Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Research paper

Altered brain regional homogeneity is associated with depressive symptoms in COVID-19

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ABSTRACT

Background: COVID-19 is an infectious disease that has spread worldwide in 2020, causing a severe pandemic. In addition to respiratory symptoms, neuropsychiatric manifestations are commonly observed, including chronic fatigue, depression, and anxiety. The neural correlates of neuropsychiatric symptoms in COVID-19 are still largely unknown.

Methods: A total of 79 patients with COVID-19 (COV) and 17 healthy controls (HC) underwent 3 T functional magnetic resonance imaging at rest, as well as structural imaging. Regional homogeneity (ReHo) was calculated. We also measured depressive symptoms with the Patient Health Questionnaire (PHQ-9), anxiety using the General Anxiety Disorder 7-item scale, and fatigue with the Multidimension Fatigue Inventory.

Results: In comparison with HC, COV showed significantly higher depressive scores. Moreover, COV presented reduced ReHo in the left angular gyrus, the right superior/middle temporal gyrus and the left inferior temporal gyrus, and higher ReHo in the right hippocampus. No differences in gray matter were detected in these areas. Furthermore, we observed a negative correlation between ReHo in the left angular gyrus and PHQ-9 scores and a trend toward a positive correlation between ReHo in the right hippocampus and PHQ-9 scores.

Limitations: Heterogeneity in the clinical presentation in COV, the different timing from the first positive molecular swab test to the MRI, and the cross-sectional design of the study limit the generalizability of our findings.

Conclusions: Our results suggest that COVID-19 infection may contribute to depressive symptoms via a modulation of local functional connectivity in cortico-limbic circuits.

1. Introduction

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has spread rapidly worldwide, thus causing a severe pandemic (Zhu et al., 2020). The most common symptoms are fever, cough, and dyspnea, followed by weakness, fatigue, nausea, vomiting, diarrhea, hyposmia, and hypogeusia (Wiersinga et al., 2020). Epidemiological studies have shown that around 80 % of patients with COVID-19 have no or mild manifestations, 15 % severe manifestations, and 5 % have life-threatening manifestations, respectively (Epidemiology Working Group for NCIP Epidemic Response, 2020). Besides the most common clinical symptoms, neuropsychiatric manifestations are increasingly recognized. In particular, meta-analytic evidence has shown that patients affected by COVID-19

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have a higher chance of developing encephalitis, stroke, acute neuropathies such as Guillain-Barré syndrome, chronic fatigue, depression, anxiety, sleep disorders, and stress-related disorders (Ellul et al., 2020; Wu et al., 2021). Psychiatric and cognitive symptoms are likely associated with the neural effects of viral infection or the treatment provided, but could also derive from the psychosocial factors associated with SARS-CoV-2 infection, such as the worry of getting severely ill or of infecting others, lifestyle changes, social isolation, and worsening of living conditions (Dinakaran et al., 2020; Zhang et al., 2020). These disturbances may appear during the acute phase of the infection and may persist for months after recovery, being perpetrated by grief, loss, survivor guilt, post-traumatic stress, economic worries, and feelings of uncertainty about the future (Georgieva et al., 2021; Pinto et al., 2020). Among cognitive disturbances, a central role is played by mental fatigue, or mental fog, described by Rudroff et al. (2020) as "the decrease in physical and/or mental performance that results from changes in central, psychological and/or peripheral factors due to COVID-19 disease" (Rudroff et al., 2020). Although new studies with longer follow-up will help to elucidate long-term sequelae of COVID-19, the available literature shows that up to 69 % of patients report symptoms of mental fatigue three months after recovery (van den Borst et al., 2021).

