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Primary progressive aphasia

Primary progressive aphasia (PPA) is a heterogeneous group of neurodegenerative diseases related to focal degenerations of the brain and mainly manifested by a gradual loss of speech functions. This symptom is characterized by specific speech disorders. The article presents the etiopathogenic features of PPA, systematizes the clinical criteria for its diagnosis, and describes the modern neuroimaging characteristics of different types of PPA. The proposed PPA severity point scale allows clinicians to record the very early manifestations of aphasia. Modified scales, such as the Frontal Behavioral Inventory (FBI-mod) and the Clinical Dementia Rating (CDR), are also important for specifying the type of PPA.

Keywords: *primary progressive aphasia; dementia; tau protein; beta amyloid; magnetic resonance imaging with morphometry.*
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Primary progressive aphasia (PPA) is a heterogeneous group of neurodegenerative diseases related to focal cerebral degenerations and manifested in progressive loss of speech functions. Gradually, but in an avalanche-like manner, deficit of "search for words," understanding of words, impaired phrase formation are increasing [1], but there are no cognitive disorders and neurological symptoms. Only language functions suffer for at least two years without impairment of other cognitive functions, except praxis [2].

PPA is a term that has appeared relatively recently in medical literature. A few articles and reports about a disorder manifested in aphasia without development of dementia or any other symptoms appeared in English-language medical publications in the early 1980s. M. Mesulam was the first to describe and give the definition of PPA in his article "Slowly progressing aphasia without generalized dementia" published in the journal "Annals of Neurology" in 1982. He observed 6 patients for 5–11 years and described the prevalence of speech disorders [3]. Later, descriptions of cases of primary progressive aphasia appeared in different countries. Thus, S. Weintraub et al. (1990) observed 4 patients with PPA with decreased fluency of speech [4], and in 1991 in French-language literature V. Croisile et al. described 3 more cases of PPA [5].

Interest in PPA in Russian medical literature also arose long ago. In 1996 A.S. Kadykov et al. in the article "Progressive aphasia without dementia – the debut of the brain atrophic process" described patients with PPA [6]. V.A Stepkina, V.V. Zakharov and N.N. Yakhno (2014) presented an overview of 16 clinical cases of PPA with the analysis of data of neuropsychological tests, MRI indicators in connection with the type of PPA, and described peculiarities of optimal selection of therapy for various forms of PPA [7].

According to modern concepts of degenerative diseases of the brain, PPA belongs to the group of frontotemporal degenerations (FTD). FTD are known to possess morphological multivariance: a) most commonly they are characterized by taupathy (alterations in tau protein structure, formation of intraneuronal cytoplasmic inclusions and degeneration of the anterior structures of the brain) in combination with spongiform changes (so-called FTD with nonspecific morphology); b) more rarely, instead of this typical picture, there is neuronal degeneration due to changes in ubiquitin with formation of ubiquitin-containing intraneuronal inclusions, which are more characteristic of parkinsonism and parkinsonism-associated conditions.

In 2004 M.L. Gorno-Tempini and et al. proposed a classification of PPA based on the differences in clinical features of speech defects as well as on neuroimaging and pathomorphological data, which includes 3 basic forms of PPA:

- Semantic form of PPA without a decrease in speech fluency (semantic, fluent PPA or semantic dementia);
- Agrammatic form of PPA with reduced speech fluency (nonfluent, agrammatic or nonfluent progressive aphasia);
- Logopenic form of PPA (logopenic progressive aphasia) [8].

At present, cases of mixed PPA ("combined form") are described which have features of both semantic and agrammatic forms of PPA [9].

According to P.Hoffman et al. (2017), the existing classification requires further development, and modern research methods will allow the allocation of additional forms of PPA [10].

Current epidemiological evidence shows the prevalence of frontotemporal atrophy – 2.7–15.0 per 100 000, with PPA accounting for 20% – 40%.

The median age of PPA onset manifestations is 50 years (from 20 to 82 years), duration of the disease is nearly 7 years, regardless of the gender and age. Global aphasia, cognitive and non-cognitive symptoms of cerebral damage appear in 77% of cases [11].

