Neuroscience and Behavioral Physiology, Vol. 40, No. 3, 2010

MRI Morphometry of the Cerebral Ventricles in Patients with Attention Deficit Hyperactivity Disorder

V. M. Verkhlyutov,[1,3] G. V. Gapienko,[2] V. L. Ushakov,[2] G. V. Portnova,[1] I. A. Verkhlyutova, N. V. Anisimov,[3] and Yu. A. Pirogov[3]

UDC 616-08:612.821.3.01

Translated from Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova, Vol. 59, No. 1, pp. 34–44, January–February, 2009. Original article submitted July 29, 2007. Accepted June 9, 2008.

A total of 27 right-handed patients aged 7–30 years with diagnoses of attention deficit hyperactivity disorder were studied using standard MRI scans. Of these, 14 were aged below 13 years. The volumes of the lateral ventricles were measured using T1-weighted MRI images of sagittal sections of the brain to a precision of 3 mm^3. External head sizes were also measured to allow ventricle volumes to be normalized. All patients underwent complex neuropsychological investigations. Memory was assessed, along with visual, auditory, tactile, and spatial recognition functions and the motor and speech spheres. Test data were assessed in terms of the severity of impairments associated with one brain structure or another on a ten-point scale. Assessment points were summed for each hemisphere, for the "first area" (cortical structures), and all structures for statistical analysis. Neuropsychological testing revealed functional impairments predominantly of the frontal areas of the hemispheres, the hippocampus, and the reticular formation. Neuropsychological deficits were least linked with alterations in the postcentral and parietal areas of the cortex. Statistical analysis demonstrated a significant positive correlation between the normalized left lateral ventricle volume and the degree of neuropsychological impairments ($r = 0.5127$ at $p = 0.0063$) for the whole study group. The correlation was more marked on comparison of the normalized left ventricular volume and the severity of neuropsychological impairments related to the left hemisphere ($r = 0.6303$ at $p = 0.0004$). A relationship was seen between the volume of the intraventricular space and cortical functional impairments ($r = 0.5071$ at $p = 0.0069$) in patients less than 13 years old. A relationship between ventricular volume and linear head size was confirmed ($r = 0.5759$ at $p = 0.0017$), which was more marked in subjects less than 13 years old ($r = 0.6833$ at $p = 0.01$).

KEY WORDS: magnetic resonance tomography, morphometry, neuropsychology, minimal brain dysfunction, attention deficit hyperactivity disorder.

Morphometry of brain structures using MRI scans has entered wide use in recent years as a result of the clinical introduction of high-resolution regimes and the appearance of a new method for voxel transformation of three-dimensional data (voxel-based morphometry, VBM) [7], which in turn became possible because of the introduction of tomographs with constant magnetic fields of 3 T and above. These instruments provide good discrimination of continuous volumes of homogeneous tissues (segmentation) and are extremely sensitive to changes in the morphological parameters of brain matter.

Use of these methods yielded persuasive results on the scale of cortical abnormalities in pathologies such as Alzheimer's disease [27, 30], progressive aphasia [28],

[1] Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow.
[2] Moscow Physical Engineering Institute.
[3] M. V. Lomonosov Moscow State University; e-mail: verkhliutov@mail.ru.

dementia [21], and schizophrenia [7, 17]. Studies based on complete cortical morphometry in patients with schizophrenia [14, 20, 22–25] were preceded by reports demonstrating statistically significant increases in total cerebrospinal fluid volume and lateral ventricle volume in this condition, which the authors associated with the linked decrease in the volume of the white matter [8, 9, 11, 16]. Subsequent studies showed that widening of the ventricles was also accompanied by decreases in the anterior areas of the temporal cortex, striatum, thalamus, and hippocampus [16, 24]. Increases in the total volume of the liquor spaces of the brain were seen in schizophrenia [15], though in contrast, no increase in lateral ventricle volume was seen. Changes in the volume of the white matter are preceded by decreases in its density, as, for example, seen in the corpus callosum in patients with autism [6, 10, 12, 13].

Thus, there is a continual increases in results demonstrating that structural changes in diseases previously regarded as purely functional or associated with neurotransmitter changes can be studied. One such condition is attention deficit hyperactivity disorder (ADHD). Traditional methods of MRI analysis in ADHD do not reveal any clinically significant changes, though no MRI morphometry studies in this pathology have been reported.

The aim of the present work was to test the suggestion that there may be structural changes in the brain in patients with ADHD with no significant neurological or psychopathological disorders, the neuropsychological deficit only being detectable on detailed investigation.

METHODS

Studies were performed using MRI data from patients selected from 64 subjects investigated at the Magnetic Resonance Tomography and Spectroscopy Center, Moscow State University.

Patients generally complained of periodic headaches and vertigo. Some also complained of reduced attention and memory, which could lead to difficulties in learning and work activities. In most cases, MRI scans were ordered on repeat neurology consultations because of diagnostic uncertainty and the lack of efficacy of initial treatment.

In some patients, neurological status showed microfocal symptomatology, while ocular examination sometimes demonstrated dilation of veins in the fundus, without signs of congestion of the optic disk.

