ANATOMY

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MR anatomy, anatomical variants and morphometry of hippocampal formation

N. I. Ananyeva[1,2], E. V. Andreev[1], L. R. Akhmerova[1], T. A. Salomatina[1], L. I. Wasserman[1,2], R. V. Grebenshchikova[1], N. G. Neznanov[1], A. A. Pichikov[1], N. M. Zalutskaya[1]

[1] V. M. Bekhterev National Medical Research Center for Psychiatry and Neurology (V. M. Bekhterev NMRC PN), 3, ul. Bekhtereva, St. Petersburg, 192019, Russian Federation

[2] St. Petersburg State University, 7–9, Universitetskaya nab., St. Petersburg, 199034, Russian Federation

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Nowadays the question of limbic structures involvement in different types of brain pathology is much debated in literature. However, obtained results are often contradictory. This can be explained by the insufficient knowledge of normal volume and linear measurements of brain structures responsible for human emotional and cognitive functioning including different age periods. Different anatomical variants of these structures were described in literature indistinctly, often leading to misinterpretation of neuroimaging findings. Besides, hippocampal formation, being complex structure, consists of different parts, including subregions (head, body and tail) and subfields (CA1-CA4, subiculum, presubiculum, dentate gyrus), which changes depend on different psychological and psychiatric symptoms. In our study we have analyzed MRI data of mediobasal parts of temporal lobes in healthy volunteers based on literature review and our own experience. The incidence rate of different hippocampal anatomical variants in healthy population was specified in the study. We have also determined MR voxel-based morphometry as a method permitting to define and evaluate volumes of different hippocampal subfields. In our research we found out certain significant differences in hippocampus fissure volumes, parasubiculum, molecular layer of dentate gyrus, fimbria, CA3 and CA4 Brodmann areas, demonstrating that in adulthood morphofunctional connections are not finally formed, that's why volumes of molecular layers CA1-CA3 smaller in adulthood

than in elder population. But hippocampal fissure become smaller in elder ages because of atrophic changes.

Keywords: anatomical variants, temporal lobe epilepsy, hippocampus, MRI, segmentation.

Introduction

In the last decade neurology, psychiatry, medical psychology, neurophysiology as well as other specialties started to require more detailed information concerning normal and pathological individual anatomical variability of brain. Therefore, methods of neurovisualisation became more important [1–3].One of the most modern and promising method of brain anatomy research is magnetic resonance imaging (MRI), permitting to obtain intravital morphometric characteristic of examined brain structures [4; 5]. Majority of literature sources contains qualitative and, to a less degree, quantitative [4] MRI analysis of examined structures [6]. There are only few studies in literature describing individual and gender anatomical variability of their brain structures [7; 8]. This information can be useful as the base of brain structures alterations assessment in different pathologic states.

Nowadays question of limbic structures involvement in different types of brain pathology is much debated in literature [6; 7]. However, obtained results are often contradictory. This can be explained by insufficient knowledge of normal volume and linear measurements of brain structures responsible for the human emotional and cognitive functioning including different age periods. Different anatomical variants of these structures, described in literature, are indistinct, which often leads to misinterpretation of neuroimaging findings, especially in case of cognitive-affective proportion analysis [1]. More over, hippocampal formation is very complex structure, consisting of different parts, including subregions (head, body and tail) and subfields (CA1-CA4, subiculum, presubiculum, dentate gyrus), which changes depend on different psychological and psychiatric symptoms.

Materials and methods

We have examined 101 healthy volunteers aged 17–50 years without any neurologic or psychopathologic symptoms, 75 (70.3 %) of them were female, 30 (29.3 %) — male.

I. We used the following exclusion criteria:

1) younger than 17 years and elder than 50 years at the moment of study, which allowed to limit the influence of the age on the clinical findings and neuroimaging;
2) psychotic drug, alcohol or narcotic abuse;
3) severe decompensated somatic or neurologic disorders.

II. We examined 2 groups of normal volunteers for accurate analysis of subfields and subregions of hippocampus in young and old ages.