Etiology. At present, search for reliable biomarkers of PPA, in particular, specific neuropeptides which can be detected in the cerebrospinal fluid (total and phosphorylated tau protein, beta-amyloid) is being undertaken [12]. In addition, genetic analysis and identification of genes responsible for PPA development are carried out.

PPA syndrome is histologically heterogeneous and, as a rule, is associated with one of the three classes of the central nervous system (CNS) pathology.

Semantic form of PPA without reduced speech fluency. PPA is more often associated with intracellular accumulation of DNA-associated protein TDP-43 responsible for DNA transcription in the neurons of the frontal and temporal lobes. TDP-43-pathy develops when an excess of the transcriptor protein is accumulated in the neuron nucleus and the cell cannot remove its aggregates, which ultimately leads to neurodegeneration. In more than 90% of observations, the characteristic clinical phenotype is frontotemporal degeneration FTD (TDP-43-pathy type C) with long neurofibrillary glomeruli (revealed histologically in the cortical areas of the frontal and temporal lobes) [13].

Similar changes also occur in some agrammatic forms of PPA. According to observations made by S.J.Makaretz.et al. (2017), this clinical syndrome is rarely due to primary taupathy or Alzheimer's disease (AD) [14]. J.A. Knibb et al. (2006) regard most cases of agrammatic and semantic forms of PPA as speech variants of FTD [15].

The specific method of taupathy evaluation (the presumptive tau of PET-CT ligand flortaucipir) revealed an increase in the signal in the rostral direction from the region of the striatum (ventromedial nucleus, contiguous nucleus) with pronounced asymmetry (left > right) [16–18].

Agrammatic form with reduced speech fluency (nonfluent progressive aphasia) is more often due to accumulation of tau protein in neurons and glia, however, the pathology underlying this clinical syndrome is heterogeneous. According to D.C.Tippett et al. (2017), non-tau pathology registered in the agrammatic form of PPA also includes FTD with ubiquitin-positive inclusions and AD (deposition of β-amyloid) [19]. The agrammatic form occurs in such taupathies as progressive supranuclear paralysis and corticobasal degeneration.

Pathological changes in agrammatic PPA are found in the posterior regions of the left frontal lobe, in the region of the insula (lobus insularis) [8, 20]. In some observations, atrophy affects the premotor region and supplementary motor area separately [21].

As the disease progresses, atrophic changes extend to the dorsolateral regions of the prefrontal cortex, upper regions of the temporal lobe and medially extend to the orbital regions of the prefrontal cortex and ventral regions of the anterior cingulate cortex (cingulated gyrus), the parietal lobe and the region of the cerebral aqueduct (Figure 1) [22]. In those cases when taupathy was confirmed, autopsy showed areas of atrophy of the cerebral cortex in the frontal and temporal lobes [23].

Logopenic progressive aphasia. 30% of cases are attributed to TDP-43-pathology as a result of the presence of TDP-43 protein inclusions in the brain substance. However, in most cases, β-amyloid and tau protein (in the form of neurofibrillary glomeruli) are detected in the brain substance, which allows to regard the logopenic variant of PPA as an atypical form of AD. AD is now considered the most common pathology. [14].

The same authors observed local atrophic changes in the temporal and parietal lobes (posterior regions, supramarginal gyrus, angular gyrus) [14].

Clinical manifestations

PPA is characterized by a) gradual onset, when language functions are worsening for at least two years without impairment of any cognitive parameters except praxis [2]; b) specific speech disorders in the form of deficit of "search for words", their understanding, impaired phrase formation [1]; c) further (after 2 years) avalanche-like progression of speech disorders.

Diagnostic criteria

The diagnosis of PPA is possible only if clinical manifestations and a patient's medical history satisfy the following criteria.

1) Sudden and progressive aphasia. The diagnosis requires neuropsychological confirmation of pathological changes in one or several cognitive spheres: construction of sentences, search for words in free speech, names of objects, understanding of words and sentences, spelling, reading, repetition. It is necessary to exclude isolated disorders of articulation (dysarthria). At the beginning of the disease, aphasia is the main symptom and leads to a disruption of normal social functioning, especially in areas related to language (for example, using the phone).

2) Relatively preserved cognitive functions, such as short-term memory, constructive praxis, visual-spatial orientation. Other cognitive functions can be reduced, however, speech disorders remain the core clinical symptom throughout the disease course [24].

