathy, combined with apathy, disinhibition, irritability and executive deficit. Patients often develop various types of stereotyped and compulsive behavior as well as hyperorality and altered food preferences [4, 9–11].

svPPA is characterized by impaired single-word comprehension, anomia and the development of surface dyslexia and dysgraphia (patients cannot recognize a word as a whole, which leads to trouble with reading and writing of irregularly spelled words and inability to distinguish homophonic words), while speech production remain intact for a long time [5]. Patients with svPPA will also often develop behavioral features, and in case of right anterior temporal pole involvement semantic deficit can also extend to nonverbal information, which leads to impaired recognition of familiar visual images (faces, objects), tastes, smells and emotions [12, 13].

Unlike svPPA, the main manifestations of nfvPPA are agrammatisms (the grammatical connection within sentences is broken, grammatical errors are often encountered, the patient speaks in fragments of phrases or in separate words) and/or apraxia of speech (errors in the pronunciation of words, distortion of sounds and impaired articulation), as well as impaired comprehension of syntactically complex sentences. In addition to speech impairments non-speech orofacial and ideomotor apraxia is often observed [5, 14].

Beside speech and behavioral disorders, any FTD variant may also present with movement disorders such as motor neuron disease (MND), parkinsonism, corticobasal syndrome (CBS), and progressive supranuclear palsy syndrome (PSP) [1].

The underlying genetic causes of FTD is of particular importance—up to 40% of patients have a family history of disease, and in 13% of cases an autosomal dominant type of inheritance can be traced [15]. Currently, more than 20 different genes are known to cause FTD, however, the majority of cases are associated with mutations in three genes—*C9orf72*, *GRN*, and *MAPT* [16]. FTD is also characterized by a variety of pathological variants. According to the autopsy

results, several main subtypes are distinguished: FTD with the accumulation of TDP-43 protein (FTD-TDP-43), FTD-tau, and FTD with FET-positive inclusions (FTD-FET) [17].

There are no definite correlations between clinical, genetic and pathological variants of FTD, but there are some associations. For example, in the overwhelming majority of cases, svPPA is characterized by TDP-43 pathology, while in nfvPPA cases tau protein accumulation is commonly observed [18]. FTD-FET is usually associated with an earlier age of onset (usually before the age of 45) and higher rate of disease progression, clinically it is characterised by more prominent psychiatric features and executive deficits [19]. Carriers of mutations in the *GRN* gene accumulate the TDP-43 protein and most often develop one of the variants of PPA, in about 40% of patients it is combined with atypical parkinsonism syndrome (usually in the form of CBS). Mutations in the *C9orf72* gene, as a rule, lead to the development of FTD (usually in the form of bvFTD with a predominance of apathy), MND, or their combination. A feature of the clinical picture is the frequent presence of hallucinations, psychosis and illusions, which can lead to an initially erroneous diagnosis. The clinical picture of patients with mutations in the *MAPT* gene is most often represented by a combination of FTD with parkinsonism syndromes (more often CBS, less often PSP) and semantic disturbances (although primary speech disorders are rare) [16, 18].

Such heterogeneity and the lack of clear comparisons between clinical, genetic and pathological variants of FTD significantly complicate the study and timely diagnosis of the disease. In addition, the symptoms characteristic of FTD are common both in various psychiatric illnesses and in other dementias [20, 21]. This necessitates the search for and introduction into clinical and research practice of reliable and sensitive markers of the neurodegenerative process. Brain magnetic resonance imaging (MRI) has long been used in the clinic and in the study of the disease. Identification of typical patterns of atrophy according to structural MRI data is one of the diagnostic criteria of the disease and allows to increase diagnosis reliability from possible to probable [4, 5]. However, the use of standard MRI modes has several limitations. In the early stages of the pathological process, cortical atrophy is often minimally expressed. In addition, the visual assessment of MRI data is subjective and depends on the investigator's experience. According to some studies, the sensitivity of this approach in detecting bvFTD among clinically similar diseases varies from 59 to 70% [22, 23]. All this led to the search for ways that would circumvent such limitations and increase the diagnostic accuracy of MRI.

