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A Comparison of Regional Brain Volumes in Older Adults With and Without History of COVID-19

Региональные объемы мозга у пожилых людей с наличием и отсутствием COVID-19 в анамнезе

Original Research

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ABSTRACT

BACKGROUND: Recent studies have shown that SARS-CoV-2 can have neuropsychiatric consequences and has the ability to penetrate the blood-brain barrier. If SARS-CoV-2 has a specific route of entry into the brain, it may leave imprints in the form of specific changes in brain morphology. Older individuals are most vulnerable to the neuropsychiatric COVID-19 complications. This study aims to compare regional brain volumes in older adults individuals with and without COVID-19 history (COVID+ and COVID-, respectively).

METHODS: Individuals over 65 years old who applied for treatment to the Memory Clinic (Mental-Health Clinic No. 1 named after N.A. Alexeev, Moscow, Russia) were assessed between October 2020 and April 2021. Their COVID-19 history was determined by the self-report and COVID-19 certificate. Individuals with severe neuropsychiatric or acute or severe chronic somatic or infectious disease and those taking medications potentially affecting cognitive functioning were excluded. All participants underwent MRI examinations followed by image segmentation and morphometric quantitative analysis. Regional brain volumes were compared in COVID+ and COVID- people.

RESULTS: 207 participants were included in the study. The COVID+ group consisted of 24 participants. The comparison between groups revealed statistically significant differences in left amygdala area (median 1199.3 mm^3 in COVID+ vs. 1263.7 mm^3 in COVID-) and right postcentral gyrus volumes (median 8055.5 mm^3 in COVID+ vs. 8434.0 mm^3 in COVID-). Then case-control analysis was performed in individuals matched for gender, age and common somatic causes of structural brain changes (hypertension and/or diabetes mellitus type 2) for 22 subjects in each group. Statistically significant differences in regional brain volumes between groups were absent.

CONCLUSION: We did not find strong evidence for any regional brain volumes changes in people older than 65 years with a history of COVID-19 in comparison to those without history of COVID-19. Though, given study limitations, these results cannot be generalized to other people who recovered from COVID-19.

АННОТАЦИЯ

ВВЕДЕНИЕ: В недавних исследованиях было показано, что SARS-CoV-2 может иметь нейропсихиатрические последствия и обладает способностью проникать через гемато-энцефалический барьер. Если коронавирус имеет специфический путь проникновения в головной мозг, то это может оставлять отпечатки в виде характерных изменений морфологии мозга. Лица старшей возрастной группы являются наиболее уязвимой популяцией в отношении последствий COVID-19. Данное исследование нацелено на сравнение морфологии головного мозга у лиц пожилого возраста, перенесших (COVID+) и не перенесших (COVID-) новую коронавирусную инфекцию.

МЕТОДЫ: В период с октября 2020 по апрель 2021 года отбирались лица старше 65 лет, обратившиеся в Клинику памяти (Москва), у которых путем анкетирования определялся статус перенесенного COVID-19. Не включались лица, имеющие тяжелые нейропсихиатрические и соматические заболевания и принимающие лекарственную терапию, потенциально сказывающиеся на когнитивном функционировании. Всем участникам проведено МРТ-обследование с последующей сегментацией изображений и количественным анализом морфометрических данных. Сравнивались региональные объемы головного мозга.

РЕЗУЛЬТАТЫ: 207 участников включено в исследование. COVID+ группу составили 24 участника, из которых 4 были госпитализированы вследствие COVID-19. Сравнение выявило наличие статистически значимых различий объемов левого миндалевидного тела (медиана 1199.3 мм^3 у COVID+ vs. 1263.7 мм^3 у COVID-, U=1839.0, p=0,044, тест Манна-Уитни) и правой постцентральной извилины (медиана 8055.5 мм^3 у COVID+ vs. 8434.0 мм^3 у COVID-, U=1821.5, p=0,045, тест Манна-Уитни). При проведении анализа методом случай-контроль у лиц, сопоставленных по полу, возрасту и распространенным соматическим причинам структурных изменений головного мозга, не было выявлено статистически значимых различий между COVID+ и COVID- группами.