1. 10 healthy volunteers 13–21 years old;
2. 10 healthy volunteers 55 years and older.

All of the participants underwent quantitative evaluation of depression symptoms using HamiltonDepression Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS). Severity of anxiety symptoms was evaluated using Hamilton Anxiety scale (HAM-A). Total statistical analysis of the study results was performed using statistical packages “Statistica 6.0 for Windows” and SSPS 25.

MRI was performed using 1.5 T AtlasExelartVantageXGV (Toshiba, Japan) with 8-channel head coil. Standardized brain MRI protocol included fast spin echo sequences (FSE) for obtaining T1 weighted images (T1-WI), T2-WI, and T2-FLAIR. For detailed examination of mediobasal parts of temporal lobes we used additional exam protocol, which included T2 FLAIR and Real IR in the oblique coronal plane with 2.2 mm slice thickness, obtained perpendicular to long hippocampus axis. These sequence structures of temporal lobes mediobasal parts include entorhynal cortex, head, body and tail of the hippocampus, temporal horns of lateral ventricles, and basal cisterns.

T2 FLAIR was performed using the following parameters: TR = 8000, TE = 105, FOV = 22.0, MTX = 30, ST = 2.2, GAP = 0.6, FA = 90/180.

To obtain REALIR we used the following parameters: TR = 3450, TE = 18, FOV = 22, MTX = 320, ST = 2.2, GAP = 0.6, FA = 90/160.

MR-images of the mediobasal parts of temporal lobes obtained in the oblique coronal plane were used for evaluation of hippocampal shape and degree of rotation; we measured hippocampal volume and level of head height, body and tail.

Hippocampal anatomical variants were assessed according to N. Bernasconi criteria [9]. We performed visual analysis of hippocampal shape and measurement of parahippocampal gyrus angle (for the assessment of vertical orientation of the hippocampus), and the distance between the third ventricle and fimbria (for the assessment of medial position).

At next stage, 3D MPRAGE sequence was obtained using the following parameters: TR = 12, TE = 5, FOV = 25.6, MTX = 256, ST = 2.0, FA = 20. For evaluation of brain structures volume we performed post-processing and voxel volumetry was obtained automatically (software environment FreeSurfer), partly automatically and manually (program package DISPLAY) [6].

FreeSurfer- is a program package initially developed only for the segmentation of brain cortex, however, was later upgraded to full value instrumental segmentation and visualization of structural and functional elements (FreeSurfer/Massachusetts General Hospital. URL: http://surfer.nmr.harvard.edu). We used FreeSurfer 6.0 also for accurate analysis of subregions and subfields hippocampal formation.

MINI-Display represents a program, developed for object visualization and manipulations in three dimensions, generally for cortex surfaces. This program is able to reflect and to segment MRI, PET and other imaging modalities, and has many additional functions. User interface of the MINI-Display in nonconventional and menu-orientated system is based on the keypress and mouse manipulation (Montreal Neurological Institute, Quebec, Canada).

Results

Mean height of hippocampus in healthy volunteers equals 8.56 mm at head level, 6.34 mm at body level and 5.12 mm at tail level.

Hippocampal volumes of healthy volunteers measured using voxel morphometry with FreeSurfer post-processing program are represented in Table 1.

We have not found significant age correlation of the hippocampal volumes in healthy volunteers aged 18–50 years. But we did have indicated significant age correlation, that is, right and left hippocampus in healthy men was remarkably higher than in healthy women with high confidence (Table 2).

Table 1. **Hippocampal volumes of healthy volunteers measured using voxel morphometry with FreeSurfer post-processing program**

Structure	Volume (mm^3)	
	Right	Left
Hippocampus	4297.08 ± 413	4403.29 ± 191
Amygdala	1577 ± 206	1504 ± 171

Table 2. **Gender correlation of hippocampal volumes**

Gender	Right hippocampus	p	Left hippocampus	p
Men	4584.41 ± 316.625	0.000	4631.56 ± 280.232	0.000
Women	4163.83 ± 385.626		4297.42 ± 388.50	

Different anatomical variants were observed in 43.5 % of cases in the following proportions: choroidal fissure asymmetry was found in 7.9 % of healthy volunteers (8); deep vertical collateral fissure was observed in 8.9 %.