One of them is voxel-based morphometry (VBM), which is a method of MRI processing. When using VBM, T1-weighted MR images are segmented into separate voxels of gray, white matter and cerebrospinal fluid and subjected to smoothing using the Bayesian algorithm. Then the obtained images are normalized by registration in the same template image (stereotaxic space). Such normalized and processed images can then be compared with each other voxel by voxel to identify areas of atrophy characteristic of a particular disease, which can be further used for diagnostic purposes [24].

In this review, we will discuss the possibilities of using VBM in the study and diagnostics of various forms of FTD.

1. PATTERNS OF ATROPHY IN DIFFERENT VARIANTS OF FTD

Initially, with the help of the VBM, certain patterns of atrophy were identified, which are characteristic of various variants of the VBM. Since VBM is a comparison method, these data are obtained by comparing the volume of gray matter (GM) of different parts of the GM of patients with FTD with a control group comparable in gender and age.

1.1. Behavioral Variant FTD

According to the current diagnostic criteria, bvFTD is characterized by relatively symmetrical atrophy of the frontal and anterior parts of the temporal lobes of the GM on both sides [4] (Fig. 1). However, VBM allows a more thorough analysis. In 2012 Pan et al. conducted a meta-analysis on MRI morphometry in bvFTD, which included 11 studies, including data on 237 patients with bvFTD and 297 healthy volunteers. The greatest atrophy in comparison with the control group was noted in the anterior parts of the middle frontal gyri (Brodmann's field [BA] 9) with extension to other parts of the frontal lobes (BA 8, BA 46, OFC [BA 10] and the anterior cingulate cortex [BA 24/32]), as well as insular lobes and striatum on both sides [25]. Interestingly, the meta-analysis found no significant atrophy of temporal lobes, despite the fact that it was noted in some studies. The authors assumed that the damage of temporal lobes does not occur in all cases of bvFTD, but only in a separate subpopulation of patients. Another possible explanation is that temporal lobes are affected in bvFTD at later stages, and this pattern of atrophy does not prevail in a general group.

The insular lobes are also worth considering. This area is also affected in nfvPPA. Mandelli et al. in their work showed that in these two variants of FTD insular atrophy has differences. In bvFTD mainly the anterior ventral regions on both sides and the dorsal anterior part of the right insula are affected. In nfvPPA there is a more significant atrophy of the superior precentral gyrus of the left insular [26].

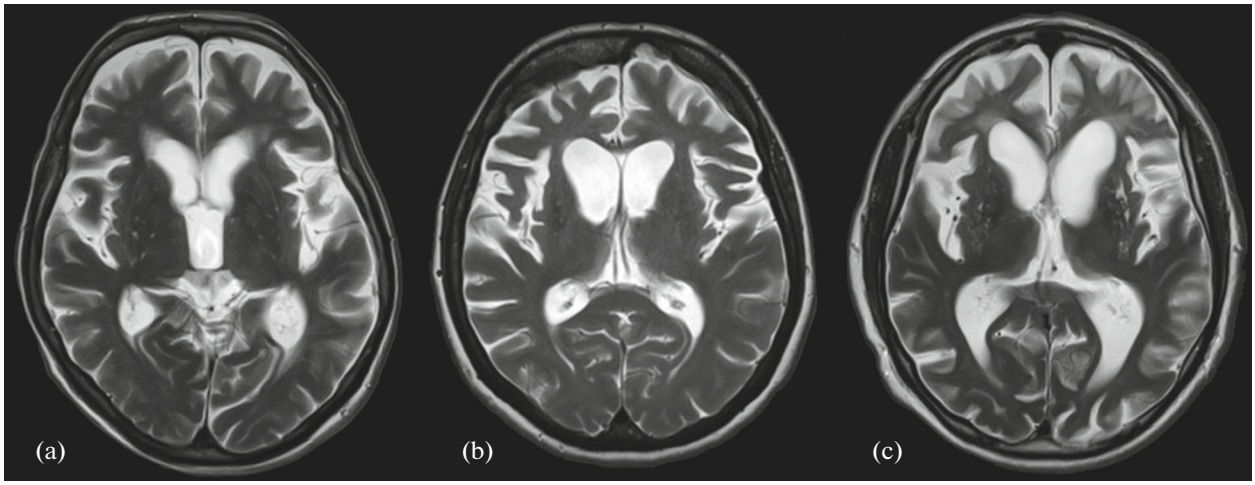

Fig. 1. MRI of the bra in in bvFTD (T2-weighted images). (a) bvFTD without pathogenic mutations in *C9orf72*, *MAPT*, *GRN* genes. (b) bvFTD associated with a mutation in *GRN* gene. (c) bvFTD associated with a mutation in *C9orf72* gene.