ЗАКЛЮЧЕНИЕ: Мы не обнаружили значимых свидетельств изменений региональных объемов головного мозга у лиц, перенесших и не перенесших COVID-19. Однако, учитывая имеющиеся ограничения исследования, эти результаты не могут быть перенесены на всех пациентов после COVID-19.

INTRODUCTION

Studies have shown that advanced age is one of the greatest risk factors for higher severity and worse outcome of COVID-19 [1–4] with neurological and psychiatric symptoms affecting 33–62% of patients within six months of recovery [5]. Some researchers suggest that SARS-CoV-2 may have an ability to invade the brain via the olfactory tract, circumventricular organs, leaky blood-brain barrier due to inflammation or direct damage of brain vascular endothelium or with migrating immune cells [6].

If specific routes of SARS-CoV-2 to enter the brain do exist than it may be associated with the distinct patterns of brain morphology changes. A recent article systematically reviewed brain imaging case series, case-control and cohort studies in patients with COVID-19 and found that alterations associated with COVID-19 predominated in the olfactory brain network, limbic and prefrontal structures [7]. About half of these studies used only visual evaluation of MRI scans, and among studies that used image statistical processing approach there were none that used matched control of age, gender and comorbidity (hypertension and/or diabetes mellitus type 2) in brain morphology analysis in older population affected and non-affected by COVID-19.

Moreover, none of these studies evaluated brain changes specifically in older (65+ years old) population. Therefore, case-control study of MRI scans using image statistical processing approach and matched case-control analysis of elderly individuals with and without COVID-19 history is relevant.

Since October 2020 a longitudinal cohort study of patients with mild cognitive impairment (MCI) compared to healthy control was initiated in Psychiatric clinical hospital No 1 (Moscow, Russia) to identify unmet needs of MCI patients during COVID-19 pandemic. One of the aims of this study is a MRI-morphometry of brain scans in patients with mild cognitive impairment (MCI) and healthy control with and without reported COVID-19 history.

Our research question was: are there specific brain alterations in older people with reported history of COVID-19 infection compared to those without COVID-19 history?

METHODS

Study population

This study is a part of multidisciplinary project 'Impact of the COVID-19 pandemic on the mental health of the elderly' and is supported with grant of RFFI 20-04-60546. Individuals over 65 years old were eligible in the study. The study participants were selected among those who attended the Memory Clinic to treat cognitive impairment or at the outpatient unit of Moscow outpatient clinic No 152 (both are the branches of the Mental-Health Clinic No. 1 named after N.A. Alexeev) to treat somatic disorders other than acute or severe chronic somatic or infectious disease. Individuals with contraindications to MRI, with a history of dementia, Parkinson's disease, Huntington's disease, psychotic or other severe psychiatric disorders known to affect cognitive functioning, mood and anxiety disorders with onset before 45 years old, exacerbations or severe forms of chronic somatic diseases were not included. Also, people taking drugs with known negative or positive effect on cognitive functions were not allowed to participate in the study (see Supplements for a full list of exclusion criteria). The COVID-19 history was determined by the self-report and COVID-19 certificate. Current COVID-19 status was not checked with polymerase chain reaction rest (PCR) and none of participants were vaccinated as the study period ended before national vaccination campaign had been initiated.

Study design

This one-year study has longitudinal observational cohort design. Enrollment of subjects was performed 4th October 2020 to 30th April 2021. All participants underwent clinical examination by a psychiatrist and collection of medical history using checklist designed specifically for this study, including a checklist of individually significant neuropsychiatric and cognitive symptoms. Cognitive performance was assessed using Mini-mental state examination scale (MMSE) [8] and Montreal cognitive assessment scale (MoCA) [9]. After examination MRI-scanning was performed.

MRI scanning and Image processing

A MRI scanner (Toshiba, 1.5 Tl) at the Mental-health Clinic No1 Named After N.A. Alexeev was used to obtain structural MRI scans. The structural study was performed using a Sg 3d T1-weighted sequence (TR=12 ms, TE=5 ms, 200 sagittal slices, FOV 256 mm, FA 180, TI=300 ms, voxel size 1x1x1 mm^3, average 2).