Different morphological variants were observed in 43.5 % cases in the following proportions: choroidal fissure asymmetry — 7.9 % (8); deep vertical collateral fissure — 8.9 % (9); asymmetry of the poles in temporal horns of lateral ventricles — 8.9 % (9); round shape of hippocampus solely — 8.9 % (9); round shape associated with deep vertical collateral sulcus — 8.9 % (9).

Pair-wise comparison proved that the volume of the round shape hippocampus is reliably lower than the volume of the hippocampus with typical morphology.

Comparative analysis with Mann-Whitney criteria of young and old volunteers groups determined significant differences in hippocampus fissure volumes, parasubiculum, molecular layer of dentate gyrus, fimbria, CA3 and CA4 Brodmann areas.

In case of old age volunteers, volume of hippocampal fissure was larger on 28 % in right and 27 % in left hemisphere.

But volumes of CA3 and C4 fissure were larger on 14 % and 13 % in right and 9 % and 4 % in left hemisphere, respectively, in volunteers of old age, than in young volunteers.

Also molecular layer of dentate gyrus was higher by 13 % in right and 4 % in left hemisphere in volunteers of old age, than in young volunteers.

Volume of parasubiculum was larger on 12 % in right and on 3 % in left side, volume of fimbria — on 3 % in right and 11 % in left side in case of young age volunteers.

Discussion

Tremendous development of science requires more detailed neuro morphological study of the brain structures with due account for individual variability. Nowadays neuroimaging methods, such as magnetic resonance imaging (MRI) of human brain allow accurate evaluation of different brain structures. However, in spite of the 25 years of experience using MRI for the identification of structural changes of human brain, many questions of morphometry and anatomical variants of different brain parts remain unclear. This also relates to limbic system and to mediobasal parts of temporal lobes in particular.

Therefore, detailed study of the hippocampal development is highly important for the understanding of normal and pathological hippocampal morphology.

Hippocampus obtains curved shape during early ontogenesis. Before the 10-th week of prenatal development dentate gyrus and cornu Ammonis represented rudimentary structures located in line one by one along posteromedial wall of lateral ventricle [8]. Its anterior margin is located close to medial part of perforated substance. From the 10th week dentate gyrus thickens was followed by formation of hippocampal fissure between the dentate gyrus and cornu Ammonis. On the 12–14-th weeks dental gyrus thickening leads to its rotation towards cornu Ammonis, hippocampal fissure becomes deeper and more differentiated, and orientates between the walls of cornu Ammonis and parahippocampal region (which includes parahippocampal gyrus and subiculum). Due to growth of dentate gyrus, medial surface of the hemisphere starts to press on lateral ventricle. In the brain of three-month fetus, opened from the lateral side, one can observe that hippocampus arches from the rostral and dorsal sides of the interventricular foramen. Further hippocampus turns back and forms ventromedial part of the pallidum. Along its ventral border vascular fissure is developing, containing vessels forming choroid plexus of lateral ventricle. At 15–16 week of the pregnancy this fissure appears thinner and to 18–21 weeks of pregnancy it obliterates together with pia mater and small vessels. However, residual cavities can remain, which can be visualized on MRI as hippocampal cystic lesions. Hippocampus at 24-th week appears the same as in the brain of the adult.

Some authors consider that abnormality of the hippocampal formation during prenatal development is associated with hippocampal anatomical variants [9]. N. Bernasconi distinguished following variants of hippocampal morphology:

— medial position in respect to the temporal horn of lateral ventricle (in this case anterior part of hippocampus is located close to cerebral peduncle (on the level of hippocampal head and anterior part of the body), and posterior part of hippocampus is located close to quadrigeminal (posterior part of the body and tail);
— round (globular) shape and vertical orientation of hippocampus;
— empty choroid fissure;
— dystopia of fimbria;
— deep and vertical collateral fissure;
— bulging of the collateral fissure towards the empty choroidal fissure; in appropriate location of subiculum;
— partial reduction of parahippocampal gyrus (our data submitted in Fig. 1, N. Ananyeva).

