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Relationships between the Fear of COVID-19 Scale and regional brain atrophy in mild cognitive impairment

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Abstract

Background: Several studies have reported that the pandemic of coronavirus disease 2019 (COVID-19) influenced cognitive function in the elderly. However, the effect of COVID-19-related fear on brain atrophy has not been evaluated. In this study, we evaluated the relation between brain atrophy and the effect of COVID-19-related fear by analysing changes in brain volume over time using magnetic resonance imaging (MRI). *Methods:* Participants were 25 Japanese patients with mild cognitive impairment (MCI) or subjective cognitive decline (SCD), who underwent 1.5-tesla MRI scan twice, once before and once after the pandemic outbreak of COVID-19, and the Fear of Coronavirus Disease 2019 Scale (FCV-19S) assessment during that period. We computed regional brain atrophy per day between the 1st and 2nd scan, and evaluated the relation between the FCV-19S scores and regional shrinkage. *Results:* There was significant positive correlation between the total FCV-19S score and volume reduction per day in the right posterior cingulate cortex. Regarding the subscales of FCV-19S, we found significant positive correlation between factor 2 of the FCV-19S and shrinkage of the right posterior cingulate cortex. *Conclusions:* There was positive correlation between the FCV-19S score and regional brain atrophy per day. Although it is already known that the psychological effects surrounding the COVID-19 pandemic cause cognitive function decline, our results further suggest that anxiety and fear related to COVID-19 cause regional brain atrophy.

Significant outcomes

- The higher the FCV score, the more atrophy of the right posterior cingulate cortex was observed over time in patients with mild cognitive impairment or subjective cognitive decline.
- The COVID-19 epidemic might affect not only cognitive function but also cerebral morphology.

Limitations

- All subjects were not only exposed to psychological stress in relation to the COVID-19 disaster but also decreased their social and physical activity due to restrictions on going out to prevent the spread of infection. It is difficult to clarify the interaction among these factors.
- If changes in regional brain volume were affected by anxiety or depression, it is necessary to consider whether these changes will be reversible after the diminishment of the pandemic.

Introduction

To combat the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on April 7, 2020 the government of Japan issued a state of emergency in seven major cities in conjunction with the Special Measures Law and then further expanded the directive to all of Japan on April 16th. As a result, people refrained from going out and attending schools, and the operation of restaurants and entertainment facilities was restricted. The state of emergency was lifted after approximately 6 weeks, but the infection has continued to spread since then, and the government has urged people to change their lifestyles, such as by taking various measures to prevent infection and curtail their activities.

Hospitals were also required to undergo major changes. Each hospital was required to set up a dedicated COVID-19 ward, and measures were taken such as restricting visits, limiting acceptance of inpatients and bed occupancy rates, reducing the frequency of outpatient visits, and replacing various types of hospital visits with telephone visits. In addition, in psychiatric departments, dementia day care had to be interrupted, and the rehabilitation of cognitive functions for day care users was temporarily suspended (at our hospital, Tsukuba University Hospital, dementia day care was suspended from March 2020 to October and has since restarted with limited activity). Restrictions of hospital visits were similarly initiated by the patients themselves, who tended to avoid going out in their daily lives, and refrained from visiting the hospital due to the fear of COVID-19 infection. With increasing reports of the severity of COVID-19 infections, fear of infection grew stronger, especially in the elderly (Alonso-Lana *et al.*, 2020; Shahid *et al.*, 2020).

Reduction of social activities, such as restrictions on going out to prevent the spread of COVID-19, caused deterioration of cognitive function in patients with dementia. Isolation has been reported to impair cognitive function in patients with dementia, including by deteriorating memory (Ismail *et al.*, 2021) and by promoting agitation, depression, anxiety, and apathy (Barguilla *et al.*, 2020; Lara *et al.*, 2020). It has also been reported that the longer the isolation, the more severe these neuropsychiatric symptoms become (Boutoleau-Bretonnière *et al.,* 2020). Moreover, actual infection with the SARS-CoV-2 virus has been reported to have direct effects on the brain, such as olfactory bulb inflammation and oedema (Mahalaxmi *et al.*, 2021; Miners *et al.*, 2020; Paliwal *et al.*, 2020).

