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MRI Morphometry of the Brain and Neurological Diseases

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Abstract

The diagnosis of diseases of the brain is based on additional methods, confirming the clinical diagnosis. One of the most objective methods is magnetic resonance imaging (MRI). A detailed quantitative evaluation became possible after the introduction of MRI voxel-morphometry—statistical analysis of structural MRI images using a computerized segmentation matter of the brain gray and white matter. The decrease in the volume of the brain, as a manifestation of cerebral atrophy, is a common feature of many neurological diseases. We performed a study of brain structures in multiple sclerosis, Parkinson's disease, and cerebrovascular diseases. In patients with multiple sclerosis the correlation was found between the score on a scale of Expanded Disability Status Scale and the total thickness of the cerebral cortex. In our study of the brain in Parkinson's disease, the amount of the substantia nigra was slightly lower than in the control. In patients with long-following Parkinson's disease, the volume of substantia nigra was significantly higher than in patients with early stage. The increased volume was determined by the accumulation of organic iron compounds as a sign of neurodegeneration.

Keywords: magnetic resonance imaging, voxel morphometry, brain, gray matter, white matter, neurodegeneration, multiple sclerosis, Parkinson's disease

1. Introduction

The human brain is the most important organ that controls the functions of all the other organs in the human body through neuronal connectivity and neuronal signal transmission. Central nervous system (CNS) is the most complex but a very poorly understood structure in the human body. The diagnosis of many diseases of the brain is based on additional research methods, confirming the clinical diagnosis. One of the most objective and intuitive methods

is magnetic resonance imaging (MRI). The technology to image the structure and function of the brain noninvasively (MRI, other methods of neuroimaging) has transformed our understanding of neurological disorders, opening new approaches to treatment and prevention. For a long time, MRI was based on a visual qualitative analysis of the obtained images. The development of the method led to the emergence of different modes of research, there are fundamentally new methods—diffusion-weighted image, the tensor image, perfusion MRI, functional MRI, and a method of MRI spectroscopy. However, these methods are mostly qualitative.

Neuroimaging may be divided into structural neuroimaging, which evaluates anatomic changes that occur in neurodegenerative conditions, and functional neuroimaging, which evaluates CNS activities such as blood flow and metabolism. For example, structural neuroimaging with computed tomography (CT) and magnetic resonance imaging (MRI) has defined patterns and rates of brain volume loss in neurodegeneration. Moreover, structural neuroimaging may detect treatable conditions that may present with dementia-like symptoms. Functional neuroimaging with MRI (fMRI), single photon emission CT (SPECT), and positron emission tomography (PET) have greatly assisted in the understanding of blood flow, metabolism, and amyloid deposition. Application of MR spectroscopy (MRS) has also yielded novel information about neurodegeneration [1, 2].

A detailed quantitative evaluation became possible after the introduction of MRI voxel-morphometry—statistical analysis of structural MRI images using a computerized segmentation matter of the brain GM and WM. Data about this technique were first published in 2000 [3]. MRI voxel morphometry requires the processing of data obtained by MRI study in the mode of the T1-weighted images (WI) with a slice thickness of 1 mm.

Voxel morphometry is based on the calculation of local differences in brain tissue after leveling expressed differences in anatomical structure and spatial position. This is achieved by spatial normalization (registration) of structural images into a single stereotactic space, further segmentation of gray and white matter, cortical rectification of furrows and convolutions, and statistical analysis to detect differences between the experimental groups. By segmentation, we can separate the major cerebral and extracerebral structures (GM, WM, and cerebrospinal fluid, CSF), also using voxel morphometry, we can reveal focal anatomic lesions [4, 5].

The decrease in the volume of the brain, as a manifestation of cerebral atrophy, is a common feature of many neurological diseases. There is the general (total) and regional (local) atrophy. Under the general atrophy, we can understand the volume reduction of brain parenchyma and the increase of subarachnoid spaces and ventricles of the brain. The decrease in the volume of certain brain structures is called regional atrophy. In brain tissue, the atrophy is accompanied by loss of neurons and connections between them that allows to consider it as one of the markers of the severity of the disease.