Neuroimaging literature has grown exponentially in the last two years, and a large body of research is now available on structural brain alterations in COVID-19. With regards to Magnetic Resonance Imaging (MRI) in patients with severe COVID-19, signal abnormalities have been described in the medio-temporal lobe, along with diffuse white matter microhemorrhages (Kremer et al., 2020). A descriptive review of the literature highlighted that the most common findings in MRI studies were subacute infarcts, leukoencephalopathy and microhemorrhages, enhancement of leptomeningeal contrast, and abnormality of the cortical FLAIR signal (Gulko et al., 2020). In addition, a longitudinal study conducted on 785 participants of UK Biobankreported a reduction in gray matter (GM) thickness in the orbitofrontal cortex and parahippocampal gyrus and in global brain size after the SARS-CoV-2 infection compared to healthy controls (HC) (Douaud et al., 2022).

Also, positron emission tomography (PET) hypometabolism in patients with COVID-19 encompassing the olfactory gyrus and the connected limbic/paralimbic regions, extended to the brainstem and the cerebellum (Guedj et al., 2021), and in the right parahippocampal gyrus and the right thalamus (Sollini et al., 2021) were reported. However, despite the several structural brain abnormalities described so far, to our knowledge, only one resting-state functional MRI (rs-fMRI) investigation has been carried out in patients with COVID-19. Specifically, an rs-fMRI study has been conducted in a mechanically ventilated patient with severe COVID-19 and has described intact functional connectivity within the default mode network (DMN), despite minimally conscious state and structural abnormalities of the brain (Fischer et al., 2020). Here, we conducted the first rs-fMRI in patients who recovered from COVID-19 without major neurological and psychiatric symptoms or sequelae. We used regional homogeneity (ReHo) to identify alterations of regional brain functional connectivity (FC). ReHo is a measure that reflects local or short-distance (at the level of 10–15 mm) synchronization of the BOLD signal, and its changes are considered to reflect abnormalities in the regulation and coordination of local neuronal activity (Zang et al., 2004). Unlike other rs-fMRI measures that estimate functional connectivity in the resting state (rs-FC) between remote brain regions, ReHo is an index of the concordance in the amplitude of the BOLD signal within a group of a voxel's nearest neighbors (Zang et al., 2004). Interestingly, due to its voxel-wise nature, ReHo allows the identification of local brain abnormalities of the brain at rest without a priori constraints (Iwabuchi et al., 2015). Regionally localized alterations in rs-FC within large-scale networks have been reported in several affective disorders, including major depressive disorder (Iwabuchi et al., 2015), bipolar disorders (Cattarinussi et al., 2022; Vargas et al., 2013) and anxiety disorders (Lai, 2018). In addition, abnormalities in ReHo have also been associated with affective psychopathology, including depressive symptoms (Fang et al., 2021), melancholia (Yan et al., 2021), and trait anxiety (Hahn et al., 2013).

We hypothesized that: a) patients with COVID-19 would show greater depressive symptoms, anxiety, and mental fatigue in comparison with HC; b) patients with COVID-19 would show ReHO alterations in brain areas associated with depressive symptoms, anxiety, and mental fatigue relative to HC; and c) alterations of regional functional connectivity would correlate with psychopathological symptoms.

2. Methods

2.1. Participants

A total of 85 patients with COVID-19 (COV) and 21 age- and sex-matched HC were enrolled at the University Hospital of Padova, Padua, Italy from May to November 2020, when wild type SARS-CoV-2 was predominant and only a few cases of Alpha variant were reported (Lai et al., 2021). COV were included in the study only if they had a positive molecular swab test for SARS-CoV-2. We excluded patients if they a) had a previous diagnosis of neurological or psychiatric disorders; b) were taking psychopharmacological treatments. Only HC that presented a negative molecular swab test for SARS-CoV-2 before the scan ($n = 21$) were included in the study. Exclusion criteria for HC were to have at the time of the scan a) previous or current positive molecular swab test for SARS-CoV-2; b) presence of symptoms associated with COVID-19, such as fever, cough, hyposmia, or hypogeusia; c) past or current neurological or psychiatric disorders; 4) active psychopharmacological treatments. MRI scan was acquired within nine months since the first positive swab test for COVID-19. All participants gave written consent, and the study was approved by the local Ethics Committee (NEUROCOVID, Ethical Committee Prot. 056881). After MRI session, five COV and four HC were excluded (see below). Sociodemographic and clinical data of the final sample are shown in Table 1.