It is known that anxiety promotes the progression of dementia (Mah *et al.*, 2015) and reduces the volume of brain regions including the amygdala (Blackmon *et al.*, 2011; Yang *et al.*, 2017), but there has been no report on the relationship between the fear caused by COVID-19 and brain volume. Therefore, we hypothesised that fear of COVID-19 may cause brain atrophy, just as anxiety causes atrophy in amygdala.

In this study, we analysed potential associations between changes in regional brain volume over time, as measured by magnetic resonance imaging (MRI), and COVID-19-related fear, as quantified by the Fear of Coronavirus Disease 2019 Scale (FCV-19S).

Methods

Participants

Twenty-five elderly participants who regularly attended our hospital's dementia day care programme and were diagnosed with mild cognitive impairment (MCI) (Petersen, 2004) were enrolled. All participants had a score of 24–30 on the Mini-Mental State Examination (MMSE-J) (Ideno *et al.*, 2012) or a Clinical Dementia Rating (CDR) (Morris, 1993) of 0.5 or had been diagnosed with subjective cognitive decline (SCD) (Jessen *et al.*, 2014) at the time of examination in 2020.

All participants regularly visited the outpatient Department of Psychiatry at the University of Tsukuba Hospital and undertook cognitive tests and an MRI scan once a year. Applicants were excluded if they had a prior medical history of central nervous system disease or severe head injury, or if they met the criteria for substance abuse or dependence. After the study was explained to each participant, his or her written informed consent was obtained for participation in the study. This study was approved by the Ethics Committee of the University of Tsukuba Hospital, Japan (approval no. H28-187).

Table 1. Characteristics of the participants

	Mean ± SD	Range
Age (years)	75.6 ± 6.5	61–90
Male/female	15/10	
MMSE	27.8 ± 1.8	24–30
Education (years)	14.0 ± 3.0	6–20
Duration of the MRI scans (days)	424.2 ± 72.7	310–636

MMSE: Mini-Mental State Examination; SD: standard deviation.

The Fear of Coronavirus Disease 2019 Scale (FCV-19S)

FCV-19S is a quantitative measure of COVID-19 fear (Ahorsu *et al.*, 2020), and previous studies have validated its usefulness (Midorikawa *et al.*, 2021). The FCV-19S includes seven items with a 5-point Likert scale (1–5) (1: strongly disagree; 2: disagree; 3; neither agree nor disagree; 4: agree; 5: strongly agree) and has the following two subscales: emotional fear reaction consisting of anxiety and fear (factor 1: questions 1, 2, 4, and 5) and symptomatic expressions of fear consisting of sweating, palpitation, insomnia, etc. (factor 2: questions 3, 6, and 7). They indicated validity and reliability by verifying the correlation between the total score and subscale (factor 1, factor 2) of FCV-19S and Kessler Screening Scale for Psychological Distress, Generalized Anxiety Disorder-7 and Impact of Event Scale-Revised (Midorikawa *et al.*, 2021).

In this study, the total score and subscales were evaluated. The participants took the FCV-19S during the COVID-19 outbreak period.

MRI data acquisition and processing

MRI scans were undertaken twice for each participant, once before (from January 2019 to February 2020) and once after the outbreak of the COVID-19 pandemic (after April 2020). MRI scans were performed on a 1.5-tesla MR system (Avanto, Siemens, Erlangen, Germany). Three-dimensional T1-weighted images were acquired in the sagittal plane (repetition time/echo time, 2400/3.52; voxel size, $1.25 \times 1.25 \times 1.2\ mm^3$; field of view, 240×240 mm; flip angle, 8°; number of signals acquired, 1), yielding 160 contiguous slices through the brain.

Post-processing of the MRI data

To evaluate the individual differences of regional brain volume longitudinally, we calculated the regional grey matter volume and intracranial volume automatically using the longitudinal image processing function in the Freesurfer (ver. 6.0.0) software package (http://surfer.nmr.mgh.harvard.edu/fswiki/Fstutorial/LongitudinalTutorial) running on Ubuntu 18.04 based Lin4Neuro (Nemoto *et al.*, 2011). FreeSurfer automatically segmented the brain along the line of the Desikan-Killiany and Aseg atlas. Then, we estimated the atrophy rate of the regional grey matter using the following formula:

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Table 2. Regional mean volumes of the participants