Image processing and segmentation were performed using Freesurfer v6.0 software package and morphological indices (thickness and volume of gray matter, volume of white matter, gyrification index, volume of gray matter by subcortical structures, etc.) were derived. Regional brain volumes (gray matter and white matter volumes) were selected for the purpose of this work.

FreeView imager (v7.1.0) was used to visually assess segmentation quality. Reproducibility of results was ensured by means of quality control of structural MRI (T1) images based on mriqc package and Image Quality Metrics (IQM) [10].

All calculations were performed on a cluster at Skoltech (Skolkovo Institute of Science and Technology), consisting of two computing units of the following configuration each: CPU: Intel Xeon 6 cores; RAM 64 GB; Storage: 1 TB GPU: 3 NVIDIA GeForce GTX 1080 Ti with 3584 Cuda cores, Memory capacity 11 GB, frequency 1500 MHz.

Statistical processing

Database was extracted on 9 September 2021. The primary endpoint was finding the differences in MRI volumes between those who experienced COVID-19 (COVID+) and those who had not (COVID-) in a whole study population. Mann-Whitney test was used to compare continuous variables while participant's distribution by the categorical variables between groups was performed using Fisher

exact test. All regional brain volumes were n-1 normalized to standardize the variables using the unbiased standard deviation. Group profiles of brain volumes means and medians of received z-scores were than additionally visually analyzed using parallel coordinates plots. In all statistical tests two-tails p <0.05 considered as statistically significant. We didn't use multiple p correction because it would preclude finding of any significant differences given large number of regions (109 regions) to compare highly variable volumes.

To compare regional brain volumes, we also used case-control approach in subpopulations of COVID+ and COVID- groups matched by age, gender and history of hypertension and type II diabetes. The following strategy was used to search for matched subjects: exact matches on gender, hypertension stage and type II diabetes and fuzzy search for age within 2 years range.

Statistical processing was performed using Addinsoft (2022), XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com/en.

Ethics

The study was conducted according to Helsinki declaration and Good Clinical Practice (GCP) principles. It was approved by the local Ethical Committee of State Budgetary Institution of Health Care "Research Clinical Institute of Otorhinolaryngology named after L.I. Sverzhevsky" of the Department of Health of the City of Moscow (Protocol №5 from 20.09.20). All study participants signed informed consent.

RESULTS

Study population

Overall, 207 participants had processed Visit 1 MRI scan information in the study database as of 9th September 2021. Among them 24 indicated that they had a history of COVID-19 (either outpatient or hospitalization) before Visit 1 of the study (before October, 2020), with 4 of 24 (16.7%) were hospitalized with COVID-19. Thus, 24 participants were categorized in COVID+ group and n=183 in COVID- group. Their socio-demographic and medical characteristics are summarized in the Table 1.

Table 1. Clinical and socio-demographic characteristics of study population

	Valid n	COVID- (n=183)	COVID+ (n=24)	Test Statistic
Age, median, 1st and 3rd quantile	207	71 (66, 77)	71 (68.4, 77.0)	U=1973, p=0.418*
Gender: Male, n (%)	207	33 (18.0%)	3 (12.5%)	p=0.774**
Education, n (%)	205			p=0.539**
College		52 (28.7%)	8 (33.3%)	
School		15 (8.3%)	3 (12.5%)	
University		114 (63.0%)	13 (54.2%)	
Work type in the life: Intellectual, n (%)	200	144 (81.8%)	21 (87.5%)	p=0.774**
Still working, n (%)	200	6 (3.4%)	2 (8.3%)	p=0.247**
Family: Yes, n (%)	203	125 (69.8%)	18 (75.0%)	p=0.812**
Self-efficient: Yes, n (%)	202	135 (75.8%)	18 (75.0%)	p=1.000**
Hobby: Yes, n (%)	207	132 (72.1%)	18 (75.0%)	p=1.000**
Somatic health				
Any chronic disease: Yes, n (%)	207	166 (90.7%)	22 (91.7%)	p=1.000**
Diabetes type II: Yes, n (%)	204	24 (13.3%)	5 (20.8%)	p=0.350**
Hypertension, n (%)	207			p=0.459**
1 stage		46 (25.1%)	5 (20.8%)	
2 stage		58 (31.7%)	9 (37.5%)	
3 stage		16 (8.7%)	4 (16.7%)	
No		63 (34.4%)	6 (25.0%)	

