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**Structural Brain Morphometry in Children with Attention Deficit Hyperactivity Disorder and Comorbid Mild Cognitive Impairments**

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***Background.*** *Even though mild cognitive impairments are common in patients with attention deficit hyperactivity disorder (ADHD), there are no studies of morphometric brain parameters in children with ADHD and comorbid mild cognitive impairments.* ***Objective. The aim of the study is to*** *determine and perform comparative analysis of MR-morphometric brain parameters in children with ADHD depending on the presence or absence of comorbid mild cognitive impairments.* ***Methods.*** *Participants are children aged from 7 to 8 years with ADHD without comorbid pathology (CP), ADHD with mild cognitive impairment (MCI), MCI without ADHD, and healthy children. All participants underwent brain magnetic resonance imaging followed by morphometry to obtain quantitative parameters of large brain structures, cerebral cortex gyri, basal ganglia, cerebellum, and lateral ventricles.* ***Results.*** *90 children were examined. ADHD with MCI group has shown significant decrease in the volumes of caudate nuclei bilaterally and hippocampus on the right, as well as decrease in the volumes of right superior parietal gyrus, supramarginal gyrus, and frontal cortex. ADHD without CP group has shown different changes: decrease in the volume of putamen on both sides and thalamus on the left, increase in the volume of six and decrease in the volume of the cortex of four gyri, cortex thinning of four gyri with cortex thickening of one gyrus, volume increase of four cerebellar lobules. MCI without ADHD group has shown bilateral enlargement of lateral ventricles, decrease in the volume of right pallidum and seven gyri cortex, mostly on the right side, as well as decrease in the volume of four cerebellar lobules. Direct comparison between the two ADHD groups has shown significant differences up to lower total cortex volume with 5 gyri of left hemisphere and 7 gyri of right hemisphere in the ADHD with MCI group. Participants of ADHD groups compared to healthy individuals and the MCI without ADHD group did not show any age-related dynamic decrease in the volumes of cerebral cortex.* ***Conclusion.*** *ADHD is characterized by parallel presence of two pathogenetic processes: cerebral cortex hypoplasia and delayed age-related changes in other areas. Significant differences in morphometric parameters were revealed between ADHD without CP and ADHD with MCI. It suggests individual treatment for such patients and revision of approaches to morphometric brain studies in patients with ADHD. Enlargement of lateral ventricles in MCI may indicate the effect of perinatal pathology on these conditions’ etiology.*

***Keywords:*** *brain morphometry, ADHD, mild cognitive impairments, children, ADHD and comorbid pathologies, structural MRI*

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**Table 1.** General characteristics of participants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Healthy (group 1)** | **ADHD without CP (group 2)** | **ADHD with MCI (group 3)** | **MCI without ADHD (group 4)** |
| Number of participants, *n* | 25 | 13 | 15 | 37 |
| Mean age ± standard error of mean, years | 8,13 ± 0,15 | 7,91 ± 0,20 | 8,12 ± 0,16 | 7,99 ± 0,11 |
| Female gender, % | 44 | 7,7 | 20 | 24,3 |

*Note.* ADHD (СДВГ) — attention deficit hyperactivity disorder; CP (КП) — comorbid pathology; MCI (ЛКН) — mild cognitive impairment.

**Table 2.** Characteristics of participants with ADHD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ADHD type** | **Quantity** | **Average inattention score ± standard error of mean** | **Average hyperactivity/impulsivity score ± standard error of mean** | **Grade point average ± standard error of mean** |
| Inattentive | 11 | 18,0 ± 0,8 | 10,9 ± 1,0 | 28,9 ± 1,6 |
| Hyperactive-impulsive | 4 | 13,0 ± 0,4 | 17,3 ± 0,3 | 30,3 ± 0,6 |
| Combined | 13 | 17,5 ± 0,9 | 18,4 ± 0,7 | 35,8 ± 1,5 |
| Total | 28 | 17,1 ± 0,6 | 15,3 ± 0,8 | 32,3 ± 1,1 |
|  |
| ADHD without CP (group 2) | 13 | 17,5 ± 1,1 | 16,9 ± 1,0 | 34,4 ± 1,7 |
| ADHD with MCI (group 3) | 15 | 16,7 ± 0,7 | 13,9 ± 1,2 | 30,5 ± 1,4 |

*Note.* ADHD (СДВГ) — attention deficit hyperactivity disorder; CP (КП) — comorbid pathology; MCI (ЛКН) — mild cognitive impairment.