Region	Pre-scan		Post-scan	
	Mean volume (mm^3)	SD	Mean volume (mm^3)	SD
Left bankssts volume	2348.8	365.9	2330.2	370.4
Left caudal anterior cingulate volume	1574.7	431.3	1568.2	434.8
Left caudal middle frontal volume	5197.4	899.8	5120.2	812.2
Left cuneus volume	3160.0	564.1	3135.7	559.9
Left entorhinal volume	2094.6	522.5	2056.0	543.9
Left fusiform volume	8706.7	1396.4	8581.8	1383.9
Left inferior parietal volume	11,946.8	1484.0	11,760.5	1450.1
Left inferior temporal volume	9905.4	1399.8	9791.7	1364.9
Left isthmus cingulate volume	2438.0	377.0	2414.9	387.4
Left lateral occipital volume	10,960.7	1798.0	10,831.2	1732.1
Left lateral orbito frontal volume	6748.5	766.9	6690.0	767.6
Left lingual volume	6231.4	880.5	6144.4	864.0
Left medial orbito frontal volume	5248.0	680.0	5160.1	668.1
Left middle temporal volume	9945.4	1130.3	9802.6	1122.1
Left para-hippocampal volume	1706.4	292.2	1681.7	287.6
Left para-central volume	3185.1	356.3	3158.0	347.4
Left pars opercularis volume	3859.4	476.3	3810.2	461.8
Left pars orbitalis volume	2056.7	287.3	2043.7	308.8
Left pars triangularis volume	3133.1	442.5	3091.3	460.1
Left peri-calcarine volume	2290.9	508.5	2267.0	490.3
Left post-central volume	8419.2	1197.7	8348.8	1208.5
Left posterior cingulate volume	2998.7	526.1	2981.8	529.3
Left pre-central volume	12,428.1	1446.8	12,265.5	1381.5
Left precuneus volume	9035.8	895.0	8915.1	865.8
Left rostral anterior cingulate volume	2117.2	466.8	2106.2	474.0
Left rostral middle frontal volume	13,237.1	1580.9	13,076.1	1536.9
Left superior frontal volume	19,625.2	1974.5	19,433.2	1884.6
Left superior parietal volume	12,232.0	1301.6	12,017.1	1288.2
Left superior temporal volume	11,109.2	1132.8	10,997.9	1132.7
Left supra-marginal volume	9175.2	1070.3	9041.2	1095.6
Left frontal pole volume	865.6	135.8	842.8	136.4
Left temporal pole volume	2298.2	374.7	2220.0	370.2
Left transverse temporal volume	1001.1	174.4	992.5	168.2
Left insula volume	6713.2	716.9	6643.6	716.7
Left Lateral Ventricle	18,926.5	10,577.4	19,655.9	10,808.7
Left Inferior lateral ventricle	1350.3	823.1	1448.8	923.6
Left cerebellum white matter	12,345.8	1724.3	12,336.2	1606.7
Left cerebellum cortex	48,214.5	4747.7	48,264.2	4943.2
Left thalamus proper	6838.2	722.7	6786.7	709.8
Left caudate	3654.8	574.6	3626.0	564.6
Left putamen	4629.3	621.0	4599.1	646.6
Left pallidum	1825.3	235.0	1820.3	238.1

(*Continued*)

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Table 2. (*Continued*)