2.2. Functional MRI

2.2.1. Imaging acquisition and processing

Imaging acquisition was performed using a 3 T MR scanner (Philips Ingenia, Best, The Netherlands) with a 32-channel quadrature head-coil. Whole-brain 3D-T1 (magnetization prepared rapid gradient echo sequence in the sagittal plane; TR/TE = 6676 ms/3 ms; FOV = 240 mm; flip-angle = 8°; resolution = 1 × 1 × 1 mm^3) and rs-fMRI (flip angle = 90°, TR/TE = 2922/30 ms, imaging matrix = 68 × 66, FOV = 200 × 200 mm, 55 slices and slice thickness = 3 mm) were acquired.

Structural and functional magnetic resonance imaging data were pre-processed using Data Processing & Analysis for Brain Imaging

Table 1
Sociodemographic and clinical characteristics of the final sample.

	COV (n = 79)	HC (n = 17)	χ^2 or t or U	p
Age [m (SD), years]	42.8 (13.8)	35.8 (11.7)	U = 461	0.043
Sex [Male (%)]	41.8 (33)	64.7 (11)	$\chi^2 = 2.964$	0.085
Education [m (SD), years]	15.5 (3.6)	17.7 (1.3)	$t = -3.592$	0.004
Symptoms at swab (%)	84.8 (67)[a]	NA	NA	NA
Symptoms at scan (%)	60.3 (44)[a]	NA	NA	NA
Hospitalisation (%)	38.4 (28)[a]	NA	NA	NA
PHQ-9 Total score [m (SD)]	4.3 (4.2)	2.4 (2.2)	$t = 1.964$	0.044[b]
GAD-7 Total score [m (SD)]	3.4 (4.3)	2.4 (2.2)	$t = 0.488$	0.305[b]
MFI Total score [m (SD)]	56.8 (15.3)	59.3 (5.7)	U = 481	0.867

COV: COVID-19 patients, HC: healthy controls, m: mean, SD: standard deviation, PHQ-9: Patient Health Questionnaire, GAD-7: General Anxiety Disorder-7, MFI: Multidimension Fatigue Inventory, NA: not applicable.

[a] Percentage evaluated on 73 patients.

[b] FDR corrected.

(DPABI, http://rfmri.org/dpabi) and Statistical Parametrical Mapping 12 (SPM12) (http://www.fil.ion.ucl.ac.uk), running under the MATLAB R2020b (The Mathworks, Sherborn, MA, USA). First, all images were inspected for anatomical abnormalities or artefacts by an expert neuroradiologist (RM). The images were then reoriented and realigned to correct for head motion. The mean root-mean-square (RMS) of the translation parameters in mm was calculated to estimate the overall motion for each subject. After this, T1-weighted images were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF). The GM images were then normalized to the Montreal Neurological Institute (MNI) space with a resulting isotropic voxel size of 3 × 3 × 3 mm.

MRI scans in COV were acquired after swab negativization (time-interval between COVID-19 detection and MRI: 132 ± 67 days). From the initial sample, we excluded five COV and four HC who did not complete the fMRI acquisition and one COV due to the presence of a neuroanatomical abnormality. The final sample included 96 subjects, 79 COV and 17 HC.