3) Neuroimaging evidence of the neurodegenerative nature of the disease [2].

Newly diagnosed patients who meet the above stated criteria need a long-term follow-up and a comprehensive examination.

The diagnosis of PPA is recommended on the basis of "the rule of two years". If after two years a relatively isolated and functionally pronounced aphasia persists in the clinical picture of the disease, one can assume that the patient has PPA. This approach

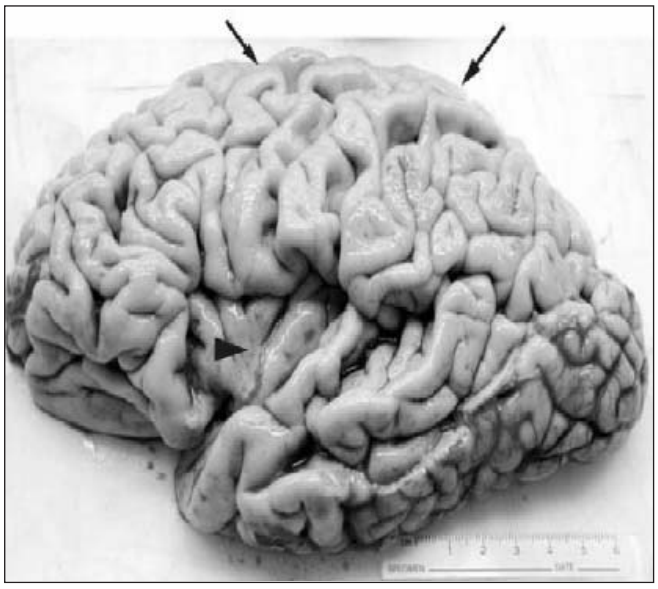

Figure 1. *The left hemisphere of a patient with PPA, a semantic variant with a predominant lesion of the temporal lobe (local atrophy of the cerebral cortex) [22]*

makes it possible to differentiate patients with rapidly progressing aphasias, for example, in Creutzfeldt-Jakob disease (CJD) [2]. "The rule of two years" may contribute to the nosological homogeneity of patients with PPA syndrome.

However, according to M.M. Mesulam et al. (2012), this approach is one-sided, and distracts clinicians from seeking early, prodromal symptoms of the disease, directing clinical and