	Pre-scan		Post-scan	
Region	Mean volume (mm^3)	SD	Mean volume (mm^3)	SD
Left hippocampus	3345.5	569.5	3297.9	594.9
Left amygdala	1226.9	232.6	1203.7	211.6
Left accumbens area	345.8	91.9	334.4	99.6
Left ventral diencephalon	3535.2	341.7	3511.7	336.1
Left vessel	106.5	36.7	106.4	35.7
Left choroid plexus	1640.8	286.4	1653.2	273.8
Right bankssts volume	1621.9	268.7	1606.3	273.9
Right caudal anterior cingulate volume	1634.6	423.0	1617.4	415.8
Right caudal middle frontal volume	5295.0	799.4	5210.4	767.6
Right cuneus volume	2896.5	424.3	2846.8	410.6
Right entorhinal volume	1895.2	458.0	1859.5	468.0
Right fusiform volume	8428.4	1291.4	8324.8	1358.2
Right inferior parietal volume	12,061.4	1633.0	11,843.8	1665.8
Right inferior temporal volume	10,066.9	1266.3	9864.2	1223.6
Right isthmus cingulate volume	2378.1	330.1	2368.6	339.1
Right lateral occipital volume	10,912.6	1339.5	10,794.8	1367.7
Right lateral orbito frontal volume	6939.2	797.8	6926.4	796.8
Right lingual volume	5941.7	1015.2	5896.5	999.8
Right medial orbito frontal volume	4997.8	582.2	4949.3	633.9
Right middle temporal volume	10,131.3	1203.7	9953.6	1194.6
Right para-hippocampal volume	1807.0	299.6	1777.1	305.4
Right para-central volume	3757.9	487.8	3671.0	424.3
Right pars opercularis volume	3322.5	474.2	3278.6	466.1
Right pars orbitalis volume	2383.3	365.7	2369.7	360.2
Right pars triangularis volume	3667.8	708.9	3641.9	681.5
Right peri-calcarine volume	2257.5	447.4	2235.2	451.0
Right post-central volume	9113.0	1324.2	8976.1	1228.3
Right posterior cingulate volume	2832.7	513.5	2833.3	523.0
Right pre-central volume	12,430.5	1099.1	12,242.6	1097.0
Right precuneus volume	9090.0	984.2	8902.8	949.3
Right rostral anterior cingulate volume	1808.5	524.8	1784.5	503.7
Right rostral middle frontal volume	13,101.4	1792.9	12,954.0	1696.1
Right superior frontal volume	18,666.2	2045.1	18,395.4	2094.8
Right superior parietal volume	11,688.2	1236.8	11,527.2	1196.4
Right superior temporal volume	10,453.6	1237.5	10,269.8	1155.7
Right supra-marginal volume	10,370.4	1329.1	10,188.5	1268.9
Right frontal pole volume	1037.4	160.7	1019.0	164.8
Right temporal pole volume	2403.1	345.1	2315.4	374.9
Right transverse temporal volume	922.9	206.7	897.6	207.4
Right insula volume	6739.4	712.1	6685.6	725.9
Right lateral ventricle	22,434.4	11,485.1	23,267.5	11,745.7
Right inferior lateral ventricle	1186.1	777.7	1278.1	892.3

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Table 2. (*Continued*)

Region	Pre-scan		Post-scan	
	Mean volume (mm^3)	SD	Mean volume (mm^3)	SD
Right cerebellum white matter	12,456.2	1643.2	12,377.5	1549.8
Right cerebellum cortex	48,338.5	4858.4	48,093.6	4906.9
Right thalamus proper	6492.3	652.0	6405.0	647.6
Right caudate	3617.5	547.0	3602.8	583.1
Right putamen	4569.1	630.5	4538.3	634.1
Right pallidum	1793.4	231.7	1790.8	234.8
Right hippocampus	3199.6	566.4	3146.6	616.7
Right amygdala	1308.8	221.6	1286.2	227.7
Right accumbens area	457.1	101.9	456.5	96.8
Right ventral diencephalon	3608.9	298.0	3574.8	306.9
Right vessel	127.7	50.4	125.1	53.9
Right choroid plexus	1556.9	278.6	1575.9	274.2
3rd ventricle	2194.9	665.9	2231.8	670.6
4th ventricle	2281.1	675.0	2293.0	680.2
Brain stem	20,772.4	2290.2	20,675.8	2221.1
CSF	1596.6	435.7	1621.9	434.6
5th ventricle	2.7	5.0	2.6	4.2
Optic chiasm	329.9	50.5	331.2	55.6
Corpus callosum posterior	919.3	145.4	921.8	139.7
Corpus callosum mid posterior	359.0	91.4	356.6	93.7
Corpus callosum central	390.3	51.6	385.4	47.7
Corpus callosum Mid anterior	410.0	65.5	402.0	53.1
Corpus callosum anterior	787.5	120.0	778.8	119.7

$$\text{atrophy rate per day} = [(\text{regional volumes}_{pre}/\text{eTIV}_{pre}) - (\text{regional volumes}_{post}/\text{eTIV}_{post})]/\text{duration of the scans}$$

Here, eTIV means the estimated total intracranial volume automatically calculated using the Freesurfer software.