There are two basic methods of studying the volumes of the brain: using separation of gray and white matter manually or using special computer programs. Both methods have both positive and negative sides. We have tested both approaches. We performed a study of brain structures in multiple sclerosis, Parkinson's disease, and cerebrovascular diseases (CVD).

2. Morphometry of the brain in multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the CNS affecting more than 2 million people worldwide and leading to chronic progressive disability in the majority of cases. MS is heterogeneous both clinically and histopathologically, suggesting that different effector cells and molecular mechanisms are involved in the induction of tissue destruction. The most common form of MS, known as relapsing–remitting MS (RRMS), is associated with acute inflammatory episodes that reduce neurological function. RRMS patients may experience some recovery between relapses, but in 80% of cases, the disease evolves to a more progressive form with neurodegeneration termed secondary progressive MS (SPMS). The latter is associated with a gradual loss of neurological functions and is less dependent on inflammation [6–8]. Currently, it is generally assumed that immune, inflammatory, and neurodegenerative mechanisms involve in the pathogenesis of MS; it is a balance between the activity of inflammation, progressive degeneration, and reparative mechanisms and determines the clinical manifestations at each stage.

The main method of diagnosis in MS is magnetic resonance imaging (MRI). Standard techniques MRI is essential to confirm the nature determination of the activity of the pathological process and monitoring of the disease. Now, we use modern methods of MRI, which aims at clarifying the pathogenesis and pathophysiological mechanisms of formation of neurological deficit, the development of effective prognostic criteria, and new markers for the monitoring of the flow of inflammatory and neurodegenerative, atrophic component [9–11].

Initially, the presence of atrophy of the brain in MS patients was identified qualitatively, describing the extension of the ventricles and subarachnoid spaces and reducing the amount of substance of a brain. The next step was the quantitative assessment of atrophy of the brain with no differentiation of GM and WM. Currently, studies use different methods of MRI to assess how the global (brain in general) and regional atrophy. One of the most commonly used methods is to estimate the fraction of the brain parenchyma (BPF), which is determined by the ratio of the brain to the amount of the substance of the brain and cerebrospinal fluid (CSF). It is believed that in patients with MS, the regional atrophy may serve as a more sensitive marker of the severity of the disease than the general atrophy, but the results obtained in different studies often directly contradict each other. In recent years, it has been suggested that atrophy of cortical and subcortical gray matter prevails over the decrease in the volume of the white matter of the brain and largely determines the degree of disability of MS patients. Many researchers have noted that different types of MS course are characterized by their patterns of atrophy [12].

First, when an MS that the key importance was given to inflammatory demyelination of the WM and therefore considered that it undergoes atrophy. However, damage to axons within the WM lesions lead to atrophy, which was most likely evolving in two ways: the loss of substance in the demyelination and further Wallerian degeneration pathways associated with the lesion. WM atrophy affected certain areas of the brain, including both hemispheres of the brain, the brain stem, and the cerebellum. In patients with relapsing-remitting multiple sclerosis (RRMS) compared with the control group, most pronounced atrophy of almost all

parts of the WM: the corpus callosum, cingulate gyri on both sides, certain divisions of the frontal lobes (including the upper sections of the radiate crown and the upper longitudinal beams), and temporal and occipital lobes (arch, upper and lower longitudinal beams, inferior frontal-occipital tracts [13, 14].

Atrophy of the brain in MS is the result of a comprehensive process of demyelination, axonal degeneration, and neuronal death [15]. In the treatment of MS, special attention is paid to the prevention of neurodegenerative component, and recently, several studies have been conducted for the evaluation of drugs. It was discovered that the degree of disability of the patients is determined with a therapeutic effect on a neurodegenerative component of the disease. However, the relationship is ambiguous. After the usage of MS-modifying drugs, there is a decrease in the degree of atrophy of the brain in the first year, then the physician can see the stabilization of process [16]. Thus, it may be the gradual, progressive atrophy of brain substance in MS but may be the fluctuations of its volume. In particular, acute inflammation with swelling of the brain tissue and the formation of new lesions during exacerbation of MS leads to a temporary increase in the volume of the brain and vice versa—glucocorticoid treatment leads to a temporary reduction of brain tissue—the so-called pseudoatrophy [17]. As suggested, this is the result of reducing inflammation and swelling in the brain.

