Title: COVID-19 and the Brain: A Psychological and Resting-state fMRI Study of the Whole-brain Functional Connectivity

Authors: : Mohammad Niroumand Sarvandani¹ , Javad Sheikhi Koohsar² , Raheleh Rafaiee³, Maryam Saeedi ⁴, Seyedeh Masoumeh Seyedhosseini Tamijani ⁵, Hamed Ghazvini ⁶, Hossein Sheibani^{7,*}

1. *PhD Candidate, Student Research Committee, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.*
2. *MSc, Center for Health Related Social and Behavioral Sciences Research, Shahroud University of Medical Sciences, Shahroud, Iran.*
3. *Assistant professor, Department of Neuroscience, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.*
4. *Assistant professor, Department of Neurology, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.*
5. *Assistant professor, Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari.*
6. *Assistant professor, Department of Neuroscience, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.*
7. *Assistant professor, Clinical Research Development Unit, Imam Hossein Hospital, Shahroud University of Medical Sciences, Shahroud, Iran.*

***Corresponding Author:** Assistant professor, Hossein Sheibani, Imam Hossein Hospital, Shahroud University of Medical Sciences, Shahroud, Iran. E-mail:sheybani@shmu.ac.ir

To appear in: **Basic and Clinical Neuroscience**

Received date: 2021/05/11

Revised date: 2021/06/27

Accepted date: 2021/07/31

This is a “Just Accepted” manuscript, which has been examined by the peer-review process and has been accepted for publication. A “Just Accepted” manuscript is published online shortly after its acceptance, which is prior to technical editing and formatting and author proofing. *Basic and Clinical Neuroscience* provides “Just Accepted” as an optional and free service which allows authors to make their results available to the research community as soon as possible after acceptance. After a manuscript has been technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as a published article. Please note that technical editing may introduce minor changes to the manuscript text and/or graphics which may affect the content, and all legal disclaimers that apply to the journal pertain.

Please cite this article as:

Niroumand Sarvandani, M., Sheikhi Koohsar, J., Rafeiee, R., Saeedi, M., Seyedhosseini Tamijani, SM., Ghazvini H., & et al. (In Press). COVID-19 and the Brain: A Psychological and Resting-state fMRI Study of the Whole-brain Functional Connectivity. *Basic and Clinical Neuroscience*. Just Accepted publication Sep. 1, 2021. Doi: <http://dx.doi.org/10.32598/bcn.2021.1425.4>

DOI: <http://dx.doi.org/10.32598/bcn.2021.1425.4>

Abstract

Background: Coronavirus 2019 (COVID-19) spreads rapidly worldwide and causes severe acute respiratory syndrome. The current study aimed at evaluating the relationship between the whole-brain functional connections in resting state and cognitive impairments in patients with COVID-19 compared with that of a healthy control group.

Methods: Resting-state fMRI and Montreal cognitive assessment (MoCA) data were obtained from 29 patients of the acute stage of COVID-19 on the third day of admission and 20 healthy controls. Cross-correlation of the mean resting-state signals was determined in the voxels of 23 IC (Independent Components) of brain neural circuits. To assess cognitive function and neuropsychological status, MoCA was performed on all participants. The relationship between rs-fMRI information, neuropsychological status, and paraclinical data were analyzed.

Results: The COVID-19 group got a lower mean MoCA score and showed a significant reduction in the functional connectivity of the IC14 ($P < 0.001$) and IC38 ($P < 0.001$) regions compared with controls. The increase of functional connectivity was observed in the COVID-19 group compared with controls at baseline in the default mode network (DMN) IC00 ($P < 0.001$) and dorsal attention network (DAN) IC08 ($P < 0.001$) regions. Furthermore, alternation of functional connectivity in the mentioned ICs was significantly correlated with the mean Montreal Cognitive Assessment (MoCA) scores and inflammatory parameters-ie, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Conclusions: Functional connectivity abnormalities in four brain neural circuits associated with cognitive impairment and increased inflammatory markers in patients with COVID-19.

Keywords: Whole-brain Functional Connectivity, Cognitive Impairment, COVID-19, Neuropsychology, Resting-state Functional Magnetic Resonance

Introduction

The novel coronavirus 2019 (COVID-19) has spread all around the world (Organization, 2020). COVID-19 is a disease with the core feature of the acute respiratory distress syndrome (ARDS), and the commonest symptoms of fatigue, cough, and fever, as well as headache, hemoptysis, and dyspnea as other manifestations (Singhal, 2020).