Statistical analysis

The statistical analyses were performed using SPSS software ver. 23 (SPSS Japan, Tokyo). We also evaluated the relationship between the atrophy rate per day and the scores of FCV-19S by partial correlation analysis using the subjects' age, sex, and years of education as covariates. For multiple comparisons, a p value ⩽0.001 was regarded as statistically significant.

Results

The demographic and clinical characteristics of the participants are shown in Table 1. The mean age was 75.6 ± 6.5 years (range: 61–90 years), and there were 15 men and 10 women. The mean score on the MMSE performed in 2020 was 27.8 ± 1.8 (range: 24–30), and the mean education history was 14.0 ± 3.0 years (range: 6–20 years). The mean interval between the MRI examinations in 2019 and 2020 was 424.2 ± 72.7 days.

We compared brain MRIs in 2019 (pre-epidemic) and 2020 (post-epidemic). The mean regional grey matter volumes are shown in Table 2. Table 3 shows the correlation between the daily atrophy rate and FCV-19S. There was a positive correlation between the total score of FCV-19S and the atrophy rate per day in the right posterior cingulate cortex ($p = 0.002$, $r = 0.617$). We then evaluated the correlation between the subscales of the FCV-19S and grey matter shrinkage of the subjects. We found that there was also a significant positive correlation between the score of factor 2 and the reduction of the right posterior cingulate cortex volume per day ($p < 0.001$, $r = 0.657$).

Discussion

In this study, we examined changes in regional brain volume on head MRI between before and after the start of the COVID-19 epidemic in patients with MCI or SCD to clarify the effect of fear of COVID-19 on the regional brain volume over time. We found that the FCV-19S score was associated with the right posterior cingulate cortex volume. To our knowledge, this is the first study to show a relationship between fear of COVID-19 and the rate of regional brain atrophy.

The shock caused by the COVID-19 pandemic is severe, and previous studies have shown an increase in mental problems, including anxiety, depression, insomnia, and post-traumatic stress disorder (PTSD), in the general population (Serafini *et al.*, 2020, Talevi *et al.*, 2020). The FCV-19S is a scale that quantitatively

Table 3. Relationships between the regional atrophy rate and the fear of COVID-19 scale

	Total score		Factor 1 score		Factor 2 score	
Region	Correlation coefficient	*p* value	Correlation coefficient	*p* value	Correlation coefficient	*p* value
Left bankssts volume	0.384	0.077	0.261	0.241	0.468	0.028
Left caudal anterior cingulate volume	0.287	0.196	0.261	0.240	0.261	0.240
Left caudal middle frontal volume	0.285	0.198	0.156	0.488	0.397	0.068
Left cuneus volume	0.140	0.534	0.104	0.645	0.159	0.481
Left entorhinal volume	0.118	0.600	0.119	0.597	0.093	0.681
Left fusiform volume	0.334	0.128	0.190	0.398	0.456	0.033
Left inferior parietal volume	0.187	0.406	0.115	0.612	0.243	0.276
Left inferior temporal volume	0.231	0.301	0.111	0.622	0.341	0.120
Left isthmus cingulate volume	0.181	0.421	0.093	0.681	0.259	0.245
Left lateral occipital volume	0.255	0.253	0.216	0.333	0.253	0.256
Left lateral orbito frontal volume	0.145	0.520	0.029	0.898	0.267	0.230
Left lingual volume	0.106	0.639	−0.042	0.851	0.279	0.208
Left medial orbito frontal volume	0.472	0.027	0.347	0.114	0.539	0.010
Left middle temporal volume	0.201	0.370	−0.003	0.990	0.427	0.047
Left para-hippocampal volume	0.175	0.436	0.048	0.831	0.305	0.167
Left para-central volume	−0.342	0.119	−0.429	0.046	−0.158	0.482
Left pars opercularis volume	0.136	0.546	0.067	0.767	0.199	0.375
Left pars orbitalis volume	0.060	0.790	−0.028	0.901	0.164	0.466
Left pars triangularis volume	0.334	0.129	0.288	0.194	0.326	0.138
Left peri-calcarine volume	0.112	0.619	0.132	0.558	0.063	0.780
Left post-central volume	−0.008	0.971	−0.036	0.875	0.029	0.896
Left posterior cingulate volume	−0.027	0.906	−0.081	0.720	0.050	0.824
Left pre-central volume	−0.092	0.683	−0.177	0.431	0.038	0.867
Left precuneus volume	0.101	0.653	0.039	0.863	0.162	0.470
Left rostral anterior cingulate volume	−0.066	0.770	0.015	0.948	−0.158	0.481
Left rostral middle frontal volume	−0.009	0.967	−0.109	0.630	0.123	0.585
Left superior frontal volume	0.079	0.726	0.010	0.966	0.154	0.493
Left superior parietal volume	0.251	0.260	0.145	0.519	0.338	0.123
Left superior temporal volume	0.226	0.313	0.059	0.794	0.398	0.067
Left supra-marginal volume	0.097	0.669	−0.025	0.912	0.237	0.289
Left frontal pole volume	0.207	0.356	0.202	0.368	0.171	0.447
Left temporal pole volume	0.287	0.195	0.111	0.623	0.459	0.032
Left transverse temporal volume	−0.161	0.474	−0.142	0.528	−0.153	0.497
Left insula volume	0.326	0.139	0.218	0.329	0.401	0.064
Left Lateral Ventricle	−0.332	0.131	−0.188	0.402	−0.453	0.034
Left Inferior lateral ventricle	−0.386	0.076	−0.249	0.264	−0.487	0.022
Left cerebellum white matter	0.273	0.218	0.283	0.202	0.205	0.361
Left cerebellum cortex	0.234	0.295	0.152	0.500	0.294	0.184
Left thalamus proper	−0.054	0.813	−0.123	0.584	0.049	0.828
Left caudate	0.101	0.656	0.146	0.515	0.020	0.931
Left putamen	0.001	0.996	−0.048	0.831	0.066	0.771
Left pallidum	−0.237	0.287	−0.419	0.052	0.050	0.826