Expert visual analysis of MRI scans in eight patients revealed no changes. Changes not accompanied by volume effects were seen in 56 cases: increases and asymmetry in the ventricles, cystic formations in the arachnoid mater, small areas of gliosal remodeling in the white matter, the cavity of the septum pellicudum, and ectopy of the cerebellar tonsils (type I Chiari syndrome). One patient was found to have a tumor of the brainstem; its only clinical symptom was that the patient complained of mild vertigo.

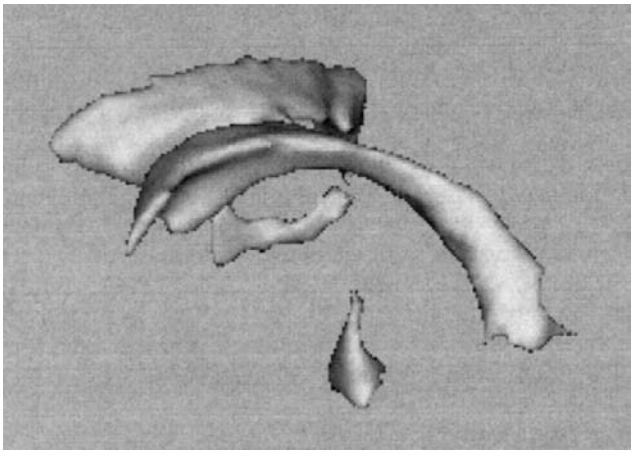

Fig. 1. Three-dimensional reconstruction of the volumes of the lateral, third, and fourth ventricles as determined by MRI studies using the Brainmatic program.

Of the 64 observations, cases of moderate hydrocephalus, asymmetry of the lateral ventricles, and cases in which experts saw no pathological changes were selected for morphometric analysis. This group included 27 right-handed subjects aged from 7 to 30 years (14 were less than 13 years old). MRI studies were performed using a tomograph with a 0.5-T field using standard regimes, i.e., RARE-T2, FLAIR-RARE, and GEFI-T1, in the axial and sagittal planes. Sections were imaged using matrix of 256×256 points with a slice thickness of 3 mm. The scanning zone in most cases was 300×300 mm. It follows that the precision of the morphometric measurements was of the order of 3–4 mm^3.

The relatively low morphometry resolution was associated with the need for minimal modification of the standard clinical MRI scan regime, which in turn restricted the time available, which has to be minimized for children. Thus, no specially planned studies were performed. The main aim was to seek clinical conclusions. Data satisfying the study requirements were selected from the results obtained.

MRI scans in three study regimes were combined to produce three-dimensional reconstructions of the ventricular system (Fig. 1) for determination of the volumes accessible to morphometric analysis. Our Brainmatic program was used to segment MRI data, identifying uninterrupted volumes of homogeneous tissues (scalp, white and gray matter) or media (blood, cerebrospinal fluid) and to create coated three-dimensional wire-frame models of anatomical formations.

Analysis of the reconstructions showed that the inferior horns of the lateral ventricles could not be identified because of their small sizes.

The volumes of the lateral and third ventricles were measured using T1-weighted MRI images of sagittal brain slices. Additional measurements were made of the external

TABLE 1. Localizations and Extents of Brain Dysfunctions from Neuropsychological Testing Results. Individual Data for Each Subject, Points (R = right hemisphere, L = left hemisphere, Σ is the total points for each hemispheres, Σ*s* is total points for each brain structure, 28.8 is the mean points score for each brain structure)

Brain structure \ Subject No.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Σ	Σ*s*
Frontal area (convexital parts)	R	1	4	4	4	4	5	7	5		1		3	7	7	5	4			1	2	1	5	7	1	5	6	3	6	98	188
	L	1	3	4	4	4	7	7	3		1			7	6	5	2			2	2		5	7		5	5	3	7	90	
Hippocampus	R					1					2	5	4	1	2			8		4		7	4	1	2	3	2	6	4	56	101
	L											5	4	1	1			8		4			4	1	2	3	2	6	4	45	
Basal and medial parts of	R	3	3	2		2	2	1	3	2			2	2	2	2	5	1	4	2	6	4	2	6	5	3	4	5		73	92
frontal area	L	3					3			2								1	4					6						19	
Reticular formation	R		3			3				3	4				4			1	6	1	9	6	4	3	3	5		6	7	68	84
	L									3								1	6					3	3					16	
Limbic system	R	1		1		2		2			3		2	1			5				6	5		1	2	3	2	5	4	45	83
	L	1		1				2					2	1			5				6	5		1		3	2	5	4	38	
Temporal-parietal-occipital	R									6		8				5			2				1		3		6		2	33	56
area (TPO)	L	1								5		5				2			2				1				4		3	23	
Diencephalic structures	R										3			1			4		2			4					3	6	5	28	49
	L													1			4		2								3	6	5	21	
Premotor area	R		1	1	4				2		2		2			4				3			1		3	4			1	28	48
	L		1	1	4						3									6						4			1	20	
Temporal area	R																						1		3					4	34
	L	1									4		5			3		2	3	6						4			2	30	
Occipital area	R							1	5					1	3			6			1	1	1		3		3			25	29
	L													1				2			1									4	
Corpus callosum	R					1	3		2			1								3		1	4			2	1			18	20
	L																					1					1			2	
Superior parietal area	R																						1		3		2			6	6
	L																													0	
Inferior parietal area	R																						1		3		2			6	6
	L																													0	
Postcentral area	R			1																			1		3					5	6
	L			1																										1	
Total points		12	15	16	16	17	20	20	20	21	23	24	24	24	25	26	29	30	31	32	33	35	36	36	39	44	48	51	55	802	28.6