2.2.2. Regional homogeneity analysis

ReHo analysis was performed using DPABI. A Kendall's coefficient of concordance (KCC) was assigned to a given voxel by calculating the KCC of times series of the voxel and the nearest 26 neighboring voxels (Zang et al., 2004). Higher ReHo values of a given voxel represent a higher degree of localized temporal synchronization within a neighboring cluster. Then, the voxel ReHo value was divided by the average ReHo value of the entire brain in each subject to ensure standardization. ReHo maps were eventually smoothed with a Gaussian kernel of 4-mm full width at half maximum. To exclude that changes in brain volume following COVID-19 could have affected functional imaging results, we estimated gray matter volume (GMV) changes for each ReHo cluster showing an effect of diagnosis. For this aim, the eigenvariate of the GMV for each cluster was calculated from segmented, normalized, and modulated GM images for each subject. Total intracranial volume (TIV) calculated as the sum of GM, WM and CSF volumes and total GMV were also compared to exclude global effects of brain volumetry. ReHo differences were tested in the overall sample and in patients with COV with and without fever.

2.2.3. Clinical assessment

We evaluated depressive symptoms using the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) and anxiety symptomatology with the 7-item General Anxiety Disorder Scale (GAD-7) (Spitzer et al., 2006) at the time of the scan. Moreover, we assessed fatigue using the total score of the Multidimension Fatigue Inventory (MFI) to measure the overall impact of general, physical and mental fatigue, reduced motivation, and reduced activity (Smets et al., 1995).

2.3. Statistical analysis

We explored the distribution of the data and the homogeneity of variances with the Shapiro-Wilk and Levene's tests, respectively. When normality was met, two-sample *t*-tests and Welch's tests were used to compare homoskedastic and heteroskedastic data between samples, respectively. To compare psychopathological and demographic data, since age, education, PHQ-9, GAD-7, and MFI scores were not normally distributed, robust independent samples *t*-tests with Yuen's methods using a trimmed median with a proportion of 0.1 and 1000 bootstrapped permutations were used. Smoothed ReHo maps were compared using a two-sample t-test in SPM12. Total (TIV and GMV) and local volumes were compared using ANCOVA with age and age and TIV as covariates, respectively. Chi-square tests were used to compare categorical data. Spearman correlations were performed to test the association between the ReHo values from clusters of significant differences between COV and HC and the severity of the psychiatric symptoms that differed between groups. We planned to test first the differences in PHQ-9 and GAD-7 scores between COV and HC, then we tested whether MFI scores differed between the two samples at an exploratory level. Multiple comparisons correction was implemented using false discovery rate (FDR) approach with an alpha = 0.05. Statistical analyses were performed using Jamovi (https://www.jamovi.org/).

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are summarized in Table 1. The two groups did not differ significantly in terms of gender and age (all p's > 0.05). COV had fewer years of education compared to controls ($p < 0.001$). During the acute phase, patients reported a mean of 5 physical symptoms, with only 6 subjects that were asymptomatic (range 0–9). The most commonly reported symptoms were fatigue (71.2 %), fever (69.9 %), muscle pain (68.5 %), headache (52.1 %) and cough (42.5 %). Twenty-eight patients were hospitalized (38.4 %). At the time of the scan, a total of 44 patients reported persistent physical symptoms. The types and prevalence of COVID-19 symptoms are presented in Table 2.

3.2. Psychopathological evaluation

We performed psychopathological evaluations on 89 subjects, 73 COV and 16 HC (49 women, mean age 41.2 years). We identified a correlation between symptoms of anxiety and depression with the MFI scores (GAD-7: rho = 0.312, $p = 0.003$, FDR-corrected; PHQ-9: rho = 0.464, $p < 0.001$, FDR-corrected). In comparison to HC, COV showed an increase in PHQ-9 scores ($p = 0.044$, FDR-corrected). No differences in GAD-7 and MFI scores between COV and HC were detected (all FDR p's > 0.1) (Table 1).