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Table 3. (*Continued*)

Region	Total score		Factor 1 score		Factor 2 score	
	Correlation coefficient	*p* value	Correlation coefficient	*p* value	Correlation coefficient	*p* value
Left hippocampus	0.241	0.280	0.149	0.509	0.313	0.156
Left amygdala	0.158	0.484	0.249	0.263	0.005	0.983
Left accumbens area	0.283	0.202	0.104	0.644	0.460	0.031
Left ventral diencephalon	0.081	0.720	0.054	0.811	0.100	0.658
Left vessel	0.075	0.740	0.051	0.821	0.091	0.688
Left choroid plexus	0.279	0.209	0.265	0.233	0.239	0.283
Right bankssts volume	0.295	0.182	0.316	0.153	0.208	0.353
Right caudal anterior cingulate volume	0.222	0.322	0.134	0.552	0.291	0.189
Right caudal middle frontal volume	0.042	0.853	0.102	0.653	−0.045	0.842
Right cuneus volume	0.093	0.681	0.002	0.993	0.193	0.390
Right entorhinal volume	0.306	0.166	0.181	0.420	0.407	0.060
Right fusiform volume	0.181	0.420	0.117	0.604	0.228	0.308
Right inferior parietal volume	0.300	0.175	0.290	0.191	0.252	0.257
Right inferior temporal volume	0.119	0.599	0.072	0.751	0.156	0.488
Right isthmus cingulate volume	0.285	0.198	0.210	0.349	0.326	0.139
Right lateral occipital volume	0.206	0.358	0.147	0.513	0.240	0.281
Right lateral orbito frontal volume	0.351	0.109	0.231	0.300	0.436	0.043
Right lingual volume	0.337	0.125	0.422	0.050	0.157	0.487
Right medial orbito frontal volume	0.370	0.090	0.218	0.330	0.494	0.019
Right middle temporal volume	0.143	0.525	0.075	0.741	0.204	0.362
Right para-hippocampal volume	0.213	0.341	0.109	0.629	0.306	0.165
Right para-central volume	−0.096	0.672	−0.206	0.357	0.069	0.760
Right pars opercularis volume	0.210	0.348	0.235	0.293	0.134	0.551
Right pars orbitalis volume	0.424	0.049	0.264	0.236	0.547	0.008
Right pars triangularis volume	0.489	0.021	0.478	0.024	0.404	0.062
Right peri-calcarine volume	0.199	0.376	0.244	0.273	0.098	0.665
Right post-central volume	−0.064	0.778	0.025	0.914	−0.167	0.458
Right posterior cingulate volume	0.617	0.002*	0.491	0.020	0.657	<0.001**
Right pre-central volume	0.003	0.989	−0.015	0.946	0.027	0.906
Right precuneus volume	0.280	0.207	0.217	0.331	0.305	0.168
Right rostral anterior cingulate volume	0.204	0.363	0.019	0.934	0.405	0.061
Right rostral middle frontal volume	0.179	0.425	0.139	0.537	0.195	0.384
Right superior frontal volume	0.100	0.659	0.025	0.912	0.177	0.430
Right superior parietal volume	0.463	0.030	0.427	0.048	0.416	0.054
Right superior temporal volume	0.102	0.653	0.090	0.691	0.096	0.670
Right supra-marginal volume	0.275	0.216	0.307	0.165	0.177	0.431
Right frontal pole volume	0.045	0.843	0.092	0.685	−0.026	0.910
Right temporal pole volume	0.401	0.064	0.344	0.118	0.394	0.070
Right transverse temporal volume	−0.135	0.548	−0.095	0.675	−0.161	0.474
Right insula volume	0.066	0.770	0.023	0.918	0.109	0.630
Right lateral ventricle	−0.367	0.093	−0.214	0.339	−0.492	0.020
Right inferior lateral ventricle	−0.320	0.146	−0.200	0.372	−0.412	0.057