1.2. Semantic Variant of PPA

svPPA is characterized by asymmetric atrophy of the temporal lobes, usually with a predominance on the left side, especially of the anterior and ventral parts [27]. In some cases at the early stages of the disease, preferential atrophy of the right hemisphere may occur [28], which led to define left- and right-sided forms of sPPA.

A meta-analysis (2007) included data on 267 patients with FTD and identified several significant regions of atrophy in svPPA—the left anterior superior and middle temporal gyri, the lower temporal poles on both sides, the subcallosal field, and the amygdala with spread to left entorial and peririnal cortex [29].

According to another meta-analysis devoted to the study of GM atrophy in svPPA and AD, which included data on 513 patients with svPPA and 2653 patients with AD, significant GM lesions in svPPA were noted in the anterior hippocampus with spread to the left fusiform gyrus and anterior regions of the right temporal lobe; middle and upper regions of the right temporal pole and upper regions of the left temporal pole; lower, middle and upper parts of the left temporal lobe; the right anterior fusiform gyrus and the right insular lobe. It should be noted that the anterior parts of the hippocampus, the lesion of which was noted in svPPA, are involved in the processing of semantic information, while their posterior parts, the atrophy of which is observed in AD, are involved in providing episodic memory [30].

When analyzing the various stages of the disease a definite sequence of lesions in various areas of the GM in svPAA was revealed. Thus at earlier stages the process involves the GM of the inferior temporal and fusiform gyri, the temporal pole as well as the parahippocampal and entorial cortex [27, 31]. With the progression of the disease atrophy spreads to the anterior regions of the GM including the OFC, the lower frontal regions, the insular lobe and the anterior cingulate cortex as well as the posterior temporal and parietal regions [27]. The fastest rate of atrophy is observed in the temporal lobes which distinguishes the semantic variant of PPA from the agrammatic where the highest rate of atrophy is observed in the frontal lobes of the GM [32].

1.3. Non-Fluent Variant of PPA

nfvPPA is also characterized by asymmetric atrophy of the left hemisphere (Fig. 2), however the involved areas differ from svPPA. Schroeter et al. in a meta-analysis identified four clusters, the lesion of which characterizes nfvPPA: the left middle frontal gyrus, the opercular part of the inferior frontal gyrus, the superior temporal pole, and the lenticular nucleus [29].

Some studies have also shown significant atrophy in the precentral gyrus, dorsal premotor and dorsolateral prefrontal cortex, insular lobe, fusiform gyrus, subcortical structures, and cerebellum [31, 33, 34]. nfvPPA with speech apraxia is characterized by additional atrophy of the premotor and supplementary motor cortex [35–37].

Initially the neurodegenerative process affects the left inferior frontal gyrus (especially its opercular part), dorsolateral prefrontal cortex, superior temporal gyrus and insular lobe, namely its superior precentral gyrus [26, 31, 38]. In progression atrophy spreads to the anterior frontal, lateral temporal and anterior parietal regions ipsilaterally, and also invades the right prefrontal cortex, temporal lobe and subcortical structures (caudate nucleus and putamen) from both sides [39]. The fastest rate of atrophy is observed in the frontal lobes of the GM [32].