COVID-19 can even spread to the central nervous system (CNS) through the respiratory tract concerning its neuroinvasive potential (Zhou et al., 2020). Although the routes of COVID-19 entering the brain are still unclear, it seems that the virus can induce an intracranial cytokine storm leading to blood-brain barrier depression with the induction of direct viral invasion (Karuppan, Devadoss, Nair, Chand, & Lakshmana, 2021). COVID-19 can also enter the cerebral blood flow via passing through the general circulation (Al-Sarraj et al., 2021). Another route for the virus to enter the brain may be through the olfactory bulb (neuronal pathways) (Wu et al., 2020) or directly enter the brain via olfactory vessels or cervical lymphatic nodes (lymphatic pathway) (Bostancıoğlu, 2020). According to the findings, human ocular tissue can provide a potent pathway to pass the SARS-CoV-2 and cause infection (Ma et al., 2020). Coronavirus infection is associated with neurological symptoms categorized as peripheral nervous system (PNS) (i.e., neuralgia, hyposmia, hypogeusia, and hypoplasia), CNS (i.e., ataxia, dizziness, acute cerebrovascular disease, epilepsy, headache, and impaired consciousness), and musculoskeletal symptoms (Matías-Guiu et al., 2020). A study conducted on 214 adult patients affected by COVID-19 reported that 36.4% had neurological symptoms indicating potential neurological symptoms of COVID-19 (Mao et al., 2020).

The evidence shows that organs with increased expression of angiotensin-converting enzyme II (ACE 2) at cell level should potentially be considered as high risk for COVID-19 infection; eg, lung, kidney, and heart. SARS-CoV-2 binds to a G-protein coupled receptor, the ACE 2, to enter the cells (Zhang, Penninger, Li, Zhong, & Slutsky, 2020). ACE 2 and its receptors are also found in the brain, especially in CNS neurons, including excitatory and inhibitory ones and glial cells, mainly astrocytes and oligodendrocytes (Chen et al., 2021). The role of ACE 2 in the CNS is beyond the regulation of cardiovascular function; ACE2 in the adult brain is involved in cognition, behavior, and locomotion. Wang et al., (2016) reported that the knockout of the ACE 2 caused a significant cognitive impairment in mice. Alterations in the activity of ACE 2, as a viral receptor,

lead to cognitive impairment and neuronal dysfunction (Wang et al., 2016). In particular, ACE 2 contributes to different brain functions-eg, depression, stress, memory consolidation, and cerebroprotection (Guimond & Gallo-Payet, 2012). In humans, ACE2 is expressed in the posterior cingulate cortex, olfactory bulb areas, and middle temporal gyrus, although the number of cells expressing ACE 2 in the prefrontal cortex and the hippocampus was zero and very few, respectively (Chen et al., 2020). Due to the spread of ACE 2 receptor through neural networks of the brain, useful information was obtained by a whole-brain scan about the COVID-19 cognitive impairment mechanism.

The brain networks' intrinsic connectivity can be studied by the resting-state functional MRI (rfMRI) that maps blood oxygen fluctuations depending on signals that are temporally synchronous, spatially distributed, and have a spontaneous low frequency (<0.08 Hz) (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007). More information can be obtained using rfMRI regarding the intrinsic functional organization of the brain (Fox & Greicius, 2010).

The present study aimed at evaluating the whole-brain neuronal circuits in patients with COVID-19 using rfMRI and finding its correlation with the cognitive impairment using the Montreal cognitive assessment (MoCA), which is a reliable brief test to detect mild cognitive impairments. This instrument includes the main cognitive domains-i.e., visuospatial ability, language, episodic memory, executive functions, orientation, and attention. This is the first study that investigates cognitive impairments in patients with COVID-19 in terms of rsfMRI characteristics. The study examines the alteration of the neural circuits of the brain in the group of patients affected by COVID-19 compared with the healthy controls.

Materials and Methods

Participants

The current study with a cross-sectional design was conducted in a teaching hospital in Shahroud, Iran, on subjects selected by the convenience sampling method. Informed consent was obtained from all the subjects for participation in the study, then they underwent an interview and MoCA test by a psychologist, and fMRI scanning by a radiologic technologist. The procedures were in accordance with the principles of the Declaration of Helsinki (2013), and the study protocol was approved by the Ethics Committee of Shahroud University of Medical Sciences.