**Table 3.** Distribution of ADHD types among participants groups

|  |  |  |
| --- | --- | --- |
| **ADHD type** | **ADHD without CP (group 2)** | **ADHD with MCI (group 3)** |
| ***n*** | **%** | ***n*** | **%** |
| Inattentive | 3 | 27,3 | 8 | 72,7 |
| Hyperactive-impulsive | 2 | 50 | 2 | 50 |
| Combined | 8 | 61,5 | 5 | 38,5 |

*Note.* ADHD (СДВГ) — attention deficit hyperactivity disorder; CP (КП) — comorbid pathology; MCI (ЛКН) — mild cognitive impairment.

**Table 4.** Distribution of MCI among study participants

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Groups** | **Developmental dysphasias** | **Dyspraxias** | **Dyslexias** | **Dysgraphias** | **Discalculias** | **Others** |
|  | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| ADHD with MCI (group 3, 15 participants)  | 12 | 80,0 | 7 | 46,7 | 2 | 13,3 | 2 | 13.3 | 1 | 6,7 | 0 | 0 |
| MCI without ADHA (group 4, 37 participants) | 30 | 81,1 | 21 | 56,8 | 6 | 16,2 | 5 | 13,5 | 5 | 13.5 | 6 | 16,2 |
| Total MCI (52 participants) | 42 | 80,8 | 28 | 53,8 | 8 | 15,4 | 7 | 13,5 | 6 | 11,5 | 6 | 11,5 |

*Note.* Other cognitive disorders included neurodynamic disorders that are not isolated as an independent disorder in ICD-10; thus, this variety was recorded only as an addition to MCI presented in ICD-10. ADHD (СДВГ) — attention deficit hyperactivity disorder; MCI (ЛКН) — mild cognitive impairment.

**Table 5.** Brain structures characteristics in participants according to MRI assessment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Structural changes variants** | **Healthy, *n* = 25** | **ADHD without CP, *n* = 13** | **ADHD with MCI, *n* = 15** | **MCI without ADHD, *n* = 37** |
| Ventricular asymmetry / mild ventricular dilation, *n* | 4 | 4 | 3 | 13 |
| Minimal cystic residual lesions, *n* | 0 | 0 | 2 | 4 |
| Hypothalamic hamartoma, *n* | 0 | 0 | 1 | 0 |
| Grey matter heterotopy, *n* | 0 | 0 | 0 | 1 |
| Virchow-Robin spaces extensions, *n* | 0 | 1 | 0 | 3 |
| Arachnoid cysts, *n* | 01 | 0 | 31 | 1 |
| Empty sella syndrome, *n* | 0 | 2 | 0 | 1 |
| Normal variants (minimal dilation of cisterna magna, hippocampal asymmetry, speculum cyst), *n* | 3 | 2 | 2 | 4 |
| Conditional minimal structural pathology, total | n | 4 | 5 | 9 | 17 |
| % | 16,0 2, 3 | 38,5 | 60,02 | 44,73 |

*Note*. <1> — *р* chi-square = 0,02; <2> — *р* chi-square = 0,01; <3>— *р* chi-square = 0,044. ADHD (СДВГ) — attention deficit hyperactivity disorder; CP (КП) — comorbid pathology; MCI (ЛКН) — mild cognitive impairment.