sizes of the brain with an accuracy of 1 mm using T2-weighted images, to allow normalization of ventricular volumes. Measurements were made on axial MRI slices passing through a level above the eyes. The axial line connecting the outer surface of the frontal and occipital areas of the head, half of which served as the first radius, passed through the interhemisphere cleft. A perpendicular was constructed from the midpoint of this line to intersect the temporal surfaces of the head. The arithmetic mean of these sections was used as the second radius. The third radius was obtained from sagittal T1 slices, constructed from the midpoint of the axial line to the vertex. The three radii were used to calculate the volume of an ellipsoid, which was taken as the subject's head volume. Volumes were averaged and used for normalization of ventricular system volumes, which increased the sensitivity of the method. Linear head sizes were assessed using the size of a semicircle which was calculated as π multiplied by the mean of the three radii measured. These measurements were also performed using our own program suite, Brainmatic.

All patients selected for correlation analysis underwent complex neuropsychological investigations. Memory was studied, along with visual, auditory, tactile, and spatial recognition and the motor and speech spheres.

In accordance with the neuropsychological syndrome analysis method developed by Luriya [3, 5], different neuropsychological tests are sensitive to impairments in the functioning of different brain structures. Analysis of errors in these tests and their severity and stability with subjects' age were used to establish the degree of dysfunction of particular areas of the brain, assessed on a ten-point scale: 0 points corresponded to the absence of impairment and 10 to maximal impairment. Neither the expert neuropsychologist nor the subjects were familiar with the MRI investigations used here.

Preliminary analysis did not identify any significant correlation between neuropsychological impairments associated with dysfunctions in any brain structure and ventricle size. Thus, all points assessments of the severity of neuropsychological impairments due to dysfunctions in individual brain structures were summed. Along with the summed parameter, total points scores for neuropsychological impairments to each hemisphere were determined, as were total points scores for impairments to cortical structures.

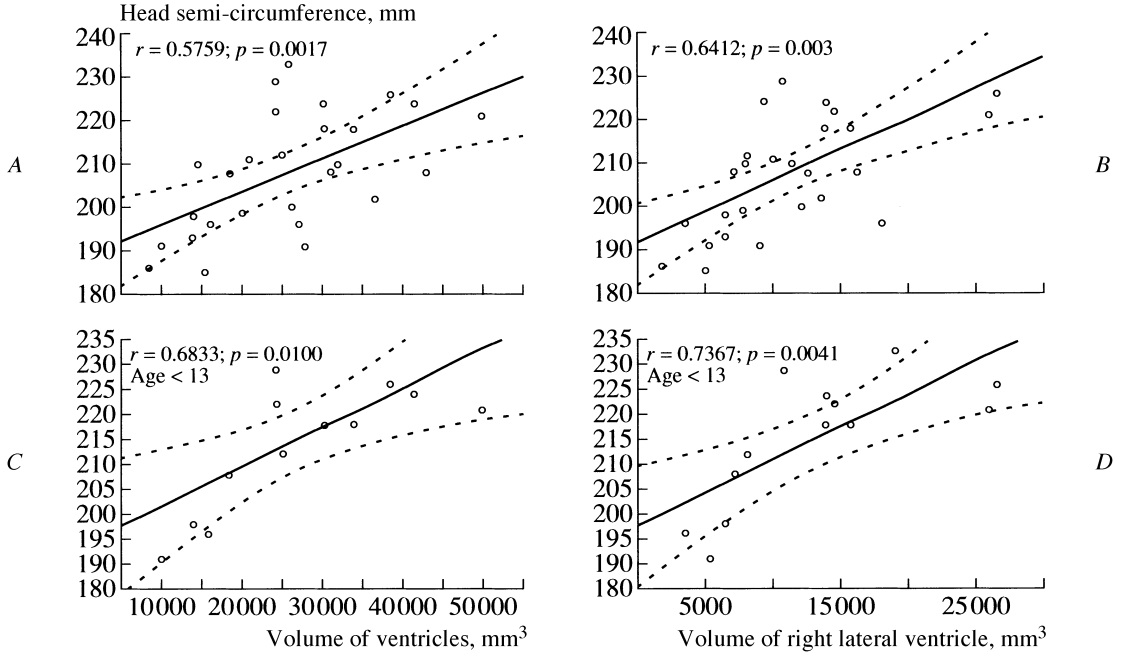

Fig. 2. Positive correlation between linear head size and ventricular volume: *A*) total volume; *B*) right lateral ventricle; *C*) total volume in the group aged less than 13 years; *D*) right lateral ventricle in group aged less than 13 years.