3.3. ReHo analysis

Compared to HC, COV showed reduced ReHo in the left angular gyrus ($p = 0.034$), right superior/middle temporal gyrus (STG/MTG) ($p = 0.047$) and left inferior temporal gyrus (ITG) ($p = 0.031$) (Fig. 1.a) and higher ReHo in the right hippocampus (0.044) (Fig. 1.b). Within the COV group, we did not find any effect of fever on ReHo ($p > 0.1$). To exclude undue effects due to confounding variables, we compared motion and brain volumes between samples. The mean RMS did not differ between samples, and so did the TIV and GMV in diagnosis-related groups (right hippocampus, left angular, right STG/MTG, left ITG) and in the entire brain (all p's > 0.05; see Supplementary Material). No statistically significant differences in ReHo values were observed between COV with and without fever (see Supplementary Material).

Table 2
COVID-19 symptoms during acute phase.

Symptoms	n (%)[a]
Fever	51 (69.9)
Cough	31 (42.5)
Fatigue	52 (71.2)
Muscular pain	50 (68.5)
Sore throat	20 (27.4)
Diarrhea	17 (23.3)
Conjunctivitis	6 (8.2)
Headache	38 (52.1)
Hyposmia, hypogeusia	26 (35.6)
Skin rush	5 (6.8)
Dyspnoea	27 (37)
Chest pain	14 (19.2)
Movement disorders	1 (1.4)
Extrapyramidal symptoms	1 (1.4)

[a] COVID-19 symptoms evaluated on 73 patients.