Table 1. Clinical and socio-demographic characteristics of study population (continued)

	Valid n	COVID- (*n*=183)	COVID+ (*n*=24)	Test Statistic
Ischemic heart disease: Yes, *n* (%)	204	51 (28.3%)	7 (29.2%)	*p*=1.000**
Myocardial infarction history: Yes, *n* (%)	207	6 (3.3%)	1 (4.2%)	*p*= 0.584**
Oncology history: Yes, *n* (%)	204	27 (15.0%)	7 (29.2%)	*p*=0.087**
Obesity: Yes, *n* (%)	204	38 (21.1%)	4 (16.7%)	*p*=0.790**
Takes any antihypertensive drug: Yes, *n* (%)	204	97 (53.9%)	14 (58.3%)	*p*=0.828**
Takes any antidiabetic drug: Yes, *n* (%)	204	7 (3.9%)	2 (8.3%)	*p*=0.286**
Takes any anticoagulant: Yes, *n* (%)	204	14 (7.8%)	1 (4.2%)	*p*=1.000**
Takes aspirin: Yes, *n* (%)	204	44 (24.4%)	10 (41.7%)	*p*=0.086**
Mental health				
MMSE total score, median, 1st and 3rd quantile	204	27.0 (26.0, 28.0)	28.0 (27.0, 29.0)	U=1719, *p*=0.099*
MoCA total score, median, 1st and 3rd quantile	204	24.0 (21.0, 26.0)	25.0 (22.4, 27.0)	U=1789, *p*=0.170*
Any affective disorder history: Yes, *n* (%)***	204	23 (12.8%)	4 (16.7%)	*p*=0.533**
Any anxiety disorder history: Yes, *n* (%)***	204	5 (2.8%)	3 (12.5%)	*p*=0.054**
OCD: Yes, *n* (%)***	204	1 (0.6%)	0 (0.0%)	*p*=1.000**
Significant symptoms				
Apathy: Yes, *n* (%)	203	16 (8.9%)	4 (16.7%)	*p*=0.267**
Headache: yes, *n* (%)	203	47 (26.3%)	1 (4.2%)	*p*=0.019**
Vertigo, dizziness: Yes, *n* (%)	203	39 (21.8%)	5 (20.8%)	*p*=1.000**
Sleep: Yes, *n* (%)	203	89 (49.7%)	13 (54.2%)	*p*=0.828**
Poor attention, concentration: Yes, *n* (%)	203	41 (22.9%)	7 (29.2%)	*p*=0.609**
Inaccurate movements: Yes, *n* (%)	203	15 (8.4%)	1 (4.2%)	*p*=0.699**
Fatigue, retardation: Yes, *n* (%)	203	55 (30.7%)	9 (37.5%)	*p*=0.492**
Hypothymia: Yes, *n* (%)	203	26 (14.5%)	2 (8.3%)	*p*=0.541**
Gastro-intestinal: Yes, *n* (%)	203	38 (21.2%)	3 (12.5%)	*p*=0.423**
Irritability: Yes, *n* (%)	203	37 (20.7%)	8 (33.3%)	*p*=0.190**
Affective liability: Yes, *n* (%)	203	45 (25.1%)	5 (20.8%)	*p*=0.803**
Heart palpitations: Yes, *n* (%)	203	26 (14.5%)	6 (25.0%)	*p*=0.229**
Weakness in legs: Yes, *n* (%)	203	39 (21.8%)	6 (25.0%)	*p*=0.794**
Anxiety: Yes, *n* (%)	203	38 (21.2%)	5 (20.8%)	*p*=1.000**
Spatial orientation: Yes, *n* (%)	203	20 (11.1%)	2 (8.3%)	*p*=1.000**
Memory fixation: Yes, *n* (%)	203	101 (56.4%)	15 (62.5%)	*p*=0.663**
Calculation: Yes, *n* (%)	203	44 (24.6%)	5 (20.8%)	*p*=0.804**
Tinnitus: Yes, *n* (%)	203	44 (24.6%)	8 (33.3%)	*p*=0.454**

Note: Valid n — number of non-missing value. * — Mann-Whitney test. ** — Fisher exact test. *** — With onset after 45-year-old.