Statistical correlation analysis was performed at the final stage of the study; this consisted of evaluation of interactions between ventricle volumes and the extent of neuropsychological impairments and between ventricular volumes and linear head sizes. Correlation functions were calculated using Statistica 6.0.

RESULTS

All patients selected for investigation made errors on performing neuropsychological tests. The mean points score for the overall neuropsychological assessment of impairments to the functions of all brain areas was 28.6, ranging from 6 to 188 (Table 1). Our data indicate that the greatest impairments, in terms of group averages, were associated with dysfunction in the convexital parts of the frontal area of the cerebral cortex. The mean points score for impairments to this structure was 6.714 (Table 2). Assessments of the extent of functional impairments in the hippocampus was just over half this score, at 3.607 (Table 2). The data indicate that there were also significant impairments in the basal + medial parts of the frontal areas, the reticular formation, and the limbic system. The mean points scores were 3.286, 3.000, and 2.964, respectively (Table 2). The lowest impairments were seen in relation to the temporal cortex, the occipital area, and the corpus callosum. There were virtually no disorders associated with the postcentral and parietal cortex (Table 2).

All subjects, with rare exceptions, showed changes associated with the convexital parts of the frontal areas (Table 1). In the absence of these particular impairments, notable changes in hippocampal functions were seen in two patients and in reticular formation functions in one (Table 1).

The quite marked changes in the hippocampus suggested a relationship between these impairments and the sizes of the temporal intraventricular spaces, though three-dimensional MRI reconstructions showed that the analysis excluded volumes including the lower horns of the lateral ventricles (Fig. 1). For this reason, no data were obtained on any kind of relationship between tests for memory impairments and the volume of the ventricular system.

Our data indicate that the mean volume of the ventricular system was 25.53 ± 10.56 cm^3 for the group, which was slightly greater than the intraventricular spaces in normal subjects (19.6 ± 6.2 cm^3) aged from 18 to 55 years reported by other authors [15]. The maximum volume of the ventricular system was 49.5 cm^3 and the minimum was 7.6 cm^3.

Assessment of the relationships of the linear sizes of the head demonstrated a positive correlation ($r = 0.5759$ at $p = 0.0017$) between ventricular volume and linear head size (Fig. 2, *A*), which was more marked in children aged less than 13 years old ($r = 0.6833$ at $p = 0.01$; Fig. 2, *C*). The cor-

TABLE 2. Localizations and Severities (mean points scores) of Neuropsychological Impairments in the Study Group

Frontal area (convexital parts)	6.714
Hippocampus	3.607
Basal and medial parts of frontal areas	3.286
Reticular formation	3.000
Limbic system	2.964
Temporal-parietal-occipital zone (TPO)	2.000
Diencephalic structures	1.750
Premotor area	1.714
Temporal area	1.214
Occipital area	1.036
Corpus callosum	0.714
Superior parietal area	0.214
Inferior parietal area	0.214
Postcentral area	0.214

relation between left ventricular volume and linear head size was less than 0.5, while right ventricular volume had a significant correlation with head size ($r = 0.6412$ at $p = 0.0003$; Fig. 2, *B*). This relationship was stronger for children aged less than 13 years ($r = 0.7367$ at $p = 0.0041$; Fig. 2, *D*).

There were no significant relationships between total points scores for neuropsychological deficits in the overall study group and the mean normalized volume of the ventricular system. The only relationship was in the subgroup of children younger than 13 years ($r = 0.6464$ at $p = 0.017$; Fig. 3, *D*).

At the same time, analysis demonstrated a significant correlation between the normalized left lateral ventricular volume and the severity of neuropsychological impairments ($r = 0.5127$ at $p = 0.0063$) for the whole study group (Fig. 3, *A*). The correlation was more significant when left ventricular volume was compared with the severity of neuropsychological impairments in the left hemisphere ($r = 0.6303$ at $p = 0.0004$; Fig. 3, *C*). A link could be seen between the normalized volume of the left ventricle and impairments in cortical structures ($r = 0.5071$ at $p = 0.0069$; Fig. 3, *B*). This relationship was seen more clearly in the subgroup of subjects aged less than 13 years ($r = 0.6339$ at $p = 0.02$; Fig. 3, *G*). The level of correlation increased on comparison of left ventricular volume with overall neuropsychological impairment ($r = 0.6753$ at $p = 0.0113$) in children aged less than 13 years (Fig. 3, *E*). This age group showed the greatest correlation ($r = 0.8126$ at $p = 0.0007$) on comparison of left lateral ventricular volume and neuropsychological deficit due to dysfunction of the left hemisphere (Fig. 3, *F*). Impairments identified on neuropsychological investigation associated with the right hemisphere showed a significant correlation ($r = 0.5472$ at $p = 0.0529$) with the total normalized volume of the ventricular system only in the subgroup of children aged less than 13 years (Fig. 3, *H*).