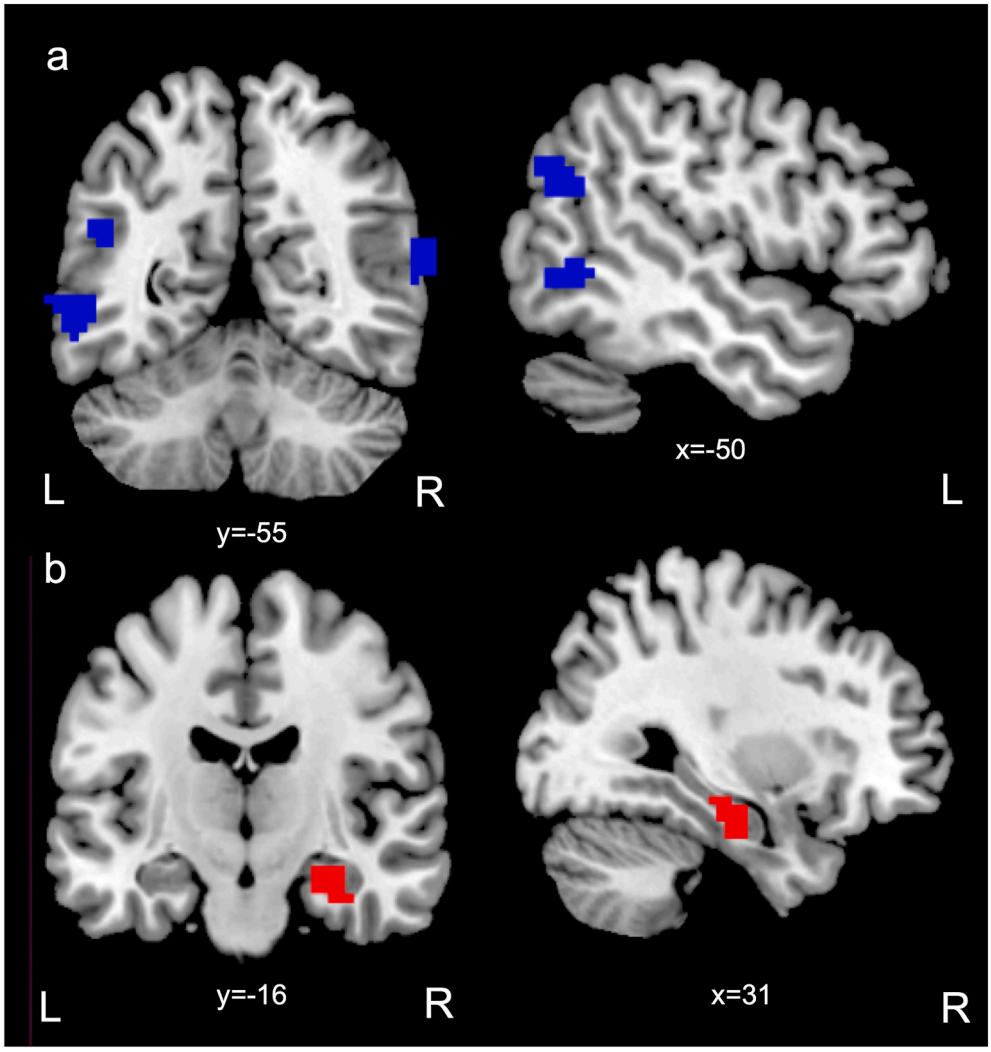

Fig. 1. Brain regions with altered local connectivity in COVID. Patients with COVID-19 had (a) reduced ReHo in the left angular gyrus, right superior/middle temporal gyrus, and left inferior temporal gyrus, and (b) increased ReHo in the right hippocampus. Statistical maps of COV < HC and COV > HC contrast images are rendered on an MNI template with a threshold of voxel-wise $p < 0.001$ and FWE-corrected $p < 0.05$ at the cluster level, respectively. MNI, Montreal Neurological Institute; FWE, family-wise error. L and R indicate the left and right brain hemispheres, respectively. x and y slice planes are indicated at the bottom of each image.

3.4. Correlations between ReHo values and psychopathological variables

We performed exploratory analyses to evaluate potential associations between abnormal local brain connectivity and the psychopathological variables in COV the resulted in a significant difference between COV and HC. We observed a negative correlation between ReHo in the left angular gyrus and PHQ-9 scores ($\rho = -0.236$, $p = 0.044$, Fig. 2). Furthermore, we detected a trend toward a positive correlation between ReHo in the right hippocampus and the PHQ-9 scores ($\rho = 0.212$, $p = 0.07$, Fig.S.1).

4. Discussion

We conducted a ReHo analysis to explore local brain FC at rest in patients affected by COVID-19. Our main finding is thatCOV show alterations in local connectivity in the temporal and parietal lobe and hippocampus compared to healthy subjects. More specifically, the analyses provide evidence of a reduction in intrinsic FC in the left angular gyrus, right superior and middle temporal gyrus, and the left inferior temporal gyrus in recovered COV, along with an increase in intrinsic functional connectivity in the right hippocampus. Moreover, COV presented higher depressive symptoms compared to healthy subjects, but not increased anxiety or fatigue. In addition, we observed a negative correlation between ReHo in the right STG/MTG and the severity of depression. We also detected a trend toward a positive correlation between ReHo in the right hippocampus and the severity of depression.

With regard to clinical symptomatology, our results are in line with a recent meta-analysis conducted in COV, that reported fever and cough as the most frequent symptoms (Li et al., 2020). Interestingly, in our study, a high percentage of patients (60.3 %) presented symptoms at the time of the scan, confirming that SARS-CoV-2 infection causes long-term effects, as recently reported (Lopez-Leon et al., 2021). As expected, we found a positive correlation between depressive and anxiety scores and intensity of fatigue, which is in agreement with what has been observed in previous community studies (Corfield et al., 2016).

Regarding FC, compared to HC, COV displayed a reduction in ReHo in the left angular gyrus, the right STG/MTG, and the left ITG. Previous studies using source-based morphometry in neurological patients showed no differences due to COVID-19. However, patients with fever had a significant volumetric reduction in the ITG/MTG and fusiform gyrus compared to patients without fever, suggesting that COVID-19 may affect the structure of the temporal lobe through the activation of inflammatory processes that cause fever (Duan et al., 2021). We did not find ReHo differences associated with fever.