(*Continued*)

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Table 3. (*Continued*)

Region	Total score		Factor 1 score		Factor 2 score	
	Correlation coefficient	*p* value	Correlation coefficient	*p* value	Correlation coefficient	*p* value
Right cerebellum white matter	−0.061	0.787	−0.133	0.556	0.046	0.841
Right cerebellum cortex	0.329	0.135	0.262	0.240	0.350	0.110
Right thalamus proper	−0.007	0.974	−0.073	0.747	0.080	0.723
Right caudate	−0.157	0.485	−0.193	0.389	−0.078	0.730
Right putamen	0.418	0.053	0.336	0.126	0.439	0.041
Right pallidum	−0.051	0.821	−0.082	0.718	−0.001	0.998
Right hippocampus	0.119	0.598	0.010	0.965	0.237	0.287
Right amygdala	0.190	0.397	0.146	0.516	0.208	0.352
Right accumbens area	0.087	0.702	0.082	0.716	0.074	0.742
Right ventral diencephalon	−0.054	0.811	−0.009	0.970	−0.103	0.649
Right vessel	0.260	0.243	0.333	0.129	0.110	0.627
Right choroid plexus	−0.291	0.189	−0.139	0.537	−0.431	0.045
3rd ventricle	−0.301	0.173	−0.155	0.491	−0.432	0.045
4th ventricle	−0.205	0.360	−0.191	0.394	−0.181	0.420
Brain stem	0.180	0.422	0.092	0.685	0.260	0.243
CSF	−0.374	0.087	−0.331	0.132	−0.353	0.107
5th ventricle	0.001	0.997	−0.154	0.495	0.203	0.364
Optic chiasm	−0.102	0.651	−0.043	0.848	−0.159	0.480
Corpus callosum posterior	−0.107	0.637	−0.040	0.861	−0.173	0.442
Corpus callosum mid posterior	0.116	0.606	−0.054	0.811	0.316	0.151
Corpus callosum central	0.142	0.528	0.024	0.914	0.267	0.229
Corpus callosum Mid anterior	−0.160	0.476	−0.188	0.403	−0.092	0.684
Corpus callosum anterior	−0.080	0.724	−0.087	0.701	−0.055	0.809

*$p < 0.005$.
**$p < 0.001$.

evaluates COVID-19 fear with seven questions (Midorikawa *et al.*, 2021), and the Japanese version has also been verified (Midorikawa *et al.*, 2021; Masuyama *et al.*, 2020, Wakashima *et al.*, 2020). The total score is 7–35, and the higher the score, the stronger the fear of COVID-19. This scale has been validated to correlate with the symptom intensity of anxiety and stress (Midorikawa *et al.*, 2021).