DISCUSSION

Neuropsychological studies showed that changes in this group of patients corresponded most closely to the neuropsychological profile of patients with attention deficit hyperactivity disorder and differed significantly from the neuropsychological disorders of patients with schizotypy or schizophrenia [19]. There were virtually no functional impairments associated with changes in the corpus callosum or the parietal, temporal, or occipital areas of the cortex. Neuropsychological evaluation of impairments in the convexital areas of the frontal cortex, hippocampus, limbic system, and basal and medial parts of the frontal cortex showed similarity with disorders seen in schizotypy and schizophrenia [7, 9, 19, 30]. Unlike the situation in schizophrenia, the severity of functional impairments associated with the corpus callosum and parietal area of the cortex was less marked. Previous studies have demonstrated that in schizotypy, the volume of the inferior horns of the lateral ventricles, which is associated with smaller hippocampal volume, was often marginal and could only be detected by special morphometric procedures – voxel-based morphometry (VBM) [24]. This may also explain the absence of any significant correlation between the volume of the ventricular system and memory impairments identified in the study group. Thus, exclusion of the temporal horns from our analysis is not critical.

Overall neuropsychological assessment of the study group suggests dysfunction of structures adjacent to the

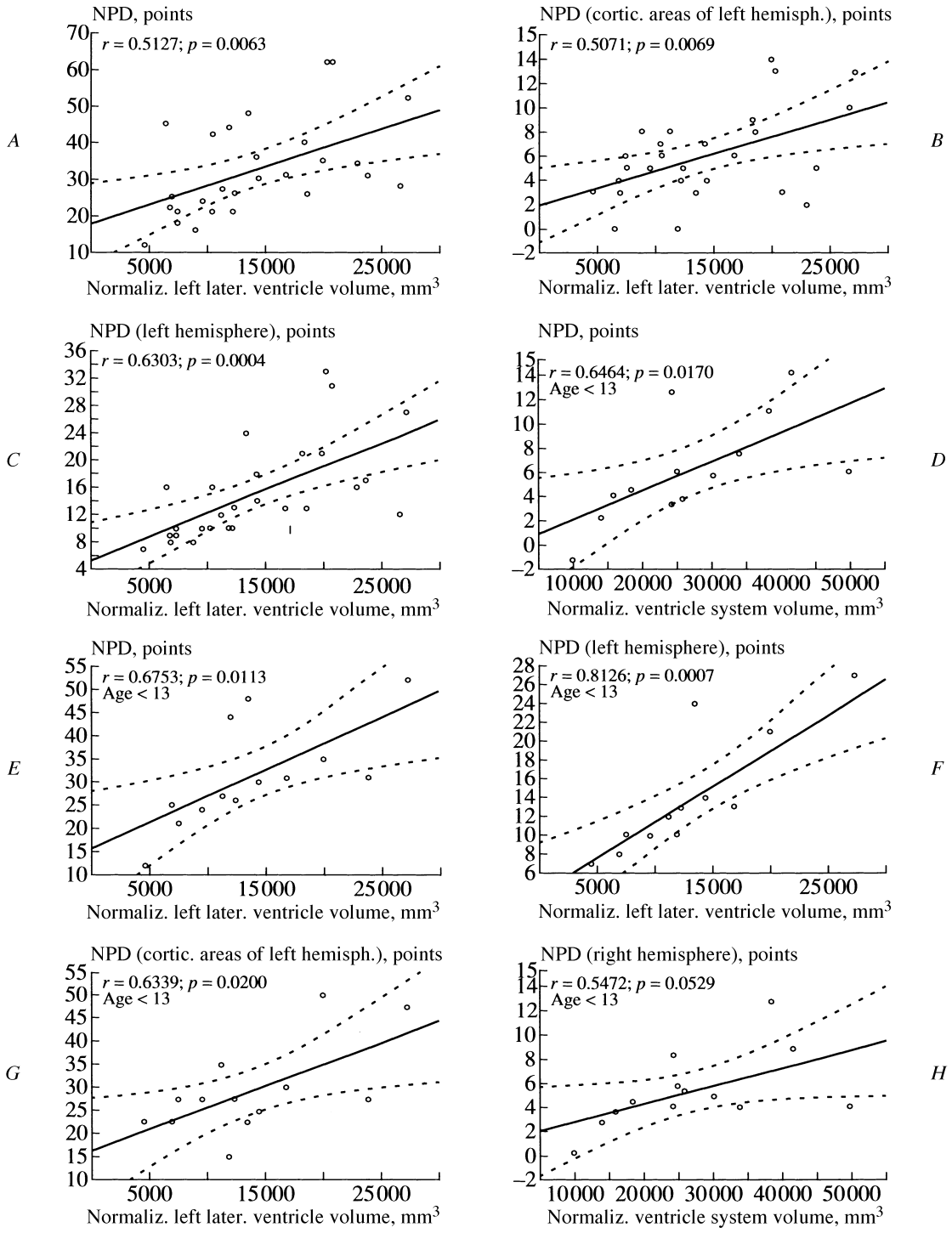

Fig. 3. Positive correlations between neuropsychological deficit in points (NPD) and normalized ventricle volume, mm^3: *A*) between NPD and normalized left lateral ventricle volume; *B*) between NPD in the cortical areas of the left hemisphere and normalized left lateral ventricle volume; *C*) between left hemisphere NPD and normalized left lateral ventricle volume; *D*) between NPD and normalized ventricle system volume in the group aged under 13 years; *E*) between NPD and normalized left lateral ventricle volume in the group aged under 13 years; *F*) between left hemisphere NPD and normalized left lateral ventricle volume in the group aged below 13 years; *G*) between NPD for the cortical areas of the left hemisphere and normalized left lateral ventricle volume in the group aged under 13 years; *H*) between right hemisphere NPD and normalized ventricle system volume in the group aged under 13 years.