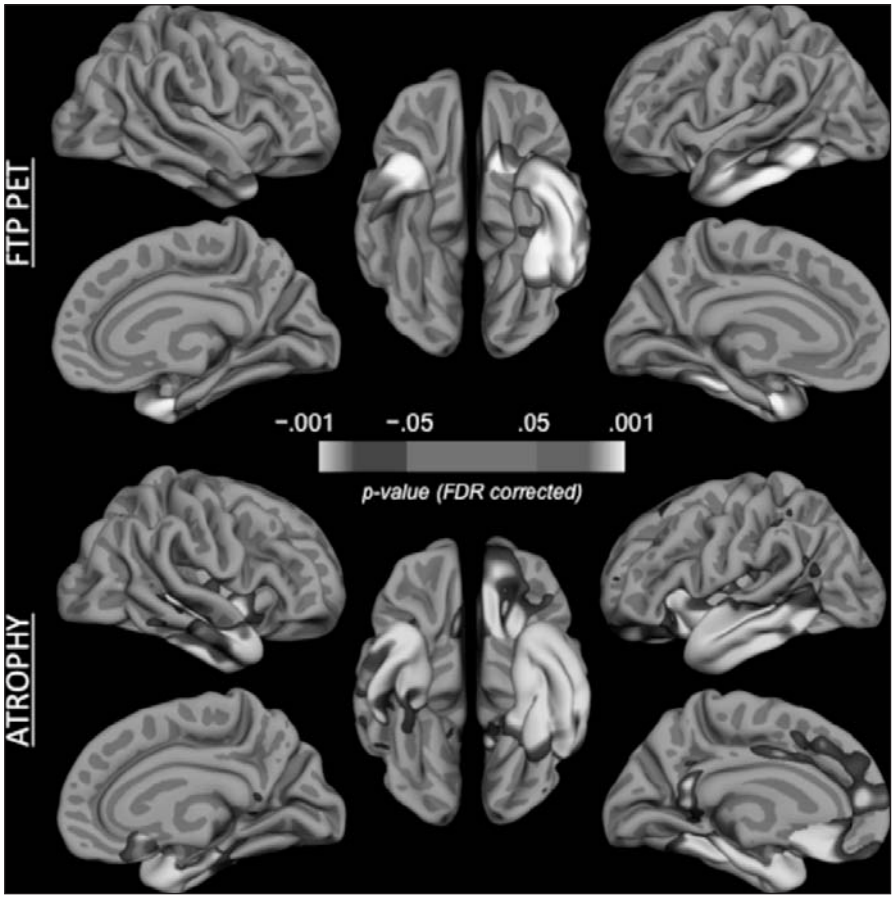

Figure 2. *Comparison of the standardized absorption coefficient of flortaucipir (the top image) and cortex atrophy (the bottom image) in patients with PPA and in controls. The lighter areas on the map of the surface of the cortex indicate those regions which differ in the group of patients with the semantic variant of PPA and in the control group [17]*

research efforts to the study of already established forms and advanced stages of the disease. [2]. Scientific information on the early symptoms of the disease is scarce and controversial [4, 25–28].

Until now, researchers mainly paid attention to the early stages of dementia of Alzheimer's type, which allowed to develop "sensitive" diagnostic criteria, single out prodromal symptoms and explain the pathophysiological mechanisms of the disease [29, 30]. Certainly, the progress in this area is due to high prevalence of AD and understanding that the risk of its development increases with age. Thus, healthy people with a high level of risk (elderly, relatives of patients with AD) got into the field of view of the researchers, which made it possible to single out clinically significant prodromal signs of the disease. The genetic studies of a number of diseases with autosomal dominant transmission, such as AD, Huntington's disease and FTD, have proved promising [31, 32, 33]. This approach is not available for PPA, primarily, because the main risk factor has not yet been established, and because of low prevalence of the disease in population. Except a few reports on cases of autosomal dominant inheritance of PPA [34], the dominant idea among researchers is that members of the families, in which genetic mutations with PPA development have been determined, remain intact [1, 35, 33].

The correctness of the diagnosis requires differential diagnostic procedures (clinical, neuropsychological, neuroimaging).

It is necessary to exclude cases of episodic and unrelated to impaired speech production speech disorders, visual-spatial orientation disorders, psychopathological disorders [14].

The semantic form of PPA without reduced speech fluency (semantic dementia) is a form of speech disorder with relatively stereotypical disturbances. Initially, isolated aphasia with a marked loss of semantic memory and relative safety of other speech spheres is diagnosed [36].

Clinical manifestations. The characteristic symptom of the semantic form of PPA is verbal paraphasia, when the patient replaces one word with another. Poor understanding of individual words is the only symptom at the early stages of the disease. Recognition monosyllabic, especially low-frequency, words is disturbed. For example, a rare word "zebra" will not be recognized, while the commonly used word "cat" is recognizable. Serious disturbances in the recognition of objects and people are observed, even when they are presented in various ways, besides verbal ones, for example, in the form of a picture or a real object, tactilely, in the form of smell or taste. Formal processes of writing and reading as a function do not suffer, but patients may not understand the meaning of the text they have read.

Table 1. Three representative domains of the Progressive Aphasia Severity Scale (PASS) (Sapolsky et al., 2010)