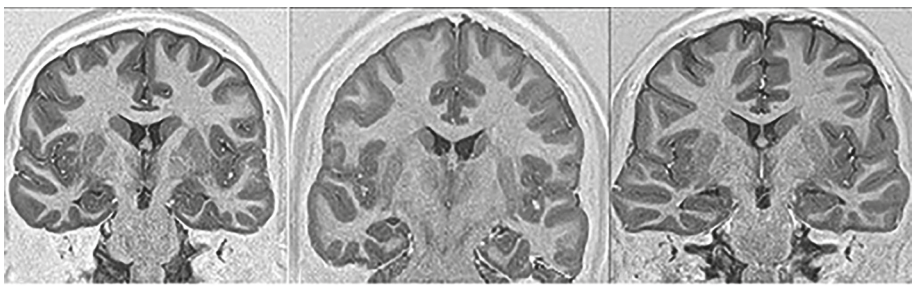
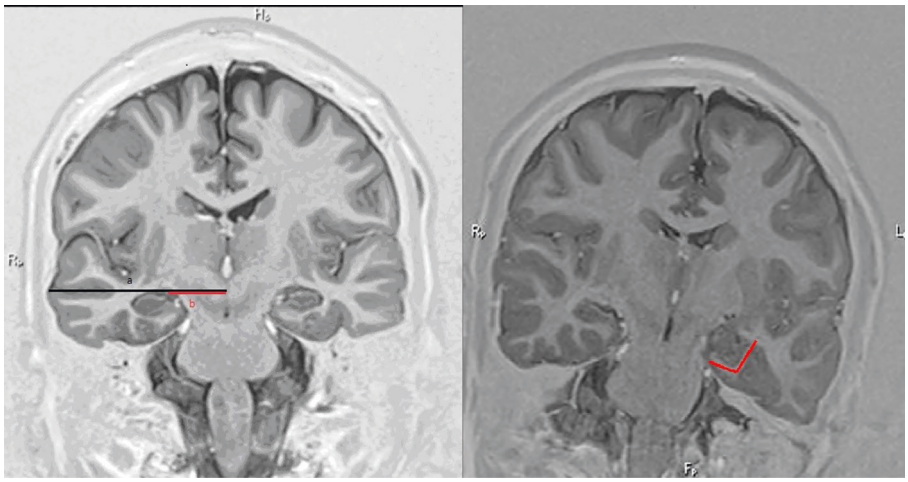


Fig. 1. Anatomical variants of mediobasal parts of temporal lobe: round shape of hippocampi (a), empty choroidal fissure (b), vertical collateral fissure (c). (Ananyeva N.)



a b

Fig. 2. Medial position (a) and vertical orientation (b) of hippocampus on coronal images on the level of hippocampal body. (Ananyeva N.)

Medial position was estimated as distance between the midline and fimbria, which forms medial border of the hippocampus. Taking into account possible differences of the individuals this measurement was compared with the distance between the midline and the border of the temporal lobe (our data submitted in Fig. 2a, N. Ananyeva).

Vertical orientation of the collateral fissure was determined by measuring of parahippocampal gyrus angle (angle between ascend and descent parts of parahippocampal gyrus (our data submitted in Fig. 2b, N. Ananyeva)).

When hippocampus is normally orientated, parahippocampal gyrus angle approaches 180°. Anatomical variants of hippocampus and round shape in particular are highly debatable item in literature. Initially a term "malrotation" was proposed. However, nowadays term "malrotation" is considered disputable and term incomplete hippocampal inversion is preferred, because it implicates incomplete inversion of hippocampus during prenatal period [10].

Moreover, some authors consider this anatomical variant only as a combination of the key criteria (round shape) with other abnormalities, such as vertical collateral fissure, unilateral involvement of the whole hippocampus, change of fornix position, enlargement of temporal horn of lateral ventricle with no signs of hippocampal MR signal abnormalities or brain congenital anomalies [10].