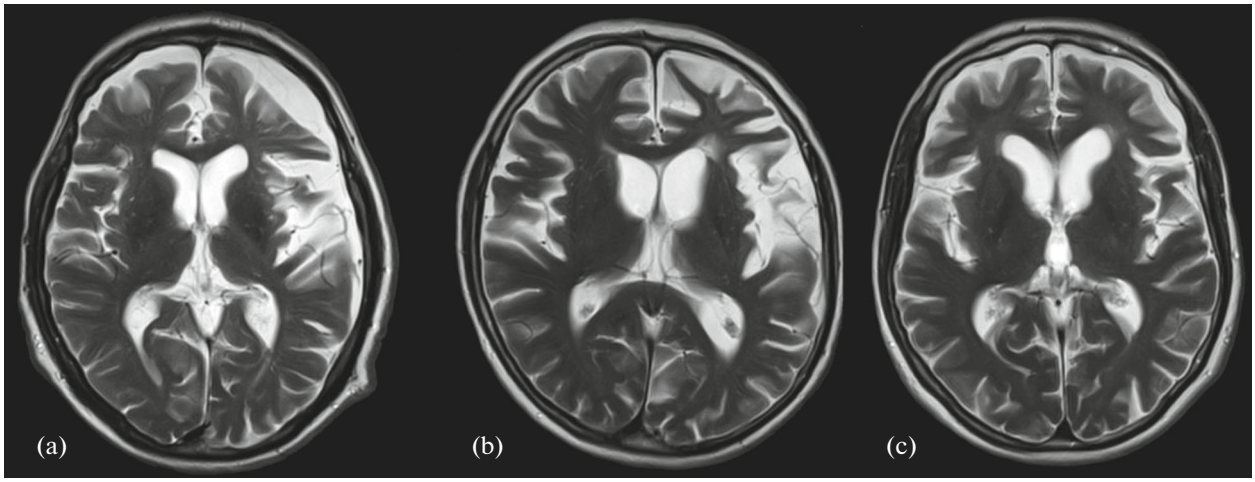

Fig. 2. MRI of the brain with nfvPPA (T2-weighted images). (a) nfvPPA without pathogenic mutations in *C9orf72*, *MAPT*, *GRN* genes. (b) nfvPPA associated with a mutation in *GRN* gene. (c) nfvPPA associated with a mutation in *C9orf72* gene.

2. PATTERNS OF ATROPHY IN DIFFERENT GENETIC VARIANTS OF FTD

Certain patterns of atrophy have also been identified for the main genetic variants of FTD. Cases associated with mutations in the *MAPT* gene are characterized by symmetric atrophy of temporal lobes, OFC, and lateral prefrontal cortex [40]. Involvement of caudate nucleus, insula, and anterior cingulate cortex has also been described [39]. Interestingly, the pattern of atrophy appears to depend on the type of mutation - one study showed that mutations in the coding region of a gene resulted in more lateral atrophy of the temporal lobes, while mutations that affect alternative pre-mRNA splicing affected the medial part of the temporal lobes [41]. In the latter case, severe symmetric atrophy of the hippocampi can lead to a misdiagnosis of Alzheimer's disease [39].

In contrast, patients with mutations in *GRN* present with a pronounced asymmetry of atrophy, with its predominance in temporal, inferior frontal and inferior parietal regions [42, 43] (Figs. 1b and 2b).

FTD associated with hexanucleotide repeat expansions in *C9orf72* is characterized by a slow rate of atrophy progression with symmetrical extensive involvement of frontal lobes (medial and dorsolateral regions, OFC), anterior part of the parietal (posterior cingulate cortex, precuneus) and temporal lobes, thalami and uncharacteristic for other FTD variants atrophy of cerebellum, occipital lobes, and sensorimotor cortex [44–46] (Figs. 1c and 2c). Thalami, cerebellum, parietal and temporal lobes atrophy may be responsible for such clinical features of *C9orf72*-associated forms as the development (often at the onset of the disease) of hallucinations and psychosis [47]. At the same time, atrophy of the upper cerebellar lobules correlates in cases of bvFTD and FTD-MND phenotype with a severity of behavioral and cognitive impairments [48].

The analysis of presymptomatic cases of genetic FTD variants is of great interest. It is believed that the neurodegeneration begins long before the clinical manifestation of the disease and symptoms occur only after irreversible loss of a critical number of neurons, and therefore the preclinical stage may be an ideal time for the application of disease-modifying therapy. For this reason, it is crucial to search for reliable biomarkers of the presymptomatic stage, which, in addition to their role in the staging of the disease, can be further useful in identifying individuals most suitable for clinical trials, as well as evaluate the effects and efficacy of disease-modifying therapies.

Within the framework of the GENFI project (Genetic Frontotemporal dementia Initiative), the study of the VBM data of 202 study participants was initiated. 109 participants were carriers of pathological mutations (24—in the *MAPT* gene, 52—*GRN*, 33—*C9orf72*), and the remaining 93 were from families with genetic variants of FTD, but did not have pathological mutations [49]. The estimated age of onset among presymptomatic carriers was defined as the average age of onset in the family.