Some studies have shown that WM atrophy is less prominent compared to GM atrophy due to more pronounced inflammatory processes that can mask atrophy [18, 19]. It is believed that patients with MS regional atrophy may serve as a more sensitive marker of the severity of the disease than the general, but the results obtained in different studies are mixed and often directly contradict each other. In recent years, it has been suggested that atrophy of cortical and subcortical GM prevails over the decrease in the volume of WM in the brain. It predominantly determines the degree of disability in patients with MS. However, many researchers note that different types of MS have the specific patterns of atrophy.

When analyzing the state of the GM in MS, it has been discovered that atrophy of the thalamus develops earlier than the atrophy of the cortex, which was demonstrated in a study of patients with RRMS and secondary progressive multiple sclerosis (SPMS) during follow-up [20, 21]. Atrophy of the thalamus observed in all types of MS course, to the greatest extent in SPMS, which is probably related to disease duration

The correlation was found between the score on a scale of Expanded Disability Status Scale (EDSS) and the total thickness of the cerebral cortex, precentral cortex, postcentral, parahippocampal, occipital gyri, and the caudate nucleus volume and a striped body. Some studies show that patients with sustained progression of disability by EDSS have a much higher rate of atrophic processes in comparison with patients with stable neurological symptoms. It is also believed that the amount of GM compared with WM volume is a more sensitive predictor of disability, measured by EDSS [22].

Cognitive impairment, including loss of memory, attention, and speed of information reproduction, has been reported in 70% of patients with MS, and they occur already at early stages of the disease (within the first 3 years). Patients with RRMS with cognitive impairment compared with patients without such revealed a decrease in volume of the brain in general and

GM of the cerebral cortex. Indeed, cortical atrophy is predictive of cognitive impairments because even mild cognitive changes are associated with significant thinning of the cerebral cortex. Also, a significant correlation was discovered with atrophy of the thalamus [23].

Thus, the modern MRI techniques, including MRI voxel-morphometry, significantly expand our understanding of the pathogenesis of MS. Numerous studies show that in addition to the WM atrophy, the GM atrophy in MS is already found in the early stages of the disease, and it progresses faster in healthy people, being a significant MRI predictor of the development of disability. Studies that show atrophy in different areas of the brain at the different types of MS course bring new contributions to the understanding of the pathophysiological mechanisms of the degenerative process. Now, we only accumulate our own data on the morphometry of the brain in MS.

We studied 10 patients with RRMS, five women, and five men. The diagnosis was based on McDonald criteria, 2010 revision. The age of the patients was from 24 to 36 years (average age/here and further data are given in the format $M \pm m/30$, 7 ± 1 , 22 years). At the time of the study, the disease duration ranged from 1 to 24 years (mean age of 8.1 ± 2.25 years). During follow-up, only three patients had one to three exacerbations. Before therapy with drugs modifying the course of the disease, mild disability (EDSS ≤ 3.0) was in eight patients, moderate (EDSS 3.5–5.5 points)—in two, and no severe disability (EDSS ≥ 6.0 points) were observed. The average EDSS score before the start of the specific therapy was 2.5 ± 0.25 , during an exacerbation— 3.5 ± 0.34 . All patients had no therapy before inclusion in the study. Therapy with glatiramer acetate (in a standard dose of 20 mg subcutaneously daily) was prescribed to three patients, but in the future, one of them was transferred to natalizumab therapy (in a standard dose of 300 mg infusion monthly) in the cause of aggressive course of the disease (three exacerbations). Seven patients had therapy with interferon beta 1-b in a dose of 9.6-million IU subcutaneously through the day. The control group (CONTROL) consisted of 10 healthy individuals, five men and five women, mean age of 21.3 ± 1.9 years.

To assess the condition of patients, we used the standard neurological examination, Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) which includes the quantitative tests that assess lower limb function/walking (Timed 25-Foot Walk) and upper limbs (9-Hole Peg Test), hearing test on addition of a sequence of digits PASAT-3 (Paced Auditory Serial Addition Test), and several subtests of the Wechsler Adult Intelligence Scale: subtest “Resemblance,” subtest “Digit span”, subtest “Coding”, subtest “Kohs Block Design Test”, Beck’s depression scale, and Beck’s anxiety scale.