**Table 6.** Significant differences in relative volumes of different brain structures between participants in healthy (group 1) and ADHD without CP (group 2) groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Brain region** | **Brain structures** | **Group** | **Relative volume,** **median** | **Relative volume, *Q*1** | **Relative volume, *Q*3** | ***P* Mann-Whitney** |
| Left hemisphere cortex | Inferior parietal gyrus | 1 | 0,00892 | 0,00849 | 0,00951 | **0,006** |
| 2 | 0,00964 | 0,00868 | 0,01082 |
| Lateral orbitofrontal gyrus | 1 | 0,00555 | 0,00486 | 0,00588 | 0,012 |
| 2 | 0,00592 | 0,00573 | 0,00625 |
| Hippocampal gyrus | 1 | 0,00132 | 0,00121 | 0,00143 | 0,025 |
| 2 | 0,00120 | 0,00110 | 0,00133 |
| Orbital part of inferior frontal gyrus | 1 | 0,00160 | 0,00141 | 0,00173 | 0,041 |
| 2 | 0,00162 | 0,00155 | 0,00175 |
| Right hemisphere cortex | Lateral orbitofrontal gyrus | 1 | 0,00550 | 0,00488 | 0,00583 | 0,010 |
| 2 | 0,00587 | 0,00552 | 0,00638 |
| Middle temporal gyrus | 1 | 0,00784 | 0,00723 | 0,00839 | 0,015 |
| 2 | 0,00834 | 0,00802 | 0,00877 |
| Hippocampal gyrus | 1 | 0,00120 | 0,00107 | 0,00124 | 0,018 |
| 2 | 0,00115 | 0,00100 | 0,00123 |
| Quadrate lobule | 1 | 0,00796 | 0,00715 | 0,00829 | 0,032 |
| 2 | 0,00759 | 0,00689 | 0,00792 |
| Rostral anterior cingulate cortex | 1 | 0,00124 | 0,00113 | 0,00134 | 0,043 |
| 2 | 0,00129 | 0,00111 | 0,00144 |
| Frontal pole | 1 | 0,00084 | 0,00080 | 0,00090 | 0,018 |
| 2 | 0,00080 | 0,00072 | 0,00082 |
| Subcortical nuclei of the left hemisphere | Thalamus | 1 | 0,00557 | 0,00517 | 0,00575 | 0,043 |
| 2 | 0,00513 | 0,00505 | 0,00526 |
| Putamen | 1 | 0,00394 | 0,00359 | 0,00405 | 0,019 |
| 2 | 0,00375 | 0,00317 | 0,00396 |
| Subcortical nuclei of the right hemisphere | Putamen | 1 | 0,00386 | 0,00363 | 0,00404 | 0,030 |
| 2 | 0,00369 | 0,00319 | 0,00388 |
| Left cerebellar hemisphere | Hemispherical lobules I.III | 1 | 0,00060 | 0,00055 | 0,00066 | 0,046 |
| 2 | 0,00063 | 0,00056 | 0,00068 |
| Hemispherical lobule VIIIB | 1 | 0,00199 | 0,00168 | 0,00225 | 0,034 |
| 2 | 0,00207 | 0,00177 | 0,00271 |
| Right cerebellar hemisphere | Hemispherical lobules I.III | 1 | 0,00063 | 0,00053 | 0,00073 | 0,049 |
| 2 | 0,00063 | 0,00053 | 0,00080 |
| Hemispherical lobule VIIIА | 1 | 0,00288 | 0,00280 | 0,00332 | 0,020 |
| 2 | 0,00328 | 0,00292 | 0,00370 |

*Note*. Values of *р* < 0,01 are bolded.

**Table 7.** Significant differences in relative volumes of different brain structures between participants in healthy (group 1) and ADHD with MCI (group 3) groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Brain region** | **Brain structures** | **Group** | **Relative volume,** **median** | **Relative volume, *Q*1** | **Relative volume, *Q*3** | ***P* Mann-Whitney** |
| Right hemisphere cortex | Superior parietal gyrus | 1 | 0,00966 | 0,00885 | 0,01009 | 0,019 |
| 3 | 0,00878 | 0,00846 | 0,00940 |
| Supramarginal gyrus | 1 | 0,00711 | 0,00636 | 0,00806 | 0,022 |
| 3 | 0,00648 | 0,00585 | 0,00745 |
| Frontal pole | 1 | 0,00084 | 0,00080 | 0,00090 | 0,039 |
| 3 | 0,00079 | 0,00067 | 0,00083 |
| Subcortical nuclei of the left hemisphere | Caudate nucleu | 1 | 0,00260 | 0,00248 | 0,00279 | 0,049 |
| 3 | 0,00240 | 0,00225 | 0,00259 |
| Subcortical nuclei of the right hemisphere | Caudate nucleus | 1 | 0,00278 | 0,00261 | 0,00297 | **0,006** |
| 3 | 0,00252 | 0,00237 | 0,00272 |
| Hippocampus | 1 | 0,00287 | 0,00276 | 0,00297 | 0,041 |
| 3 | 0,00272 | 0,00248 | 0,00277 |

*Note*. Values of *р* < 0,01 are bolded.