Among carriers of *MAPT* gene mutations, the first changes were observed in the hippocampus and amygdala 15 years before the estimated age of onset, followed by the involvement of temporal regions and insula lobes 10 and 5 years before the estimated age of onset, respectively. In case of *GRN* mutations carriers, insula involvement was noted 15 years before expected onset, followed by the temporal and parietal regions at 10 years before expected onset and atrophy of subcortical regions, namely striatum, at 5 years before expected onset. In the *C9orf72* group early changes in thalamus, insula and posterior cortical areas was observed 25 years before estimated onset, followed by the frontal and temporal regions involvement (20 years before expected onset) and cerebellar atrophy (10

years before expected onset of the disease). Asymmetry of brain atrophy was observed only among carriers of *GRN* mutations and was noted 5 years before expected onset.

Cash et al. conducted a study that included VBM data of 128 presymptomatic carriers of mutations (in the *C9orf72* gene—40, *GRN*—65, *MAPT*—23), 47 carriers of mutations with clinical manifestations of FTD, and 144 healthy controls [50]. The entire presymptomatic group analysis showed significant atrophy of the anterior insula in comparison with the control group. The study of individual subgroups showed that areas of atrophy in presymptomatic carriers, in general, coincided with atrophy patterns in symptomatic group. Among the presymptomatic carriers of the *C9orf72* gene mutation, a loss of GM volume was observed in the both thalamus, the upper-posterior areas of the right cerebellum, the superior temporal and inferior frontal regions. No significant atrophy was detected in presymptomatic carriers of mutations in the *GRN* and *MAPT* genes analysis with correction for multiple comparisons, but at the uncorrected level in the GRN group the insular, parietal, posterior frontal and anterior temporal regions and striatum involvement was observed, and in the MAPT group there was atrophy in the anterior and medial temporal regions (including the hippocampus and amygdala) and in the orbitofrontal cortex (OFC).

Jiskoot et al. studied neuroimaging biomarkers for the conversion of preclinical FTD cases to symptomatic ones [51]. The study lasted for four years, during which of 43 presymptomatic carriers of mutations, eight had the onset of the disease (three patients with mutations in the *GRN* gene and five in *MAPT*). It was shown that at least two years before the clinical manifestation, patients showed greater atrophy of the prefrontal and cingulate cortex, as well as the temporal and insular lobes. The rate of disease progression among *GRN* gene mutation carriers was faster than in the MAPT group.

3. PATTERNS OF ATROPHY IN DIFFERENT PATHOMORPHOLOGICAL VARIANTS OF FTD

Future drugs are likely to target proteins whose abnormal accumulation is in the basis of disease. Therefore the key task is to find biomarkers that could predict the pathomorphological variant of FTD, thereby increasing the accuracy of patient selection for clinical trials. Although early work in this area did not show clear differences between the various subtypes, recent studies have been able to find characteristic neuroimaging features of some variants [52].

TDP-43 proteinopathy is divided into four different subtypes (A–D) depending on the morphology of inclusions. Patients with the TDP-A subtype which is often associated with mutations in *GRN* gene exhibit symmetric atrophy extending to the frontal, temporal, and parietal regions with additional involvement of the anterior cingulate cortex and caudate nucleus [53–55]. Symmetrical atrophy of the frontal lobes as well as of the insula and anteromedial parts of the temporal lobes is observed in the TDP-B subtype in most cases associated with bvFTD and/or combined FTD-MND phenotype [43, 52]. In patients with the TDP-C subtype which usually manifests as svPPA asymmetric lesions of the anterior-lower temporal lobes are noted [43]. Also in this subtype atrophy of the frontal lobes, usually limited to OFC, can be observed, while the lesion of the parietal regions in this pathology has not been described [52]. TDP-D is the rarest subtype of TDP-43 proteinopathy which is associated with mutations in *VCP* gene, and so far the characteristic pattern of GM lesion has not yet been found [56].