Brain MRI was performed on “Initial Achieva 3.0 T” (Philips Medical System Nederland BV) with a magnetic field of 3 T. The study protocol included the use of T1-WI with slice thickness 1 mm, the distance between the slices—0 mm, and after contrast enhancement. The MRI was performed with the processing of the sequences for morphometry of anatomical MRI using FreeSurfer 5.3 (an open source software suite for processing and analyzing human brain MRI images) for segmentation and visualization of brain structures.

The results of voxel-based morphometry using the anatomical MRI T1-WI of the brain show a significant decrease in the cortical and subcortical GM volumes and WM in comparison to

CONTROL (**Table 1**). The volume of cortical GM in MS patients was 13.9% lower, while subcortical GM was 21.8%. The decline in GM of the thalamus was the highest—25.6%. The volume of WM was lower than in the CONTROL by 20.4%, and the greatest difference was found in relation to the corpus callosum—46.6%. At the same time, it was discovered an increase in the volume of the third ventricle by 31.9% and the lateral ventricles by 84.4%. It was indicated that the severity of reduction in volumetric parameters of the brain increased in proportion to the duration of MS.

It was not found a clear relationship between the level of reduction in GM and WM volume of the brain and EDSS. But there was a positive relationship between the amount of Hypo lesions in the white matter of the brain and EDSS. We discovered that the parameters of neuropsychological testing in patients with MS was worse than in CONTROL, and at exacerbation period, there was marked a more significant decline. We identified a probable correlation between reduced volumetric and neuropsychological parameters.

Parameters (mm ³)	CONTROL	MS
The total volume of cortical GM	521763.46	449010.5
The volume of subcortical GM1v	63915.5	50008.38
The total GM volume	696492.4	607442.001
The total volume of WM	503950.6	401106.7975
The volume of the lateral ventricles	14853.5	27396.225
Volume III ventricle	1221.7	1610.95
Volume IV ventricle	1764.6	1970.5
The volume of the cerebellum	158134.7	135249.45
The volume of the thalami	16330.5	12157.15
The hippocampal volume	10146.9	7818.45
The volume of the corpus callosum	3261.9	1740.55
The volume of hypointensive lesions in brain WM	899	8915.1
The volume of hypointensive lesions in brain GM	9.6	33.75

Table 1. The volume of the brain by MRI in patients with MS and CONTROL obtained by voxel morphometry (own data).

3. Morphometry of the brain in Parkinson’s disease

Parkinson’s disease (PD) is currently the most common among neurodegenerative diseases, its incidence is 200–300 cases per 100 thousand people. In Russia, according to epidemiological studies in some regions, the prevalence of PD is only 40–140 cases per 100 thousand population, which is considerably lower than in Western Europe and North America. The pathogenesis of PD is of great importance to the accumulation of intracellular inclusions (Levi

bodies) in the neurons located in the compact part of the substantia nigra (SN), reflecting progressive neurodegeneration. Motor symptoms of PD are manifested at the stage when it is killed not less than 50% of dopaminergic neurons of the SN, and the typical picture of the disease is fully formed during the destruction of 80% of the cells [24].

Due to the decrease in the number of neurons of the SN, the number of dopaminergic projections at the rear parts of the putamen is reduced that leads to the development of a triad of characteristic motor symptoms of PD—static tremor, bradykinesia, and rigidity, which is deployed in the next stages of the disease with postural instability. In the early stages of PD, not all symptoms are expressed equally; therefore, there are difficulties of differential diagnostics of PD and symptomatic parkinsonism, torsion dystonia, and essential tremor that are not associated with degeneration of nigral neurons and a deficit of dopamine in the striatum, while in 15% of cases, the diagnosis of PD is wrong [25–28]. The complexity of differential diagnosis and, to some extent, delayed the debut of the classic clinical symptoms leading to late diagnosis of the neurodegenerative process and the low efficiency of symptomatic treatment, while the possibilities for pathogenetic help have been lost.

At this time, the researchers are studying actively the predictive value of various non-motor symptoms that occur in the early stages of PD, as these symptoms of neurodegeneration manifest long before the development of the classic triad of motor symptoms. Known early signs of violations of smell, changes in the regulation of cardiac activity, disorders of motility of the gastrointestinal tract, ultrasound signs of early degeneration, disaster, and other changes, because they precede the manifestation of motor symptoms of PD in the years.