liquor spaces of the brain (the hippocampus, limbic system, diencephalic structures) and leads to the conclusion that there may be a deficit in ascending activating influences from the reticular formation and reticular nuclei in the thalamus. Dysfunction in the frontal areas may also be associated with insufficiency of the reticular tracts, which arrive in the cortex without relaying in the thalamic nuclei [18]. In addition, the possibility of impairments to neurotransmitter depots in stem structures such as the locus ceruleus, cervical nuclei, and substantia nigra should not be overlooked.

All the above can be explained as residual changes resulting from sharp but transient increases in intracranial pressure (ICP) in the distant history, which may in turn have a large number of causes. The most frequent of these are hypoxia and craniocerebral trauma. In some cases, history-taking cannot identify the cause of illness and complaints are not systematic in nature, such that this group cannot be diagnosed as ADHD.

At the same time, pathological changes in the study group can be generalized under the umbrella term minimal cerebral dysfunction (MCD) on the basis of the minimal clinical manifestations and well defined subclinical signs.

The diagnosis of MCD appeared at the beginning of the last century, though there are now some doubts regarding its existence. One of the biggest disadvantages of this diagnosis is it syndromal indeterminacy. A wide range of brain diseases at their initial stages can be identified as MCD. Among general practitioners, this diagnosis is quite popular as a preliminary diagnosis, though it is not included in the International Classification of Diseases. This may be because most patients with MCD often show improvement without treatment and rarely attend clinics. However, this does not eliminate the problems associated with the illness, where there are often difficulties with intellectual activity, behavioral abnormalities, reduced memory, and emotional and autonomic disorders. The pathology can be associated with the most diverse neuropsychological impairments, a point which is also supported by our study (Table 1). Nonetheless, the majority of patients selected for analysis in the present study had dysfunctions consistent with ADHD. Minimal changes in the variety of possible impairments make ADHD and MCD a unique model for studying different brain functions.

The relationship between linear head size and ventricular volume has long been known [26], especially in relation to hydrocephalus in children. Our studies of patients with moderately severe hydrocephalus and clinically insignificant changes in the ventricles show that in this situation, the relationship is more due to physiological factors, the large head and brain sizes pointing to some increase in ventricle size. Normalization of intraventricular volumes in relation to linear head size in this case is an entirely justified approach. The volume of the right lateral ventricle shows the greater correlation with linear size. This suggests that changes in this variable are very likely to arise in the first year of life. Conversely, the left ventricle can increase in older patients, when skull size is less able to change and there is less potential for compensation of brain functions. Despite the fact that head size is predominantly associated with the volume of the right ventricle, while neuropsychological impairments are mostly associated with the volume of the left ventricle, the possibility that measurements of linear head size have value in the diagnosis of hydrocephalus, particularly at ages of up to 13 years, cannot be excluded. On the other hand, it may be very interesting to study minimal changes in ventricular system volume associated with periods of exacerbation of diseases and deteriorations in neuropsychological measures in an older age group. Such changes may result from periodic minor increases in ICP.

The total volume of the ventricular system showed a positive correlation with the neuropsychological deficit, which can be explained in terms of the common origin of hydrocephalus and damage to brain matter, and which also leads to the conclusion that morphometry is more sensitive than linear measurements of brain structures as used by experts.

The correlation with neuropsychological impairments is stronger for the left lateral ventricle, which emphasizes the leading role of the left hemisphere in performing higher mental functions and the greater plasticity of the left hemisphere.

The increase in the relationship between neuropsychological deficit with the volume of the ventricular system in children aged less than 13 years is explained in terms of stabilization of mental functions in the postpubertal period. This suggestion is supported by the existence of a relationship between neuropsychological impairments and right ventricular volume, which we found was present only in the group of patients under 13 years old.

Asymmetry of the ventricles may be one indicator of a possible neuropsychological deficit, especially in relation to the left hemisphere in the group of patients aged less than 13 years, where the correlation coefficient approached unity (Fig. 3, *F*). As demonstrated, cortical impairments are leading because of structural changes in the brain in this group (Fig. 3, *G*), which suggests that this younger age group has smaller reserve capacities in support of cortical functions. Contrariwise, there appears to be a greater degree of compensation of brain functions at the same volume of structural changes in the older age group, as demonstrated by other authors who found no relationship between the severity of abnormalities to the cerebral cortex in patients with schizophrenia and the stage of disease [14, 29].

Thus, the data obtained here support the hypothesis that there is a relationship between structural changes in the brain and neuropsychological deficits. MRI studies have been shown to have an important role in MCD and ADHD.