Among tauopathies a typical pattern of atrophy was revealed only for Pick's disease in which there is an accumulation of round argyrophilic 3R-tau inclusions in the cytoplasm. This variant is characterized by asymmetric atrophy of the frontal lobes (mainly of the dorsolateral cortex and OFC), insular, and anterior temporal lobes [52].

FET pathology in FTD occurs much less frequently than other pathomorphological variants and accounts for only 1–6% of all cases of the disease [52]. Despite this the conducted studies were able to detect a symptom highly specific for this pathology—pronounced atrophy of the caudate nuclei on both sides. In addition to these structures in FET pathology damage of the OFC, the anterior cingulate cortex, the insula, and the anterior temporal regions is also observed [54, 57].

3.1. VBM Application for the Diagnosis of Frontotemporal Dementia

As mentioned, it can be quite difficult to distinguish between FTD and other diseases. This is especially true of bvFTD, up to 50% of cases of which are initially misdiagnosed as a mental illness [58], and the sensitivity of the visual assessment of MRI in detecting bvFTD among clinically similar diseases is insufficient and varies from 59 to 70% [22, 23]. At the same time, difficulties arise in the diagnosis of PPA. Traditionally, it is believed that svPPA and nfvPPA are included in the FTD continuum, and lvPPA is an atypical variant of AD, however, there are exceptions. According to one of the studies, up to 24% of cases of lvPPA at autopsy had no signs of AD, whereas in 8% of cases of nfvPPA and 5% of cases of svPPA, a pathological diagnosis of AD was established [7]. In addition, up to one third of PPA cases cannot be classified in any of the variants [59], and in this heterogeneous group it is even more difficult to establish the underlying pathological process. At the same time, early diagnosis of FTD is extremely important for determining the tactics of patient management, correct medical

genetic counseling, and selection of patients for clinical trials.

For a more accurate interpretation of VBM data and their application in diagnostics, programs based on machine learning methods are used. They analyze morphometric image data that belong to several known classes. The different classes can be, for example, morphometric images of GM patients with various types of dementia or forms of FTD. Next, the program compares images from several classes and finds an algorithm (function) that allows you to distinguish the classes from each other, that is, it identifies the features of atrophy that are characteristic of a particular disease (class). A program "trained" on a sufficiently large sample of images is capable of predicting with a high degree of probability [60] that new data (for example, an individual morphometric image of the brain of a patient with an unclear diagnosis) belongs to one of the known classes, thereby facilitating and increasing the accuracy of diagnosis [61, 62].

Separate studies have shown a high diagnostic accuracy of the algorithm based on a support vector machine (SVM) in determining different variants of FTD in comparison with the control group. Meyer et al. showed that the algorithm was able to distinguish patients with bvFTD from healthy volunteers with a diagnostic accuracy of 84.6% [61]. Similar work was done at the PPA. The SVM-based program with a high diagnostic accuracy (from 91 to 97% depending on the PPA variants) was able to distinguish the patients with PPA from the control group and showed good results in differential diagnosis between the disease variants—it was possible to distinguish between svPPA and lvPPA with an accuracy of 95%, svPPA and nfvPPA—78% [63]. The lowest rates were obtained when using the algorithm for differentiating between nfvPPA and lvPPA—the diagnostic accuracy was only 55%.

Bruun et al. in their work showed that it is possible to distinguish between individual variants of FTD using the asymmetry index [64]. With bvFTD, it will be closer to 1 than with PPA options, since in the latter, atrophy is more asymmetric. The asymmetry index distinguished the behavioral variant from the svPPA and nfvPPA groups with a sensitivity of 79% and a specificity of 92% (AUC 85%). In addition, it was shown that the determination of the volume of the left temporal pole can be used as a diagnostic biomarker of svPPA, since this approach allows it to be distinguished from other variants of FTD with a sensitivity of 82% and a specificity of 80% (AUC = 85%).

In addition to clinical variants, VBM can help in the differential diagnosis of various pathomorphological and genetic forms. One study showed that SVM-based software is able to distinguish between TDP-43 and tau pathology in different types of PPA with an accuracy of 92.7% [65]. In another work, the authors were able with 93% diagnostic accuracy to distinguish patients with a mutation in the *C9orf72* gene from other genetic and sporadic forms of FTD [66]. A study of a group of patients with mutations in the *GRN* gene showed that VBM helps distinguish such patients from healthy controls with a sensitivity of 86% and a specificity of 99%. However, in cases of asymptomatic carriage of mutations in the *GRN* gene, the diagnostic value of the method turned out to be much worse—the sensitivity and specificity were only 23 and 41%, respectively [67].