PASS Domain	0 (normal)	0.5 questionable/very mild impairment	1 mild impairment	2 moderate impairment	3 severe impairment
FLUENCY: Degree to which speech flows easily or is interrupted by hesitations, fillers, pauses; reduced fluency is associated with decreased phrase length and words per minute (WPM)	Normal flow of speech.	Speech contains occasional blank pauses or use of fillers (umm); reduced WPM and/or phrase length.	Speech is in short phrases, interrupted with pauses or groping for words but there are occasional runs of fluent speech.	Dysfluencies in most utterances; phrase length rarely exceeds three words.	Severely dysfluent speech; phrase length rarely exceeds one word. May not speak.
SYNTAX AND GRAMMAR: Use of word forms (run, ran), function words (the, an), and word order when forming phrases and sentences in most used modality (speech or writing)	No difficulty in the use of grammar and syntax.	Occasional agrammatism or paragrammatism (i.e., odd sentence structure such as, "I my car drive in your house."); may complain it is effortful to combine words into phrases or sentences	Frequent agrammatism; sentence structures are simple; frequent misuse/omission of grammatical words or morphology	Utterances contain mostly content words with rare use of syntactic word groupings, function words, or morphological markers	Single word utterances or no speech/writing.
SINGLE WORD COMPREHENSION: Ability to understand spoken or written single words	No difficulty understanding single words in conversation or testing.	Occasional difficulty understanding low frequency words (e.g., cork); may question the meaning of words (e.g., "What is a__?").	Displays lack of word comprehension several times in a brief conversation but able to carry on reasonably meaningful conversation.	Understands some high frequency and/or familiar words. Questions the meaning of many words in conversation.	Minimal comprehension of single words.

Semantic deficiency usually refers to a variety of categories, for example: animals, people, tools. Some patients present greater categorical coverage or selective deficiency in categories related to humans and animals. H.A Yi, P. Moore, M.Grossman (2007) observed the impairment of subject concepts with the preservation of abstract concepts [37]. In these patients, signs of atrophy of the temporal lobe on the right (Figure 2) were confirmed, and signs of psychopathological disorders were observed in the form of impaired behavior and decreased empathy.

The agrammatic form of PPA with reduced speech fluency (nonfluent progressive aphasia). The main clinical sign of this form is agrammatism in written and oral speech, which consists of short and simple phrases with omission of grammatical forms, morphemes, functional words. Speech production is the most complex function of the brain. It is damaged in the case of the agrammatic form, which leads to a "deficiency in articulation planning" [8; 38] in the form of apraxia of speech that can represent the initial signs of the disease.

Clinical manifestations. Patients have uncoordinated sound errors in the form of distortions, perseverations, literal paraphases, and agrammatism. At the same time, speech control is preserved – patients hear and see their mistakes in speech and writing. Understanding of individual words is not disturbed. Repetition of oral speech does not suffer even in the late periods of the disease. If patients have oral apraxia, both independent speech and repetition of words and phrases suffer. There are signs of misunderstanding, initially only in cases of complex syntactic constructions (for example, "The car followed by the truck is green") [39]. The prosody of speech is disturbed, and the "level" of speech is markedly reduced [8; 40]. Thus, speech errors in the use (functioning) of linguistic means may be the first symptoms of this form of the disease, which can be detected even before the appearance of speech apraxia and obvious agrammatic errors. M.L. Gorno-Tempini et al. (2011) suggested using a written test or syntactic tasks to identify early signs of a grammar disorder [14]. Dyslexia and dysgraphia in the semantic and agrammatic variants of PPA lead to disturbances of reading and writing in the form of atypical spelling and pronunciation mistakes. For example, patients "reduce" words – they may read "sew"[sou] as "su". Disturbance of speech nomination affects actions more than objects [41; 42]. M.L. Gorno-Tempini et al. (2004) noted that already at the early stages of the disease, patients with the agrammatic form of PPA can become "dumb" [8].

Logopenic progressive aphasia is the latest described variant of PPA [43]. The symptom is distinguished by the following speech disorders: the search for words in spontaneous speech, disorder of nomination of words, repetition of sentences. The speech is characterized by slowness associated with search for words. There is no agrammatism, prosody is preserved, speech errors are mostly phonological [8].

Methods of additional clinical examination. A few studies are devoted to the development and validation of scales, which allow to more accurately diagnose the form of PPA syndrome. D.C. Tippett et al. (2017) used the Frontal Behavioral Inventory (FBI-mod) [44; 45] to study psychopathological features of patients with various forms of PPA. The required information was received from patients' relatives or caretakers. Patients with the semantic form of PPA presented with anxiety and agitation, patients with the agrammatic form of PPA often showed depression syndromes [5]. E. Gomez-Tortosa et al. (2016) found no differences between the groups in the presence/absence of anxiety, irritability, apathy, hyperactivity, abnormal motor activity [46].