The significant new finding in this study is the association between the FCV-19S score and the volume reduction of the right posterior cingulate cortex. Concerning the involvement of the posterior cingulate cortex in psychiatric symptoms, previous reports showed an association between the features found in this region by brain imaging analyses and PTSD. Ke et al. (Ke *et al.*, 2017) reported an association between the activity in the posterior cingulate gyrus on functional neuroimaging and PTSD symptom severity. Zhang *et al.* (2012) showed that the white matter integrity of the posterior cingulate gyrus was linked to affective processing in PTSD by diffusion tensor imaging. When taken together with these findings indicating an association between the function of the posterior cingulate gyrus and the psychiatric symptoms of PTSD, the results of the present study suggest that the posterior cingulate cortex is involved in the processing of anxiety or fear caused by COVID-19. This may be an issue to be clarified in the future.

Another important point is that the posterior cingulate cortex is a region where glucose hypometabolism and hypoperfusion are observed in the early stages of Alzheimer's disease (AD) (Valotassiou *et al.*, 2018), a condition associated with memory impairment (Jones *et al.*, 2006; Leech & Sharp, 2014; Scahill *et al.*, 2002). Other studies reported that anxiety was associated with the progression of dementia and decreased brain volume in patients with MCI or SCD (Johansson *et al.*, 2020, Mah *et al.*, 2015). Age-related brain atrophy was reported to be exacerbated by anxiety-related stress in healthy subjects (Laird *et al.*, 2019). Further, it is known that cognitive decline, including memory impairment, occurs in elderly people affected by disasters such as earthquakes (Furukawa *et al.*, 2012; Hikichi *et al.*, 2017). Collectively, these findings may suggest that the posterior cingulate region is vulnerable to mental stress caused by disasters (earthquakes, pandemics, etc.), and resultant atrophy and cognitive decline, especially in elderly people. Our hypothesis that COVID-19 fear might cause atrophy of the amygdala was not observed in this study. It was considered that this was because the atrophy of the medial temporal lobe including the amygdala had already been caused in the early stage of dementia such as MCI (Tang *et al.*, 2015).

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The results of the present study suggest that anxiety or fear of COVID-19 might accelerate the atrophy of the posterior cingulate gyrus in patients with SCD or MCI. Reducing stress caused by anxiety and fear in the elderly might prevent the progression of brain atrophy and thereby prevent cognitive deterioration. In Japan, it has been pointed out that the COVID-19 epidemic reduced the opportunities for elderly people with dementia to receive long-term care, including day care and day services, and these changes might have aggravated cognitive decline and behavioural and psychological symptoms of dementia (BPSD) (Niimi *et al*., 2021). Similarly, increases in fear and anxiety in relation to COVID-19, exacerbated by elderly people with dementia being unable to receive long-term care services and withdrawing to their homes, may also contribute to the deterioration of cognitive function. For the future improvement of elderly care, measures should be taken to continue long-term care services while paying sufficient attention to infection prevention in order to alleviate the fear and anxiety of COVID-19 and prevent the progression of brain atrophy and cognitive decline.

However, this study has some limitations. It is known that dementia is a risk factor for the aggravation of COVID-19 infection and that the COVID-19 pandemic worsened the cognitive function and the severity of behavioural and psychological symptoms of dementia (BPSD) (Barguilla *et al*., 2020; Boutoleau-Bretonnière *et al*., 2020; Canevelli *et al*., 2020; Ismail *et al*., 2021; Lara *et al*., 2020; Miners *et al*., 2020). The background to the exacerbation of dementia is not only the psychological stress of the COVID-19 disaster but also the decrease in social and physical activity due to restrictions on going out to prevent the spread of infection. Exercise and social contact play important roles in mental health (Livingston *et al*., 2020). In this study, because all subjects were exposed to psychological stress in relation to the COVID-19 disaster and decreased their social and physical activity, it is difficult to clarify the interaction among these factors. In addition, if changes in regional brain volume were affected by anxiety or depression, it is necessary to consider whether these changes will be reversible after the diminishment of the pandemic. It is presumed that this point will be clarified by further longitudinal evaluation in the future.

In conclusion, there was a significant correlation between the fear of COVID-19 and regional brain atrophy rates. It was revealed that the COVID-19 epidemic has an indirect effect not only on cognitive function but also on cerebral morphology. In the future, we will conduct further longitudinal research to verify the effects on cognitive function and morphological changes.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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