Matching for the age (fuzzy matching ±2 years), gender (exact match), hypertension stage (exact match) and history of type II diabetes (exact match) revealed 22 matched pairs of participants leaving 2 COVID+ participants without match. These characteristics are depicted in the Table 2.

In both instances of comparison between COVID+ and COVID- subjects (Tables 1 and 2) there were no significant differences on most of variables. Most of the participants were women, retired, with the background of higher education. More than two thirds of them lived with their families and described themselves as self-efficient

Table 2. Clinical and socio-demographic characteristics of study subpopulations matched by age, gender, hypertension stage and type II diabetes history

	Valid n	COVID- (*n*=22)	COVID+ (*n*=22)	Test Statistic
Age, median, 1st and 3rd quantile	44	71,5 (68; 75,8)	71 (68,3; 77)	U=238,5, *p*=0,953*
Gender: Male, *n* (%)	44	2 (9,10%)	2 (9,10%)	*p*=1,000**
Education, *n* (%)	44			*p*=0,555**
College		5 (22,70%)	8 (36,40%)	
School		2 (9,10%)	3 (13,60%)	
University		15 (68,20%)	11 (50,00%)	
Work type in the life: Intellectual, *n* (%)	44	17 (81,00%)	19 (86,40%)	*p*=0,698**
Still working, *n* (%)	44	1 (4,50%)	1 (4,50%)	*p*=1,000**
Family: Yes, *n* (%)	44	11 (50,00%)	17 (77,30%)	*p*=0,116**
Self-efficient: Yes, *n* (%)	44	18 (81,80%)	16 (72,70%)	*p*=0,721**
Hobby: Yes, *n* (%)	44	132 (72.1%)	18 (75.0%)	*p*=1.000**
Somatic health				
Any chronic disease: Yes, *n* (%)	44	22 (100,00%)	20 (90,90%)	*p*=0,488**
Diabetes type II: Yes, *n* (%)	44	3 (13,60%)	3 (13,60%)	*p*=1,000**
Hypertension, *n* (%)	44			*p*=1,000**
1 stage		4 (18,20%)	4 (18,20%)	
2 stage		9 (40,90%)	9 (40,90%)	
3 stage		3 (13,60%)	3 (13,60%)	
No		6 (27,30%)	6 (27,30%)	
Ischemic heart disease: Yes, *n* (%)	44	4 (18,20%)	5 (22,70%)	*p*=1,000**
Myocardial infarction history: Yes, *n* (%)	44	0 (0,00%)	1 (4,50%)	*p*=1,000**
Oncology history: Yes, *n* (%)	44	6 (27,30%)	6 (27,30%)	*p*=1,000**
Obesity: Yes, *n* (%)	44	5 (22,70%)	4 (18,20%)	*p*=1,000**
Takes any antihypertensive drug: Yes, *n* (%)	44	14 (63,60%)	12 (54,50%)	*p*=0,760**
Takes any antidiabetic drug: Yes, *n* (%)	44	0 (0,00%)	1 (4,50%)	*p*=1,000**
Takes any anticoagulant: Yes, *n* (%)	44	2 (9,10%)	1 (4,50%)	*p*=1,000**
Takes aspirin: Yes, *n* (%)	44	6 (27,30%)	8 (36,40%)	*p*=0,747**
Mental health				
MMSE total score, median, 1st and 3rd quantile	44	27 (26; 28)	27,5 (27; 29)	U=183,5, *p*=0,170*
MoCA total score, median, 1st and 3rd quantile	44	25 (21; 27)	25 (23; 27)	U=221, *p*=0,843*
Any affective disorder history: Yes, *n* (%)	44	2 (9,10%)	3 (13,60%)	*p*=1,000**
Any anxiety disorder history: Yes, *n* (%)	44	0 (0%)	3 (13,60%)	*p*=0,233**
OCD: Yes, *n* (%)	44	0	0	
Significant symptoms				
Apathy: Yes, *n* (%)	44	2 (9,10%)	4 (18,20%)	*p*=0,664**
Headache: yes, *n* (%)	44	9 (40,90%)	1 (4,50%)	*p*=0,009**
Vertigo, dizziness: Yes, *n* (%)	44	8 (36,40%)	5 (22,70%)	*p*=0,510**
Sleep: Yes, *n* (%)	44	13 (59,10%)	12 (54,50%)	*p*=1,000**
Poor attention, concentration: Yes, *n* (%)	44	3 (13,60%)	7 (31,80%)	*p*=0,281**
Inaccurate movements: Yes, *n* (%)	44	1 (4,50%)	1 (4,50%)	*p*=1,000**