Other authors proposed to assess by incomplete criteria. Then incomplete hippocampal inversion is defined in 18–37 % of healthy volunteers [7; 11]. According to our studies, analyzing solely round shape of the hippocampus, it was observed in 20.4 % of examined persons. Combined round shape of the hippocampus was observed in 20.4 % of healthy volunteers. However, it is important to add that we have indicated only a combination of the round shape of hippocampus and vertical collateral sulcus, but did not observe all of the criteria proposed by P. Barsi [10].

There are some studies reporting that the volume of left hippocampus is smaller than the right, however the volume difference is insignificant. In our study we did not received such findings [11].

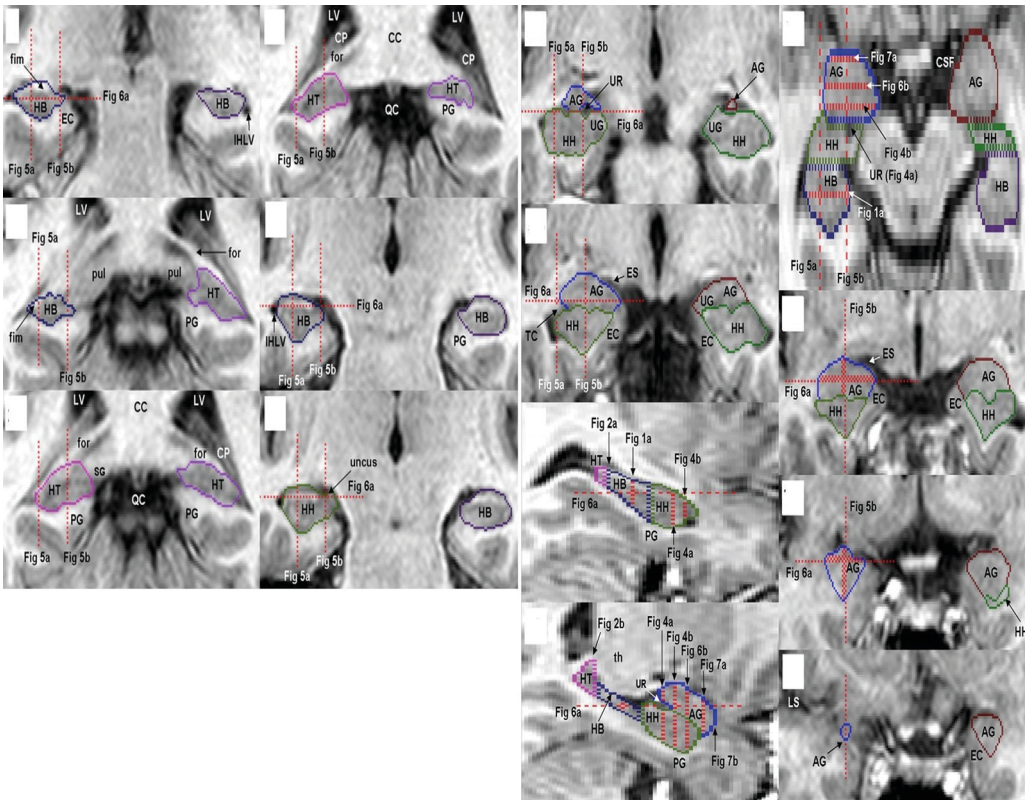


Fig. 3. Identification of hippocampal head, body and tail (N. Malykhin)

Changes of the hippocampal volume can be seen in many types of the brain pathology, however proximity of these structures makes them hard-separable on MR images, as a result there is a risk of few slices exclusion from the analysis when performing MR morphometry. Conversely, combined analysis of amigdalo-hippocampal complex can be performed. Beyond that point differentiation of hippocampal tail and thalamus can be challenging. Therefore, appeared a need in reliable method of hippocampus and amigdala volume analysis (DISPLAY, Montreal Neurological Institute, Quebec, Canada), that is also used for the evaluation of intracranial volume and performing 3-dimensional reconstructions [6].