At the beginning of the last century, basic information on the functions of the cerebral cortex was obtained from a large mass of material generalizing observations reported by neurosurgeons in patients with damage to various parts

of the brain. The introduction of contemporary MRI morphometry methods has extended our knowledge in this area, using fine structural changes which could not previously be detected by any available method. In our previous studies, we demonstrated that neurophysiological analysis could be performed using diseases such as epilepsy [4] and schizophrenia [1, 2] as models with exclusion or lesioning of particular functions. Given the data presented here, it can be suggested that less aggressive brain pathology accompanied by neuropsychological deficit may provide a more suitable model for these purposes. These studies are simultaneously directed to seeking methods for the treatment and prophylaxis of diseases resulting from these abnormalities.

CONCLUSIONS

1. Statistical analysis demonstrated a significant positive correlation between the size of the ventricular system and the severity of neuropsychological deficit in patients with attention deficit hyperactivity disorder (ADHD).

2. A relationship was demonstrated between linear head size and the volume of the ventricular system of the brain in patients with moderate and mild signs of hydrocephalus, which was clearly apparent in patients aged up to 13 years.

3. The functional impairments in the study group identified by neuropsychological testing were due mainly to dysfunction of the frontal cortex, hippocampus, limbic system, and reticular formation.

4. Dysfunction of brain structures adjacent to the liquor spaces was found to have a dominant role and a possible role for impairments to the ascending activating system in ADHD was identified.

5. The suggestion that structural abnormalities might be found in ADHD was supported, which indicates that MRI methods can be used in the complex diagnosis and future studies of this pathology.

The authors would like to thank our colleague at the Faculty of Psychology, Moscow State University, A. V. Vartanov, for methodological assistance.

This study was supported by the Russian Foundation for Basic Research (Grant No. 08-06-00393a).

REFERENCES

1. V. M. Verkhlyutov, V. B. Strelets, M. V. Magomedova, and R. A. Magomedov, "Localization of sources of spontaneous EEG rhythms in patients with schizotypy and schizophrenia," in: *Dipole Sources of EEG Rhythms in Neurophysiology and Clinical Practice* [in Russian], Working Report, 17–18 June 2002, Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, pp. 31–32.
2. V. M. Verkhlyutov, Yu. V. Shchuchkin, V. L. Ushakov, V. B. Strelets, and Yu. A. Pirogov, "Assessment of the locations and dipole moments of the sources of alpha and theta rhythms using cluster analysis in health and schizophrenia," *Zh. Vyssh. Nerv. Deyat.*, **56**, No. 1, 47–55 (2006).
3. A. R. Luriya, *Higher Cortical Functions in Humans and Alterations in Local Brain Damage* [in Russian], Moscow State University, Moscow (1962).
4. I. A. Skvortsov, Yu. A. Kholodov, É. G. Simernitskaya, A. M. Gorbach, T. N. Osipenko V. M. Verkhlyutov, G. E. Rudenskaya, V. A. Konyshev, G. E. Kharina, R. A. Maragey, A. Yu. Sagura, and A. I. Shalyapina, *Neurological and Neuropsychological Assessment of Magnetoencephalographic Data in Epileptic Syndrome in Children. Questions in Neuropathology, Psychiatry, and Addiction Medicine* [in Russian], Metsniereba, Tbilisi (1987), pp. 302–304.
5. E. D. Khomskaya, *Neuropsychology* [in Russian], Moscow State University, Moscow (1987).
6. F. Abell, M. Krams, J. Ashburner, R. Passingham, K. Friston, R. Frackowiak, F. Happe, C. Frith, and U. Frith, "The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans," *Neuroreport*, **10**, 1647–1651 (1999).
7. H. Ananth, I. Popescu, H. D. Critchley, C. D. Good, R. S. Frackowiak, and R. J. Dolon, "Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry," *Am. J. Psychiatry*, **159**, 1497–1505 (2002).
8. M. S. Buchsbaum, S. Yang, E. Hazlett, B. V. Siegel, M. Germans, M. Haznedar, S. O'Flaithbheartaigh, T. Wei, J. Silverman, and L. J. Siever, "Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging," *Schizophr. Res.*, **27**, 45–53 (1997).
9. T. D. Cannon, T. G. M. Erp, M. Huttunen, J. Lönnqvist, O. Salonen, L. Valanne, V. P. Putanen, C. G. Standertskjoeld-Nordenstrom, R. E. Gur, and M. Yan, "Regional grey matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls," *Arch. Gen. Psychiatry*, **55**, 1084–1091 (1998).
10. R. A. Carper, P. Moses, Z. D. Tigue, and E. Courchesne, "Cerebral lobes in autism: early hyperplasia and abnormal age effects," *NeuroImage*, **16**, 1038–1051 (2001).
11. S. A. Chance, M. M. Esiri, and T. J. Crow, "Ventricular enlargement in schizophrenia: a primary change in the temporal lobe," *Schizophr. Res.*, **62**, 123–131 (2003).
12. M. K. Chung, K. M. Salton, A. L. Alexander, and R. J. Davidson, "Less white matter concentration in autism: 2D voxel-based morphometry," *NeuroImage*, **23**, 242–251 (2004).
13. E. Courchesne, C. M. Karns, H. R. Davis, R. Ziccardi, R. A. Carper, Z. D. Tigue, H. J. Chisum, P. Moses, K. Pierce, C. Lord, A. J. Lincoln, S. Pizzo, L. Schreibman, R. H. Hass, N. A. Akshoomoff, and R. Y. Courchesne, "Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study," *Neurology*, **57**, 245–254 (2001).
14. C. Davatzikos, D. Shen, R. C. Gur, Z. Wu, D. Liu, Y. Fan, P. Hughett, B. I. Turetsky, and R. E. Gur, "Whole-brain morphometric study of schizophrenia revealing a spatially complex set of focal abnormalities," *Arch. Gen. Psychiatry*, **62**, No. 11, 1218–1227 (2005).
15. C. C. Dickey, M. E. Shenton, Y. Hirayasu, I. Fischer, M. M. Vogelmaier, M. A. Niznikiewicz, L. J. Seidman, S. Fraone, and R. W. McCarley, "Large CSF volume not attributable to ventricular volume in schizotypal personality disorder," *Am. J. Psychiatry*, **157**, No. 1, 48–54 (2000).
16. C. Gaser, I. Nenadic, B. R. Buchsbaum, E. A. Hazlett, and M. S. Buchsbaum, "Ventricular enlargement in schizophrenia related to volume reduction of the thalamus, striatum, and superior temporal cortex," *Am. J. Psychiatry*, **161**, No. 1, 154–156 (2004).
17. R. E. Gur, B. I. Turetsky, W. B. Bilker, and R. C. Gur, "Reduced gray matter volume in schizophrenia," *Arch. Gen. Psychiatry*, **56**, 905–911 (1999).
18. M. S. M. Izac, "Basic anatomy and physiology of sleep," *Am. J. E. N. D. Technol.*, **46**, No. 1, 18–38 (2006).