The angular gyrus is part of the temporo-parietal junction (Schurz et al., 2017), a functionally defined region that plays a central role in a variety of processes, including sensory integration, stimulus-driven attention, and social cognition (Olson et al., 2013). Seemingly, the STG and the MTG are involved in the theory of mind processing and they seem to be associated with the cognitive mechanisms involved in fear

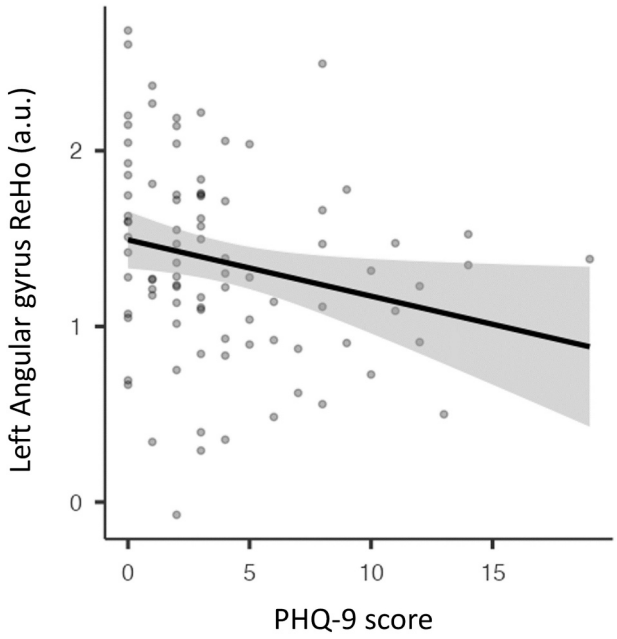

Fig. 2. Scatterplot of brain local connectivity in the left angular gyrus and depression severity in COVID. Average regional homogeneity (ReHo) in the cluster of reduced local connectivity in the left angular gyrus was negatively correlated ($\rho = -0.236$, $p = 0.044$) with PHQ-9 scores. PHQ-9, Patient Health Questionnaire-9. Black line represents the best fit and gray bands indicate 95 % confidence interval.