Understanding, diagnosis and medication correction of psychopathological manifestations of PPA are necessary to determine the prognosis for the disease, and this is the main thing that caretakers (family, guardians) expect from a clinician [47]. They are interested in the perspective of the disease and need advice.

At present time, there are no criteria for scoring the symptoms of PPA. The original Clinical Dementia Rating Scale (CDRS) used for the clinical assessment of the severity of dementia is not targeted at specific speech disorders [27]. D.Sapolsky et al. (2010) developed a supplementary to the CDR test scale for assessing fluency, syntax and grammar disorders, and word recognition for PPA (Table 1). Thus, the "Progressive Aphasia Severity Scale" is a new structured clinical tool that complements the currently applied CDR scale [27; 48].

The proposed scale allows clinicians to record changes at all stages of the disease. Estimates are made from normal (0) to questionable / very mild (0.5), moderate (1.0), moderate (2.0) or severe (3.0) disorders.

Neuroimaging. The emergence of new methods of radiation diagnostics in the clinical arsenal greatly expanded our understanding of the structure and function of the brain, made it possible not only to reveal but also to quantify a number of parameters, such as subtle structural changes in the thickness of the cortex of different brain regions, volumes of subcortical structures, the cerebrospinal fluid system [49; 50; 51].

Functional and structural changes in the brain occur long before the obvious clinical manifestations of cognitive impairment appear. Structural biomarkers of neuroimaging, reflecting the degree of neuronal damage and, accordingly, atrophic process, include the visual scale of assessment of atrophy degree in magnetic resonance imaging (MRI), as well as voxel (or voxel-based) morphometry.

It is important to supplement clinical data with a clear quantitative visualization of the atrophic changes of one or another localization. This makes it possible to conduct differential diagnosis of various pathological processes, accompanied by dementia. Combining these data with the results of positron emission tomography (PET) allows to reveal characteristic changes in the metabolism of glucose and specific radioligands (amyloid, tau protein) [52]. This applies to PPA as well. In the diagnosis of PPA, such brain studies as MRI with morphometry, PET with 18F-fluorodeoxyglucose (FDG), PET with Pittsburgh compound-B ([11C] PIB) are used.

MRI with morphometry in patients with PPA is used to detect atrophic changes in the brain. MR-morphometry helped to find certain correlations between atrophy of the brain substance and disturbances of the speech function [28]. Thus, a decrease in the "fluency of speech" is most closely related to the death of neurons in the regions located behind the traditional boundaries of Broca's area (the area of the lower frontal sulcus and the posterior part of the middle frontal gyrus). The symptom is associated with the initial lesion of the primary and secondary associative zones of the cerebral cortex responsible for articulation and "motor images." Decrease in the ability to repeat is associated with atrophy of the cortex of the posterior part of the superior temporal gyrus. Disturbances of semantic processing is due to atrophy of the anterior region of the left temporal lobe. The cause of grammatical processing disturbances is a more

widespread atrophy of the cortex, including the lower frontal gyrus, supramarginal gyrus, sensory and motor cortex, and the lower parietal lobe (Fig. 3).

18F-FDG PET is used to assess local decrease in glucose metabolism due to impairment of neuronal activity in the cerebral cortex, which may indicate active degeneration of nerve structures and subsequent development of atrophic changes. PET with FDG detects zones of hypometabolism in the brain substance corresponding to atrophic changes according to MRI data.

In patients with the semantic form of PPA, without reduced speech fluency, atrophy and hypometabolism of the anterior regions of the temporal lobes, predominantly of the left (dominant) hemisphere of the brain, are usually detected [53]. Metabolic disorders in the agrammatical form of PPA with reduced fluency are noted in the posterior parts of the frontal lobe (including the lower frontal gyrus) and insular cortex, predominantly of the dominant hemisphere. In the logopenic form, changes are found in the posterior regions of the left temporal lobe, as well as in the lower parts of the parietal lobe (in the region of the marginal and angular convolutions) with relative preservation of the frontal lobes. Some studies point out the possibility of differentiation of the logopenic form of PPA, on the one hand, and AD on the other – with the help of MR-morphometry and PET with FDG [54]. In the logopenic form of PPA, atrophy and hypometabolism of the lateral sections of the left temporal lobe, including the upper, middle and lower temporal gyrus, are more typical. In AD, on the contrary, there are changes in the medial parts of the right temporal lobe, including the hippocampus, as well as in the posterior regions of the cingulate gyrus and the orbitofrontal cortex.