Table 2. Clinical and socio-demographic characteristics of study subpopulations matched by age, gender, hypertension stage and type II diabetes history (continued)

	Valid n	COVID- (*n*=22)	COVID+ (*n*=22)	Test Statistic
Fatigue, retardation: Yes, *n* (%)	44	5 (22,70%)	9 (40,90%)	*p*=0,332**
Hypothymia: Yes, *n* (%)	44	4 (18,20%)	2 (9,10%)	*p*=0,664**
Gastro-intestinal: Yes, *n* (%)	44	5 (22,70%)	3 (13,60%)	*p*=0,698**
Irritability: Yes, *n* (%)	44	6 (27,30%)	7 (31,80%)	*p*=1,000**
Affective liability: Yes, *n* (%)	44	6 (27,30%)	5 (22,70%)	*p*=1,000**
Heart palpitations: Yes, *n* (%)	44	3 (13,60%)	5 (22,70%)	*p*=0,698**
Weakness in legs: Yes, *n* (%)	44	5 (22,70%)	5 (22,70%)	*p*=1,000**
Anxiety: Yes, *n* (%)	44	6 (27,30%)	5 (22,70%)	*p*=1,000**
Spatial orientation: Yes, *n* (%)	44	2 (9,10%)	2 (9,10%)	*p*=1,000**
Memory fixation: Yes, *n* (%)	44	13 (59,10%)	15 (68,20%)	*p*=0,755**
Calculation: Yes, *n* (%)	44	4 (18,20%)	4 (18,20%)	*p*=1,000**
Tinnitus: Yes, *n* (%)	44	5 (22,70%)	6 (27,30%)	*p*=1,000**

Note: Valid n — number of non-missing value. * — Mann-Whitney test. ** — Fisher exact test.

in most life areas. Somatic disorders had generally equal distribution between groups and prevalent (more than 90% had any chronic medical condition). Mental disorders and individually significant symptoms report
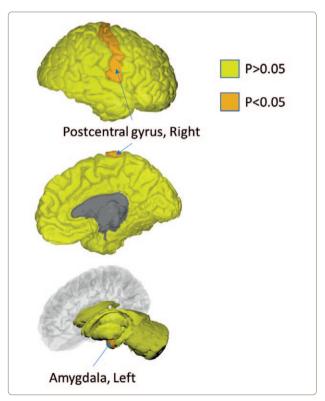

Figure 1. Significant differences between COVID+ and COVID- groups on regional brain volumes (Mann-Whitney test) in whole study population (*n*=207).

(yes / no in a specific checklist, Table 1 and 2) were equally distributed except headaches (significantly more frequent in the COVID- group). Cognitive status (total scores on MMSE and MoCA) was similar in both groups.

Both MMSE and MoCA total scores in all subjects (*n*=207) showed a significant weak correlation with total brain volume (Spearman R=0.23, *p*=0.001 and Spearman R=0.20, *p*=0.004, respectively) and cerebrospinal fluid (CSF) total volume (Spearman R=-0.23, *p* <0.001 and Spearman R=-0.27, *p* <0.001, respectively).

Regional brain volumes in COVID+ and COVID- groups

Comparison of brain regional volumes in whole study population (*n*=207) revealed differences only in two regions: right postcentral gyrus (median 8055.5 mm^3 in COVID+ vs. 8434.0 mm^3 in COVID-, U=1821.5, *p*=0.045, Mann-Whitney test) and left amygdala (median 1199.3 mm^3 in COVID+ vs. 1263.7 mm^3 in COVID-, U=1839.0, *p*=0.044, Mann-Whitney test) (Figure 1).

Detailed statistical results can be found in Supplementary 1.

Though, comparison of matched (age, gender and medical conditions) subpopulations (n=44) did not find any significant differences in regional brain volumes (Supplementary 2).