Hippocampal analysis should be performed using coronal images starting from the hippocampal tail [6]. It can be difficult to differentiate the borders of the hippocampal regions. The border between the tail and body can be seen on coronal images where the columns of fornix are fully visualized. The border between the body and the head can be seen on images where the top of hippocampal hook is clearly visualized. The most important structure that can be used for lateral, anterior and inferior borders identification of hippocampus is falciform recess of inferior horn of lateral ventricle (Fig. 3).

Volumes of hippocampal regions in healthy volunteers measured using post-processing software DISPLAY are shown in the Table 3.

Hippocampus is a part of hippocampal formation, which include also dentategyrus, subiculum, presubiculum, entorhinal cortex. Hippocampus (cornu Ammonis) is a tight

type of cells, which is extended in anterior-posterior direction along medial wall of inferior horn of lateral ventricle [12]. Main nervous cells of hippocampus include pyramidal neurons and polymorphic cells. As ancient cortex hippocampus consists of 3 main layers: *stratumoriens*, *stratumpyramidale* and *stratumradiatum* + *stratumlacunosum-moleculare* (Fig. 4).

Table 3. **Examination of subfields and subregions of the hippocampal in young and old age**

Structure	Young healthy volunteers		Old healthy volunteers		Level of significance
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	
Whole hippocampus	3350.38211	3256.182089	3445.861117	3414.173636	
Hippocampus tail	561.9416047	544.6546328	541.5249371	527.6189509	
Subiculum	402.64394	381.5967118	435.7437506	415.3908504	
CA1	584.0629195	599.7761962	621.8925157	627.5692734	
Hippocampal fissure	168.64971	164.4610933	213.692648	211.3207803	$P \leq 0.01$
Presubiculum	342.3967863	318.7739042	330.956494	301.8749004	
Parasubiculum	67.755132	62.355125	68.42057929	55.22181486	$P \leq 0.05$
Molecular layer of the hippocampus	537.55853	521.2902828	562.1268349	559.7053719	
Molecular layer of dentate gyrus	292.0825065	276.5951105	303.3211026	312.4577006	$P \leq 0.05$
CA3	191.4176447	193.1031418	209.4775464	221.8378734	$P \leq 0.05$
CA4	250.6389882	236.3428308	261.986464	267.5831651	$P \leq 0.05$
Fimbria	66.46761617	67.28637933	54.18618571	65.40572986	$P \leq 0.01$
HATA	54.4164435	54.407774	56.22470671	59.50800443	

Layer on ventral surface, *alveus*, consisting of myelinated axons of pyramidal neurons, basal dendrites and initial segments of axons, located in polymorphic layer. They are followed by pyramidal neurons layer, then s*tratum-radiatum*, consisting of trunks of apical dendrites and *stratum-lacunosum-moleculare*, consisting of pre-terminal and terminal branching of apical dendrites. Such organization of hippocampus exists on all his frontocaudal extent (laminar hippocampal organization) [6; 12].

Specificity of hippocampal organization of pyramidal layer is the basis for its dividing on 4 main areas; CA1 — CA4. Main areas of hippocampus — CA1 and CA3. CA1 area consists of 2 small tight layers of pyramidal neurons, large neurons of CA3 and axons of pyramidal neurons of CA3 named "Shaffar collaterals", contacting with apical dendrites of CA1 area. These connections are 2 main associative paths, connecting its main elements. So, we can review hippocampus as a package of morphofunctional segments series, which can function relatively independent. And CA1-CA3 area — convergence point of information traffic from associative cortex and phylogenetic ancient parts of the brain.