Positron Emission Tomography (PET) with Pittsburgh compound-B ([11C]) PIB is a radio-labeled analogue of the fluorescent dye thioflavin T, which can be used for PET detection of beta-amyloid plaques in the tissues of the nervous system [55]. PET with PIB helps to differentiate patients with the logopenic form of PPA and AD, on the one hand, and patients with other types of PPA, in which deposition of β-amyloid is rare. In this case, a diffuse symmetrical distribution of the PIB compound in the brain tissue is observed both in the logopenic form of PPA and in AD without correlation with atrophic changes (Figure 4) [56].

Conclusion. Diagnosis of different forms of PPA is carried out consistently: from clinical diagnosis to instrumental and, perhaps, to pathoanatomical. At each stage a diagnosis is made – clinical, neuroimaging, neuropsychological, psychopathological and, after autopsy – pathoanatomical. The proposed clinical approach is recommended for neurologists, psychiatrists and specialists in related areas of medicine [58]; it helps to promote interdisciplinary interaction.

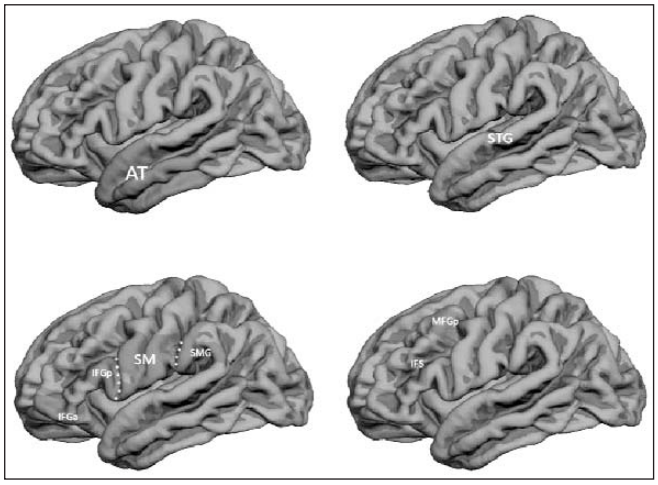

Figure 3. *Areas of the cerebral cortex that fulfill the speech functions: Semantic processing – Sentence repetition – Grammatical processing – Fluency*

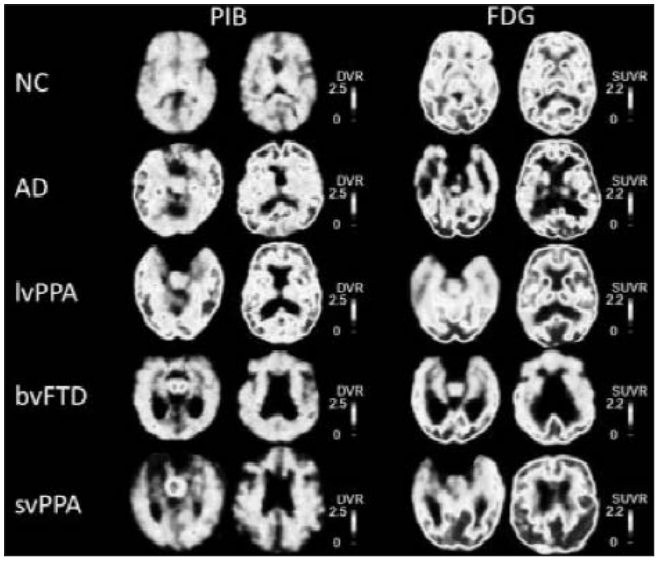

Figure 4. *Typical binding of Pittsburgh Compound B (PIB) to amyloid ligand and 18F-fluorodeoxyglucose (FDG) hypometabolism patterns in:*

- *the control group of healthy volunteers (NC),*
- *Alzheimer's disease (AD),*
- *logopenic variant of PPA (lvPPA),*
- *Behavioral variant of frontotemporal dementia (bvFTD);*
- *semantic variant of PPA (svPPA) [57]*

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