Parallel coordinate plots of normalized (n-1) MRI regional volumes are depicted on the Figure 2.
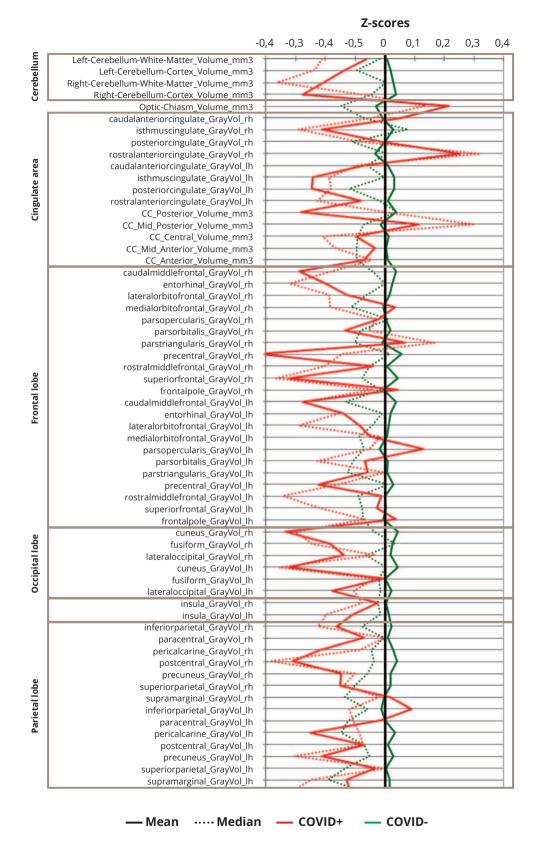
Figure 2. Standardized brain volumes profiles in COVID+ and COVID- participants (*n*=207).

Note: All means (solid line) or medians (dashed line) of residuals of regional brain volumes in both COVID+ (red) and COVID- (green) participants were within 1 standard deviation from mean values.
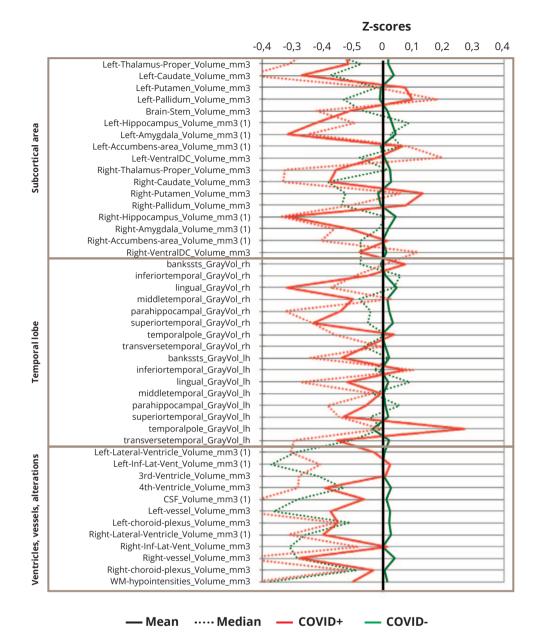
Figure 2. Standardized brain volumes profiles in COVID+ and COVID- participants (*n*=207) (continued).

Note: All means (solid line) or medians (dashed line) of residuals of regional brain volumes in both COVID+ (red) and COVID- (green) participants were within 1 standard deviation from mean values.

None of means or medians of z-scores exceed 1, reflecting that there were no differences in regional brain volumes larger than one standard deviation of study population means, though, generally most of z-scores are slightly decreased in COVID+ against COVID- subjects.

DISCUSSION

Our study revealed differences in regional brain volumes between COVID+ and COVID- groups: right postcentral gyrus gray matter and left amygdala volumes found to be significantly lower in older people who had a history of COVID-19. These differences were not supported with any differences in reporting of personally meaningful neurocognitive and neuropsychiatric symptoms, including anxiety and somatic complaints with except of headaches that were more prevalent in COVID- group.