In clinical practice, differential diagnosis of FTD with other diseases is of the greatest importance. Koikkalainen et al. investigated the possibilities of various MRI methods, such as VBM, diffusion tensor imaging, and magnetic resonance perfusion using arterial spin labeling (ASL-perfusion), in the diagnosis of FTD in a mixed cohort, including patients with early forms of FTD and AD and healthy volunteers (33, 24, and 34 people, respectively) [68]. The data obtained made it possible to speak of an acceptable diagnostic value of VBM (AUC = 72%) in the differential diagnosis of AD and FTD. At the same time, the use of all three neuroimaging methods improved the accuracy of the method (AUC = 84%).

Similar results were obtained in another study that examined the accuracy of VBM in the differential diagnosis of FTD, AD, stable and progressive forms of moderate cognitive impairment (MCI) and the control group (37, 46, 48, 16 and 26 people in each group, respectively). The highest accuracy was observed when comparing the FTD and the control group (overall accuracy 0.83, sensitivity 77%, specificity 91%), while distinguishing FTD from AD and stable MCI based on VBM was possible with an accuracy of 72 and 80%, respectively. The lowest results were obtained when comparing FTD and progressive MCI—the diagnostic accuracy of the method was 63% (sensitivity 63%, specificity 62%) [69].

Kim et al. In their work, we used data from a larger sample of patients (the study included 143 patients with all variants of FTD, 50 patients with AD at the stage of dementia, and 146 healthy volunteers), which made it possible to slightly increase the diagnostic accuracy [70]. The algorithm assumed differential diagnosis not only of FTD and AD, but also of different variants of FTD among themselves. The overall accuracy of the method was 75.8%, while the diagnostic value of the individual diagnostic stages was higher: the algorithm distinguished AD from FTD with an accuracy of 90.8%, and bvFTD from PPA and svPPA from nfvPPA with an accuracy of 86.9 and 92.1% respectively. In this case, the most important areas for diagnosis were the right frontotemporal region (its atrophy made it possible to separate bvFTD from PPA), the left frontal lobe (which made it possible to distinguish nfvPPA from svPPA), and anterior temporal areas on both sides (a specific sign of svPPA).

A more difficult task is the differential diagnosis of several conditions at once. Thus, the algorithm based

on the data on the volume of GM obtained during the VBM distinguished the FTD from four other groups (control group, AD, dementia with Lewy bodies, and vascular dementia) with an accuracy of 65.1%, and only when the VBM was used together with other neuroimaging methods, the classification accuracy was increased to 70.6%. It should be noted that the visual assessment of MR images was significantly inferior to the automated method and its accuracy in making the diagnosis was only 45% [71]. Better results were shown in another study using the anterior vs. posterior index (API). This indicator made it possible to distinguish cases of FTD from patients with AD, Lewy body dementia, vascular dementia, MCI, other dementias and subjective cognitive impairments with a sensitivity of 59% and a specificity of 95% (AUC = 83%). Moreover, an even greater diagnostic value of the API (sensitivity 63%, AUC 87%) was shown in the group of patients under 70 years of age, who constitute the bulk of FTD cases [64].

Thus, despite the fact that VBM-based methods can differentiate with a sufficiently high accuracy the cases of high pressure from the control group or individual diseases (AD, stable MCI), their use in the differential diagnosis of several conditions at once is not effective enough at the moment, which requires further improving the algorithms used and conducting studies using a larger sample of patients.

CONCLUSIONS

Neuroimaging biomarkers are becoming increasingly important in the context of developing therapeutic methods for the treatment of sporadic and genetic forms of FTD. VBM is one of the promising biomarkers of the disease which can be used both in clinical and research practice. Over the past decade it has been shown that VBM plays an important role in determining the preclinical stages of the disease, can predict the conversion of presymptomatic cases to symptomatic cases, and is able to distinguish various clinical, genetic and pathomorphological forms of FTD from each other. The first steps have been taken in the application of the method for differential diagnosis between several types of dementia.

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