response (Quirk et al., 1997; Schurz et al., 2014). Interestingly, hypoactivation of the temporal regions involved in social cognition has been described in a recent study exploring neural correlates of social exclusion (Mwilambwe-Tshilobo and Spreng, 2021). Moreover, fMRI investigations have shown that the STG and the MTG present a deactivation under exposure to anxiety cues during ostracism and consistent alterations of the right STG activity have been observed in subjects exposed to psychosocial stress (Kogler et al., 2015; Wudarczyk et al., 2015). In addition, previous evidence revealed that higher loneliness scores were associated with low-frequency fluctuations of the activity in the ITG (Yi et al., 2018), with ITG being described as a key node of the predictive model of loneliness (Feng et al., 2019). It is consistent with the crucial role of ITG in social perception, such as the processing of faces and eye gaze (Haxby et al., 2002; Perrett et al., 1985). Indeed, COV commonly report feelings of social exclusion, stigma, and guilt (Cavalera, 2020), and COVID-19 and quarantined status are commonly linked to perceived discrimination and emotional distress (Xin et al., 2020). Therefore, we could speculate that reduced ReHo detected in temporal and parietal areas might be related to feelings of social exclusion and ostracization. Moreover, ReHo values in the left angular gyrus were negatively correlated with PHQ-9 scores. Interestingly, the angular gyrus acts as a hub that receives and processes information deriving from regions implicated in emotion regulation, including the amygdala, the ventromedial prefrontal cortex, and the subgenual anterior cingulate cortex (Achard et al., 2006; Wei et al., 2018). In line with our findings, functional abnormalities in the left angular gyrus have been found to be associated with depressive symptoms (Lai et al., 2017; Wu et al., 2016). Moreover, ReHo values in the left angular gyrus appear to be increased in patients with major depressive disorder (MDD) after treatment with electroconvulsive therapy (Mo et al., 2020). Interestingly, a recent investigation showed that baseline systemic immune-inflammation in COVID-19 survivors was positively correlated with scores of depression and anxiety at follow-up (Mazza et al., 2020). Furthermore, the relationship between inflammation and social behavior could contribute to explaining our findings (Leschak and Eisenberger, 2019). Exposure to negative social experiences, such as social exclusion, can lead to increased pro-inflammatory activity, and vice versa, inflammation can cause feelings of social disconnection, which in turn can contribute to depressive symptoms (Eisenberger et al., 2010, 2017). COVID-19 infection can result in chronic activation of the immune system, which can lead to an exacerbation of the so-called "sickness behavior" and the development of depressive symptoms in vulnerable individuals (Dantzer et al., 2008). Consistent with these notions, our study suggests that COVID-19 infection can result in changes in local FC in areas primarily involved in social behavior and mood regulation, leading to the development of depressive symptoms, and these alterations may be mediated by an inflammatory response. In particular, functional abnormalities were observed in the hippocampus, which is involved in memory processing, emotion regulation, and motivation and plays a major role in the pathophysiology of MDD (Jaworska et al., 2015; Wise et al., 2017). Drug-naive patients with MDD and subjects with subclinical depression have increased ReHo in the left hippocampus compared to HC (Hao et al., 2019; Zhang et al., 2021). In line with these results, we found a trend toward a positive correlation between depressive symptoms and connectivity measures in the right hippocampus. Future larger studies are warranted to understand whether alterations if regional connectivity in the hippocampus are primarily associated with SARS-CoV-2 infection or are uniquely related to depressive symptoms. Moreover, chronic inflammation conditions associated with general distress, fear, concerns about infecting others, grief, anger, social isolation, loneliness, and stigmatization could have a direct impact on mental health in COV, resulting in depression (Deng et al., 2021; Park et al., 2020; Prati and Mancini, 2021). Additionally, the secondary effects of economic disruption related to the pandemic, including unemployment, insecure employment, changes in work (job loss or switch to smart working), and poverty, have been reported to produce an increase in peritraumatic distress (Pontoni et al., 2022), depressive and suicidal behavior (Brenner and Bhugra, 2020), which in turn has been associated with increased levels of inflammation (Miola et al., 2021). Notably, psychiatric symptoms tend to persist after the acute phase, with 35 % of survivors of COVID-19 showing these symptoms for more than six months after discharge (Ahmed et al., 2020). Therefore, we can hypothesize that also psychological distress may have contributed to depressive symptoms in COV. Future studies with longitudinal designs that evaluate the relationship between negative feelings associated with COVID-19 infection, psychiatric symptoms, and brain function are warranted.

Our study has some limitations that need to be addressed. First, due to the heterogeneity in the clinical course of COV, the time from the first positive molecular swab test for SARS-CoV-2 to the MRI scan acquisition varied greatly. Second, the clinical presentation of COVID-19 in the patients included in the study reflected the heterogeneity of the symptoms in the general population, with some experiencing major complications and others completely asymptomatic. Importantly, to reduce heterogeneity, participants who showed neurological symptoms or presented structural MRI alterations were excluded. Nonetheless, clinical heterogeneity may have influenced our results. Third, the cross-sectional design of the study limits the generalization of our findings. Lastly, psychopathological symptoms were retrospectively assessed, which may have led to recall biases.

In conclusion, this study represents the first step toward a better understanding of functional brain changes in COVID-19 and the development of psychopathological symptoms in this population. Altered local FC in parieto-temporal regions was associated with the severity of depressive symptoms. Future larger studies with more homogeneous populations and longitudinal designs are needed to replicate our findings. Specific therapeutic strategies for psychopathological symptoms may be considered to improve quality of life in patients with COVID-19.

Conflict of Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.06.061.

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