As a result of improving traditional methods of functional neuroimaging, the studies have been aimed at identifying qualitative and quantitative indicators of the morphology of the brain in PD. In this connection, the special interest is the study of dopaminergic structures of the brain stem. Despite the fact that currently there are data from multiple studies, obtained facts are rather contradictory. The difference in the results of volumetric studies of the SN in PD could be attributed to the difficulty of identifying the boundaries between the compact and reticular parts of the SN, lack of opportunity of contrasting these structures, individual differences in the volume of the midbrain and medulla in general [28, 29].

Using diffusion tensor MRI Tessa et al. [30] revealed the signs of a diffuse reduction in the volume of gray matter of the cerebral hemispheres in patients with newly diagnosed PD who did not receive specific therapy. These data are consistent with the hypothesis of PD stages of Braak [25], claiming that at the time of the manifestation of motor symptoms process of neurodegeneration is already becoming common. The authors found differences in the severity of atrophy with a predominance of rigidity or tremor obtained by using sophisticated statistical techniques, however, do not seem convincing. Some researchers using this technique revealed changes in the thalamus, SN, and its ascending and descending pathways in PD [31–33].

T1-, T2-, and T2*-WI were used previously to study the anatomy of the midbrain, it is assumed that T1-WI better reflects the lower divisions, however, none of the modes did not allow to distinguish the compact and reticular parts of CHS [34, 35]. Routine T1- and T2-WI MRI do not reveal accurate structural changes in the SN in PD, which confirms its idiopathic nature.

Morphometric studies, using voxel morphometry obtained by different researchers, are contradictory, probably due to the difficulty of tracing the boundaries of the compact part of SN.

The contrast ratio of the SN is determined by the accumulation in it neuromelanin, ferritin and other iron substances, whose concentration is changed by natural aging, so in PD and other neurodegenerations. Reticular part of SN contains more iron than its compact part, which is manifested by hypointensity of this area due to the decrease of the relaxation time T2. The compact part of SN contains more neuromelanin, and the iron atoms in them are in the bound state with the ferritin [36, 37].

Oikawa et al. [38] did not note significant changes of size and density of CHS in studies in modes T2 and proton density. Minati et al. [39] using the T1 with the suppression of the signal from gray and white matter in PD revealed hypointensity signal from the external part of the SN, mainly the reticular part of it. The authors in the study of SN at the level of the chiasm above the upper legs of the cerebellum said that there is significantly smaller area in patients with PD ($72.2 \pm 27.4 \text{ mm}^2$) than in healthy individuals at similar ($88.8 \pm 28.7 \text{ mm}^2$) or young age (of $91.8 \pm 29.4 \text{ per mm}^2$). The authors have not performed the volumetric study.

We carried out the clinical and neuroimaging examination of 4 groups of patients: 10 patients with the initial manifestations of PD, stage 1 on Hoehn and Yahr scale (PD1) [40], 10 patients with severe clinical manifestations, stage 3 on Hoehn and Yahr scale (PD2), 10 patients with early manifestations of CVD, after a transient ischemic attack (TIA) or minor/lacunar stroke with complete or almost complete regression of neurological deficits (CVD1), and 10 patients with severe manifestations of CVD after suffering repeated small/lacunar stroke (CVD2). The diagnosis of PD was established in accordance with generally accepted criteria of brain Bank of the UK PD society [41]. Control group (CONTROL) consisted of 10 apparently healthy persons aged 21–48 years.

MRI study was conducted on “Initial Achieva 3.0 T” (Philips Medical System Nederland BV) with a magnetic field of 3 T. The study protocol included the use of T2- and T2*-weighted images (T2-Wi, T2*-WI) using pulse sequences TSE (Turbo spin echo), FFE (Fast field echo), GraSE (Gradient spin echo). The orientation of slices was conducted nearly to the axial plane, parallel to the line connecting the middle of the chiasm and the lower contour of the corpus callosum splenium. To explore dopaminergic structures of the brain stem, the middle block of the scanned sections was located between the upper and lower hillocks of the corpora quadrigemina. Also, we carried out the scanning in the coronal and axial planes, perpendicular to the main axial plane.