**Table 8.** Significant differences in relative volumes of different brain structures between participants in healthy (group 1) and MCI without ADHD (group 4) groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Brain region** | **Brain structures** | **Group** | **Relative volume,** **median** | **Relative volume, *Q*1** | **Relative volume, *Q*3** | ***P* Mann-Whitney** |
| Left hemisphere cortex | Triangular inferior frontal gyrus | 1 | 0,00276 | 0,00261 | 0,00310 | 0,016 |
| 4 | 0,00256 | 0,00244 | 0,00285 |
| Superior parietal gyrus | 1 | 0,00983 | 0,00910 | 0,01079 | 0,040 |
| 4 | 0,00937 | 0,00826 | 0,01022 |
| Right hemisphere cortex | Entorhinal gyrus | 1 | 0,00081 | 0,00072 | 0,00086 | 0,032 |
| 4 | 0,00073 | 0,00065 | 0,00087 |
| Inferior parietal gyrus | 1 | 0,01072 | 0,01014 | 0,01142 | 0,047 |
| 4 | 0,01016 | 0,00934 | 0,01129 |
| Frontal pole | 1 | 0,00084 | 0,00080 | 0,00090 | 0,021 |
| 4 | 0,00079 | 0,00071 | 0,00084 |
| Temporal pole | 1 | 0,00123 | 0,00117 | 0,00135 | 0,035 |
| 4 | 0,00111 | 0,00103 | 0,00132 |
| Subcortical nuclei of the right hemisphere | Pallidum | 1 | 0,00132 | 0,00127 | 0,00146 | 0,040 |
| 4 | 0,00125 | 0,00115 | 0,00140 |
| Left cerebellar hemisphere | Peduncle lobule I | 1 | 0,01014 | 0,00911 | 0,01079 | 0,027 |
| 4 | 0,00893 | 0,00836 | 0,01004 |
| Hemispherical lobule VIIВ | 1 | 0,00486 | 0,00460 | 0,00534 | **0,007** |
| 4 | 0,00448 | 0,00405 | 0,00490 |
| Right cerebellar hemisphere | Peduncle lobule I | 1 | 0,00991 | 0,00896 | 0,01076 | 0,038 |
| 4 | 0,00904 | 0,00783 | 0,01003 |
| Hemispherical lobule VIIВ | 1 | 0,00504 | 0,00464 | 0,00572 | 0,011 |
| 4 | 0,00417 | 0,00349 | 0,00512 |
| Whole cerebellum | 1 | 0,09336 | 0,08706 | 0,09927 | 0,034 |
| 4 | 0,08801 | 0,08343 | 0,09465 |
| Lateral ventricle | Left lateral ventricle | 1 | 0,00280 | 0,00227 | 0,00383 | **0,007** |
| 4 | 0,00418 | 0,00307 | 0,00524 |
| Right lateral ventricle | 1 | 0,00264 | 0,00215 | 0,00334 | **0,003**  |
| 4 | 0,00355 | 0,00267 | 0,00484 |

*Note*. Values of *р* < 0,01 are bolded.

**Table 9.** Significant differences in relative volumes of different brain structures between participants in ADHD without CP (group 2) and ADHD with MCI (group 3) groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Brain region** | **Brain structures** | **Group** | **Relative volume,** **median** | **Relative volume, *Q*1** | **Relative volume, *Q*3** | ***P* Mann-Whitney** |
| Entire cortex of left hemisphere | 2 | 0,19814 | 0,19535 | 0,20325 | 0,036 |
| 3 | 0,18665 | 0,17547 | 0,19868 |
| Entire cortex of right hemisphere | 2 | 0,19957 | 0,19430 | 0,20299 | 0,024 |
| 3 | 0,18609 | 0,17725 | 0,19747 |
| Cerebral cortex in general | 2 | 0,39594 | 0,38966 | 0,40731 | 0,029 |
| 3 | 0,37239 | 0,35181 | 0,39502 |
| Total hemispheric grey matter (including cortex and subcortical gray matter) | 2 | 0,51317 | 0,49949 | 0,53252 | 0,044 |
| 3 | 0,49887 | 0,46410 | 0,52040 |
| Left hemisphere cortex | Inferior parietal gyrus | 2 | 0,00964 | 0,00868 | 0,01082 | 0,049 |
| 3 | 0,00860 | 0,00765 | 0,00970 |
| Inferior temporal gyrus | 2 | 0,00721 | 0,00689 | 0,00747 | 0,049 |
| 3 | 0,00661 | 0,00616 | 0,00743 |
| Superior temporal gyrus | 2 | 0,00841 | 0,00816 | 0,00920 | 0,017 |
| 3 | 0,00816 | 0,00754 | 0,00834 |
| Supramarginal gyrus | 2 | 0,00849 | 0,00821 | 0,00870 | 0,044 |
| 3 | 0,00800 | 0,00673 | 0,00847 |
| Insular gyrus | 2 | 0,00514 | 0,00489 | 0,00545 | 0,014 |
| 3 | 0,00471 | 0,00453 | 0,00523 |
| Right hemisphere cortex | Margin of superior temporal sulcus | 2 | 0,00189 | 0,00180 | 0,00205 | 0,011 |
| 3 | 0,00169 | 0,00157 | 0,00184 |
| Inferior temporal gyrus | 2 | 0,00685 | 0,00638 | 0,00705 | 0,029 |
| 3 | 0,00640 | 0,00551 | 0,00649 |
| Lateral orbitofrontal gyrus | 2 | 0,00587 | 0,00552 | 0,00638 | 0,019 |
| 3 | 0,00535 | 0,00473 | 0,00597 |
| Medial orbitofrontal gyrus | 2 | 0,00408 | 0,00364 | 0,00416 | 0,044 |
| 3 | 0,00376 | 0,00326 | 0,00397 |
| Middle temporal gyrus | 2 | 0,00834 | 0,00802 | 0,00877 | **0,005** |
| 3 | 0,00725 | 0,00695 | 0,00796 |
| Rostral part of medial gyrus | 2 | 0,01146 | 0,01076 | 0,01191 | 0,017 |
| 3 | 0,01053 | 0,00927 | 0,01099 |
| Superior frontal gyrus | 2 | 0,01550 | 0,01495 | 0,01620 | 0,029 |
| 3 | 0,01475 | 0,01298 | 0,01551 |