19. L. Krabbendam and J. Jolles, "The neuropsychology of schizophrenia," *Biol. Psychiatry*, **52**, No. 7, 631–647 (2002).
20. C. McDonald, N. Marshall, P. C. Sham, E. T. Bullmore, K. Schulze, B. Chapple, F. Bramon, F. Filbey, S. Quraishi, M. Walshe, and R. M. Murray, "Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives," *Am. J. Psychiatry*, **163**, No. 3, 478–487 (2006).
21. C. J. Mummery, K. Patterson, C. J. Price, J. Ashburner, R. S. Frackowiak, and J. R. Hodges, "A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory," *Ann. Neurol.*, **47**, 36–45 (2000).
22. R. M. Murray, "Auditory hallucinations and the temporal cortical response to speech in schizophrenia: A functional magnetic resonance imaging study," *Am. J. Psychiatry*, **15**, 1676–1682 (1997).
23. K. L. Narr, R M. Bilder, A. W. Toga, R. P. Woods, D. E. Rex, P. R. Szeszko, D. Robinson, S. Sevy, H. Gunduz-Bruce, Y. P. Wang, H. DeLuca, and P. M. Thompson, "Mapping cortical thickness and gray matter concentration in first episode schizophrenia," *Cereb. Cortex*, **15**, No. 6, 708–719 (2005).
24. K. L. Narr, P. M. Thompson, P. Szeszko, D. Robinson, S. Jang, R. P. Woods, S. Kim, M. Kiralee, K. M. Hayashi, D. Asunction, A. W. Toga, and R. M. Bilder, "Regional specificity of hippocampal volume reductions in first-episode schizophrenia," *NeuroImage*, **21**, 1563–1575 (2004).
25. G. Neckelmann, K. Specht, A. Lund, L. Ersland, A. I. Smievoll, D. Neckelmann, and K. Hugdahl, "MR morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucination," *Int. J. Neurosci.*, **116**, 9–23 (2006).
26. G. Nellhaus, "Head circumference from birth to eighteen years," *Pediatrics*, **41**, No. 1, 106–114 (1968).
27. S. A. Rombouts, F. Barkhof, M. P. Witter, and P. Scheltens, "Unbiased whole brain analysis of grey matter loss in Alzheimer's disease," *Neurosci. Lett.*, **285**, 231–233 (2000).
28. H. J. Rosen, J. H. Kramer, M. L. Gorno-Tempini, N. Schuff, M. Weiner, and B. L. Miller, "Patterns of cerebral atrophy in primary progressive aphasia," *Am. J. Geriatr. Psychiatry*, **10**, 89–97 (2002).
29. T. Sigmundsson, J. Suckling, M. Maier, S. Williams, E. Bullmore, K. Greenwood, R. Fukuda, M. Ron, and B. Toone, "Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms," *Am. J. Psychiatry*, **158**, 234–243 (2001).
30. C. Testa, M. P. Laakso, F. Sabattoli, R. Fossi, A. Beltramello, H. Soininen, and G. B. Frisoni, "A comparison between the accuracy of voxel-based morphometry and hippocampal volumetry in Alzheimer's disease," *J. Agn. Reson. Imaging*, **19**, 274–0282 (2004).