Regional assessment of the volume of brain matter of cerebral hemispheres and the CSF, GM, and WM of the midbrain were performed by the volumetric morphometry. For the region of the cerebral hemispheres, we used axial slices extending above the cavity of the third ventricle, through the bodies of the lateral ventricles, above the insula. After visual determination of the zone of interest, we performed automatic segmentation on the GM + WM and CSF.

To determine the volumetric characteristics of SN, we investigated sections of the midbrain in T2-WI and FLAIR. T2 and T2* relaxation time changes as a result of the accumulation of iron in the area of SN in PD patients (**Figure 1**). The highest contrast of images we obtained in the FLAIR MRI. Study of SN included in its entirety as Hypo-region compared to the white matter

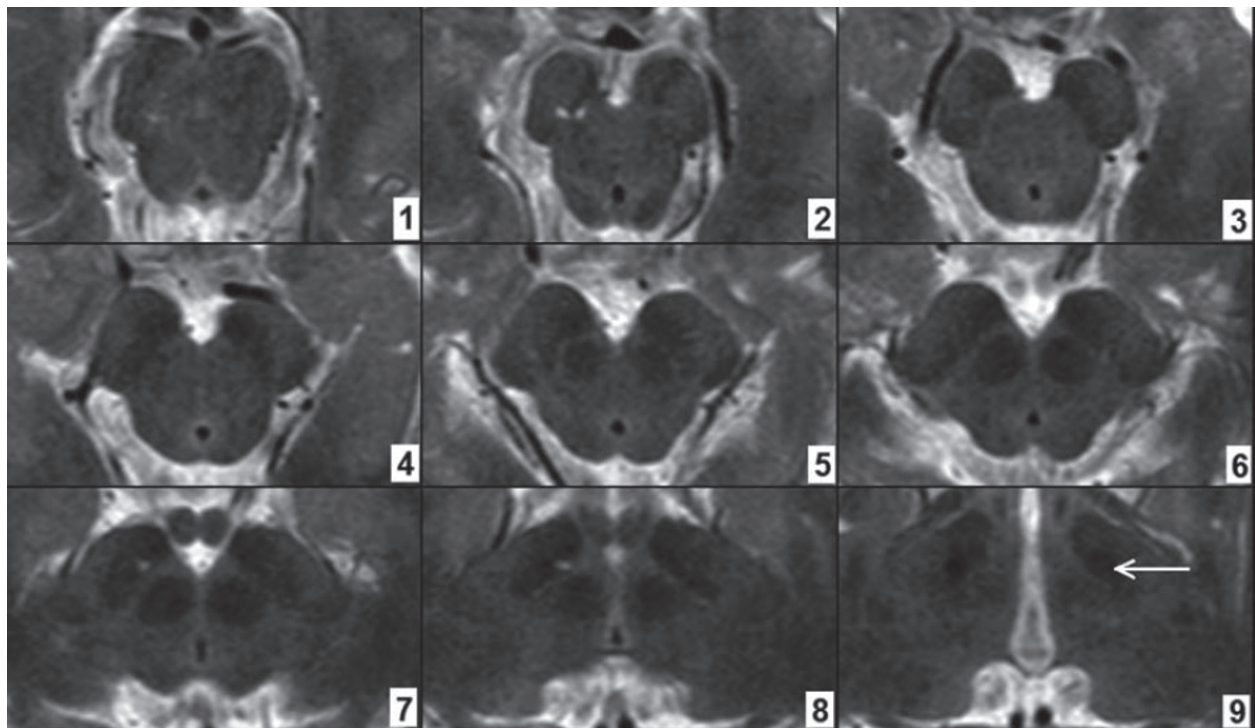


Figure 1. Images of the midbrain from the ponto-mesencephalic (1) to mesencephalic-diencephalic transition (9) on T2-WI (slice thickness 2 mm, the distance between the slices—0 mm). In Sections 3–8 visualized SN, in Sections 5–9—NR, slice 9—the subthalamic nucleus (arrow) positioned as a continuation of SN at the diencephalic level (own data).

of the midbrain. The normalization of the size SN on the volume of the midbrain did not perform. For accurate tracing of the boundaries of SN and the nucleus ruber (NR), we used schemes Duvernoy's Atlas of the Human Brain Stem and Cerebellum [42].