*Note*. Values of *р* < 0,01 are bolded.

**RESEARCH LIMITATIONS**

Small sample limits the number and size of revealed effects. Although relative volumes of cerebral cortex, subcortical nuclei, and cerebellar lobules are considered as preferable morphometric indicators for cross-sectional comparative studies, uneven correlation with intracranial volume of different gyri may cause erroneous results. Intracranial volume was used as a basis for calculation of relative volumes, which, from our point of view, better reflects the head sizes, however, alternative use as a basis for the volume of entire brain could give some insignificantly different results. Although there is no background to consider this or that calculation scheme preferable in terms of reflecting real brain changes. Traditional assessment by radiologist suggests certain amount of subjectivity.

**Table 10.** Comparison of revealed morphometric changes in pathology groups against healthy participants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Goups** | **Hemispheric gyri cortex volumes/thicknesses** | **Hemispheric subcortical nuclear volumes** | **Cerebellar structures volumes** | **Ventriculars volumes** |
| ADHD without CP | ↑↑ ↓↓ | ↓↓ | ↑↑ | – |
| ADHD with MCI | ↓ | ↓↓↓ | – | – |
| MCI without ADHD | ↓↓ | ↓ | ↓↓↓ | ↑↑↑ |

*Note*. Arrows indicate increase or decrease in parameters compared to normal values; grey color indicates highly significant differences (p< 0,01); ADHD (СДВГ) — attention deficit hyperactivity disorder; MCI (ЛКН) — mild cognitive impairment.

**Fig.** Brain gyri with lower relative cortex volume in ADHD with MCI compared to ADHD without CP.

*Note.* Continuous color indicates gyri with significant decrease in cortical volumes, shaded color — with tendency to decrease.

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**DISCLOSURE OF INTEREST**

**George A. Karkashadze** — lecturing for pharmaceutical companies Opella Healthcare Russia, Materia Medica Holding, GEROPHARM, Organon, Sotex.

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Other authors confirmed the absence of a reportable conflict of interests.

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**George A. Karkashadze** — study planning and control, patients’ enrolment, neurological examination, statistical processing and data analysis, manuscript text preparation.

**Alexey I. Firumyants** — evaluation of MR brain image, quality check of MR brain images, participation in MR morphometry, manuscript text preparation.

**Nikita S. Shilko** — IT support and software engineering of MR morphometry.

**Nataliya S. Sergienko** — patients’ enrolment, neurological examination.

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**Evgeniy V. Bogdanov** — software engineering of MR morphometry.

**Anastasiya I. Rykunova** — statistical processing and data analysis.

**Elena A. Vishneva** — study planning and control.

**Elena V. Kaytukova** — study planning and control.

**Kamilla E. Efendieva** — manuscript preparation.

**Leyla S. Namazova-Baranova** — study planning, overall guidance, manuscript text preparation.