In our research we found out significant differences in volumes of hippocampus fissure, parasubiculum, molecular layer of dentate gyrus, fimbria, CA3 and CA4 Brodmann areas, which demonstrate that in adulthood morphofunctional connections are not finally formed, that's why volumes of molecular layers CA1-CA3 smaller in adulthood than in

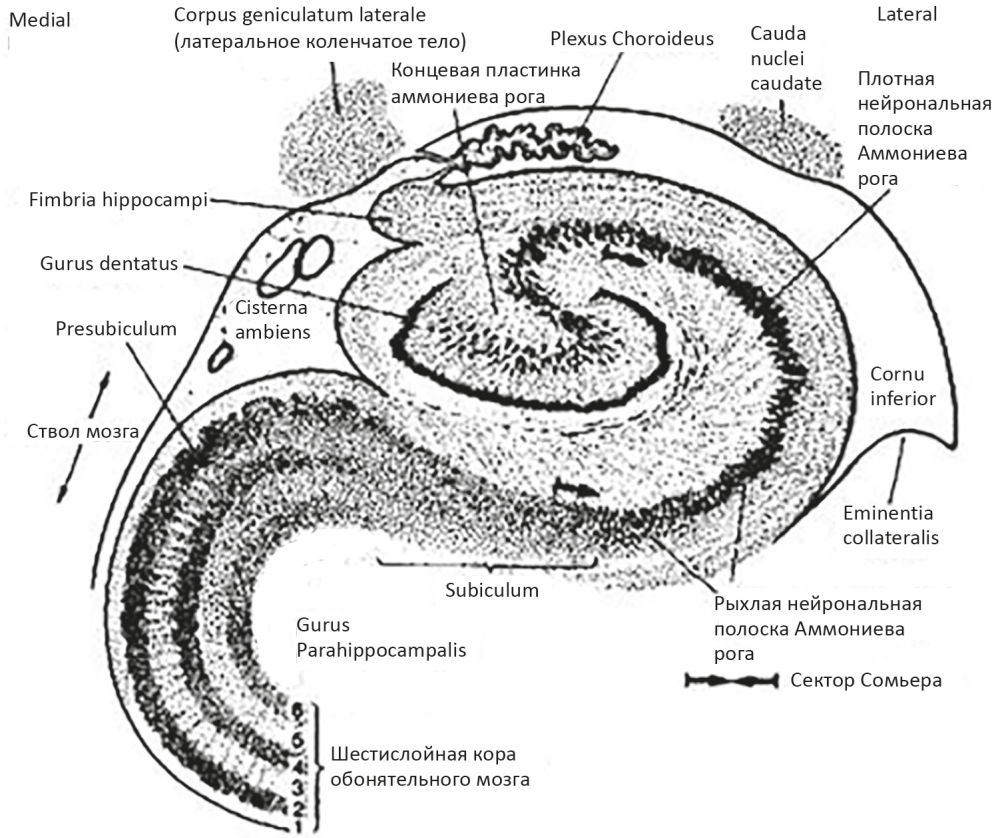


Fig. 4. Scheme of hippocampus [13]

old population. But hippocampal fissure become smaller in older ages because of atrophic changes.

Table 4. **Voxel morphometry (DISPLAY). Hippocampal volumes in healthy volunteers.**

Hippocampal region	Right hippocampus	Left hippocampus
Head	2314 ± 526	2484 ± 526
Body	1052 ± 193	987 ± 210
Tail	326 ± 125	304 ± 79

Conclusion

Neuroimaging methods are permanently upgrading and improving. This allow to feel reliance in the further success in diagnosis and understanding of different types the genesis in brain pathology that can be reached using these methods in the nearest future [14].

However, in spite of the great achievements and advantages of the instrumental methods of the inter vivo brain studies many questions of the special aspects of morphology and anatomical variants of the mediobasal part of temporal lobe remain unclear.

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Authors' information:

Natalia I. Ananyeva — MD, PhD, Full Prof; ananieva_n@mail.ru
Evgeniy V. Andreev — ev.andreev94@gmail.com
Linara R. Akhmerova — akhmerovalinaris94@gmail.com
Tatiana A. Salomatina — tani.salomatina@gmail.com
Ludvig I. Wasserman — MD, PhD, Full Prof.; ludvig_labos@mail.ru
Ruslana V. Grebenshchikova — MD; ruslana411@gmail.com
Nikolay G. Neznanov — MD, PhD, Prof.; spbinstb@bekhterev.ru
Alexey A. Pichikov — MD, PhD; sigguros@mail.ru
Natalya M. Zalutskaya — MD, PhD; nzalutskaya@yandex.ru