The boundaries of SN and NR were traced manually. The border was carried out by the regions, having approximately the intermediate brightness signal between SN and surrounding white matter. To reduce the subjective factor, the study was conducted by two experts independently from each other.

A significant decrease in the brain volume compared to the CONTROL was observed only in the groups CVD1 and CVD2, while the increase in the volume of subarachnoid spaces was observed in all patients. The PD1 group showed a trend toward increasing the share of space filled with CSF in the preservation compared to the normal shares of the brain tissue. Patients of the PD2 group, along with the increase in the share of space filled with CSF, showed a trend toward a decrease of the relative volume of brain matter. The greatest reduction in the volume of brain matter with a corresponding increase space filled with CSF was observed in the CVD2 group. The difference was statistically significant with the PD1 and PD2 groups (**Table 2**).

We carried out morphometry of SN in PD [43]. Although the amount of SN in PD1 patients was slightly lower than in the CONTROL, but the difference was not significant. At the same time in PD2 patients, the volume of SN was significantly higher than in PD1 patients (**Figure 2**). It should be emphasized that the indicators include both compact and reticular part of SN, and hypotensive of this zone was determined by the accumulation neuromelanin, ferritin, and

Group	Volume of brain matter	Volume of the lateral ventricles	Volume of the subarachnoid space
PD1	0.85 ± 0.01	0.04 ± 0.003 A	0.11 ± 0.01 A
PD2	0.82 ± 0.01 A	0.06 ± 0.01 B	0.12 ± 0.01 A
CVD1	0.81 ± 0.01 A, B	0.07 ± 0.004 B	0.12 ± 0.01 A
CVD2	0.78 ± 0.01 A, B, C	0.09 ± 0.01 A, B, C	0.12 ± 0.01 A
CONTROL	0.87 ± 0.01	0.06 ± 0.01	0.07 ± 0.01

Abbreviations: A, $p < 0.01$ value is calculated against CONTROL; B, $p < 0.01$ value is calculated against PD1; C, $p < 0.05$ value is calculated against PD2 by volume of the brain and $p < 0.01$ for the volume of the lateral ventricles.

Table 2. The ratio of the volumes of brain matter and spaces filled with CSF, in patients with PD, CVD, and control group ($M \pm m$) (own data).

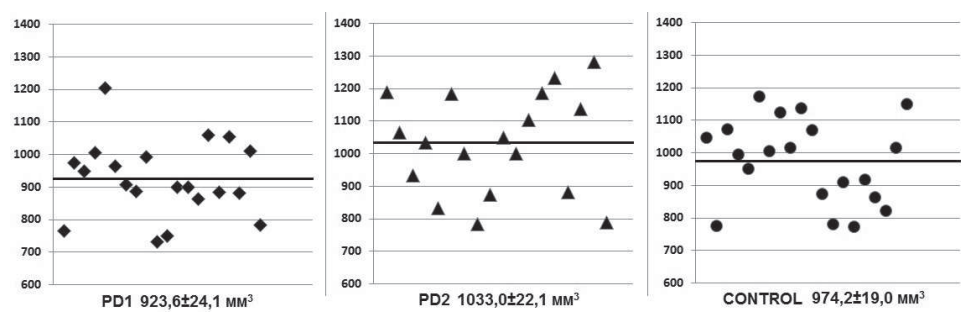


Figure 2. Volume of SN according to the results of morphometry axial slices (in mm^3) in the T2-Wi and FLAIR in PD1, PD2, and CONTROL. The horizontal line indicates the median in each group (own data).

other organic iron compounds. Previously, researchers revealed hyperechogenicity of the SN in patients with PD in transcranial ultrasonography. Obviously, in this case, MRI revealed a phenomenon similar to ultrasonography.

Thus, MRI neuroimaging of dopaminergic structures of the brain stem is feasible, it can detect volumetric changes reflecting a neurodegenerative process. Although the positron emission tomography allows to obtain more information regarding the functional state of the dopaminergic structures in PD; however, this method remains inaccessible. Therefore, voxel morphometry of SN is a useful method of diagnosis and monitoring of PD patients.

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