Olfactory tract projections are considered as a possible gateway of SARS-CoV-2 invasion into the brain. Amygdala

is a part of limbic system that receives projections from olfactory bulbs [11,12]. According to recent research [13] a comparison of MRI scans before and after COVID-19 found that patients after COVID-19 had greater grey matter loss in the central nucleus of the amygdala than those who had no history of COVID-19. Another study [14] found hypometabolism in the right temporal lobe, including amygdala in patients with long COVID-19. Though, in these studies changes in amygdala were accompanied with alterations in other brain regions, including central olfactory complex (piriform cortex, enthorhinal cortex) and secondary olfactory areas (hippocampus, thalamus, orbitofrontal cortex) [7, 13, 14].

Contrary, in our study we did not find significant morphological changes in other brain regions. One possible explanation is that our study included population who experienced mild forms of COVID-19 (only 4 of 24 reported that they were hospitalized) that did not associate with brain tissue lesions. This explanation is supported by the fact that we did not find bilateral morphological changes that can be expected from olfactory route of virus penetration through blood-brain barrier. Also, this may result from a selection bias while enrolling patients into the study, those who had more severe forms of COVID-19 may not had applied for treatment to Memory clinic due to either restriction on transit for people older than 65 years or precaution/incapacity to move across the city.

Many MRI studies of brain structural changes in patients experienced COVID-19 reported alteration in different brain areas other than olfactory system [7]. Nevertheless, most of these studies did not include control sample and studied patients with COVID-19 severe enough to be hospitalized. The recent brain imaging study before and after COVID-19 included patients with second MRI scan after 35–407 days after recovery from in most cases mild forms of the disease in comparison to healthy control [13]. This study revealed decrease of cortical thickness in the lateral orbitofrontal cortex, generally greater brain size reduction, increase in diffusion indices and CSF volume. Though, a comparison of hospitalized cases with either non-hospitalized or control subgroups failed to detect marked differences due to decrease in the sample size. While this study that was conducted on a population that was very close to our study revealed significant differences in brain morphology, it didn't account control for comorbid disorders like hypertension and

type II diabetes that also associated with brain structure changes. Moreover, these comorbid disorders are known to be associated with increased risk of COVID-19 complications [15,16]. Thus, underestimation of these medical conditions may lead to bias in the results.

In our study we attempted to control these conditions. When compared subpopulations matched on gender, age and comorbid medical condition (hypertension and/or type II diabetes) regional brain volume differences disappeared. This may be due to that controlled conditions account for more of the variability in regional brain volumes than COVID-19 history. The median MMSE score before matching was mathematically lower in the COVID- compared to COVID+ group and in opposite to our results one could expect that if COVD-19 is associated with brain leisure than the matching on MMSE score will make differences even larger. Nevertheless, as expected, total MMSE (and MoCA) scores in whole study population showed significant positive correlation with total grey matter volume and negative correlations with total CSF volume showing adequate association between structural brain alterations and cognitive functions. This may indicate that an alternative explanation can take place: the decrease in sample size reduces the statistical power to detect brain differences between groups.

Study limitations

One of the study limitations was that COVID-19 status was not confirmed in the laboratory at the study entry but only with history and COVID-19 certificate provided by the participants. Thus, it is possible that we misclassified those participants who recovered from COVID-19 but is not aware about that. Only four subjects in our study had COVID-19 severity enough to be hospitalized, thus the rest 20 subjects possibly experienced only mild forms of a disease limiting generalizability of study results. There can be a selection bias originating from personal precautions and governmental restrictions on movement amid COVID-19 pandemic. Also, we did not analyze the time between COVID-19 and MRI scan though this time unlikely exceeded a 13-month period as by 31.03.2020 only 1836 cases of COVID-19 were totally registered in Russia. Finally, only 24 participants had a known reported history of COVID-19 thus this study may be underpowered to detect brain morphology changes.

CONCLUSION

We didn't find definite associations of any regional brain volumes differences with COVID-19 history in people older than 65 years. Our study results are based on a population exposed to relatively mild forms of COVID-19. Thus, given study limitations, these results can't be generalized to other people who recovered from COVID-19. Further better balanced and controlled and larger studies on an association of brain morphology with COVID-19 experience stratified by the severity in older people would help to disentangle relationships between COVID-19 severity and brain morphology changes.

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Supplementary data
Supplementary material related to this article can be found, in the online version, at doi: 10.17816/CP145

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