The study was conducted on 29 patients with COVID-19 (the COV group) and 20 healthy controls (the CON group). The groups underwent similar cognitive assessment and fMRI procedures. Both of the groups were matched by demographic characteristics, including age, gender, socioeconomic status, smoking habit, BMI, and underlying systemic disease- ie, diabetes, hypertension, blood diseases such as any type of anemia, and chronic pulmonary and cardiovascular (coronary and cyanotic heart conditions) diseases. Inclusion criteria were: a positive RT-PCR test for COVID-19 and native Persian speaking. Exclusion criteria were: contraindication for MRI (pacemakers, metal implants, etc.), history of neurological diseases, including neurocognitive impairment or dementia, psychological problems, use of neuropsychological drugs, and having other brain pathology. The baseline characteristics, including demographics, educational level, etc., were collected by a questionnaire.

Montreal Cognitive Assessment

In the current study, the Persian version of MoCA was employed to evaluate cognitive function. This questionnaire assessing more cognitive domains is composed of more complex skills and thus is more sensitive to mild cognitive impairments compared with the mini-mental state examination. The MoCA, including executive functions (following the numbers, letters, words, and abstracts), attention, concentration, delayed recalling, language (naming and sentence repetition), orientation, visuoconstructional skills (drawing a cube or watch), calculations, and conceptual thinking, was used to assess cognitive domains in the subjects. The overall instrument score is 30; scores ≥ 26 are considered normal. One point is added to the overall score of the ones with the education level below the high school diploma (Kang et al., 2018). Emsaki et al., (2011) provided the Persian version of MoCA by translating the original version and testing it psychometrically (Cronbach's alpha: 0.77, concurrent validity: 0.79, sensitivity: 0.85, and specificity: 0.90) (Emsaki, Molavi, Chitsaz, Abtahi, & Asgari, 2011). The MoCA was performed by a research assistant (clinical psychologist) in the same environment for the participants of both COV and CON groups.

Paraclinical assessments

The results of laboratory tests, including hematologic and serologic ones, were extracted from patients' medical profiles. All the routine blood tests such as complete blood cell count, platelet count, hemoglobin (Hb), hematocrit (HCT), blood urea nitrogen (BUN), creatinine (Cr), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine aminotransferase (ALT),

aspartate aminotransferase (AST), alkaline phosphatase (ALP), sodium (Na), potassium (K), calcium (Ca), phosphorus (P), blood sugar levels (FBS/BS), prothrombin time (PT), partial thromboplastin time (PTT), and bilirubin tests, as well as the result of chest X-ray and chest CT scan, were recorded.

Image Acquisition

A 1.5T Avanto MRI scanner (Siemens, Germany) with an 18-channel parallel imaging head coil was used to obtain MR images. Resting-state fMRI data and oblique axial sections (TE: 45 ms; TR: 3300 ms; in-plane resolution = $3 \times 3 \text{ mm}^2$, slice thickness: 3.5 mm; flip angle: 90°) were acquired for 10 minutes using gradient-echo echo planar imaging sequence, containing 300 imaging volumes with time point=200, FOV=157×15.7 cm, and matrix = 64×64. The subjects closed their eyes while they were awake during scanning. T1 structural data were acquired using three-dimensional magnetization-prepared rapid-gradient-echo in sagittal view. Data acquisition parameters for T1 imaging were as follow: TR = 2000 ms, TE = 2.9 ms, matrix size = 256×256 and flip angle = 8 degrees.

fMRI data preprocessing

All data preprocessing steps were performed using FMRIB software library tools. The correction of head movements was performed rigidly using motion correction tool using FLIRT commands. Separation of the brain from the skull was performed on the volumes of motion-corrected Blood oxygenation level dependent (BOLD) images as implemented in the brain extraction tool algorithm. Confirmation of this process was done by visual inspection of the obtained results. Also, the affine algorithm in FMRIB's linear image registration tool (FLIRT) format was used to register different volumes of fMRI images on 3D T1 images of each person and also to transfer 3D T1 images to the standard space of MNI152. Images were converted to 2 mm voxels using a softener filter with a 5 mm full width at half maximum. Parameters related to the head movements of the two groups, both absolute and relative, were not significantly different from each other. Also, the absolute and relative amount of head movement in all subjects was less than the image voxel size (Jenkinson, Bannister, Brady, & Smith, 2002).

Analysis and processing of rest-fMRI images

Independent components (IC) analysis was used to process rs-fMRI images (Abou Elseoud et al., 2011). For IC analysis, we used the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) tool implemented in FMRIB software library (Beckmann & Smith, 2004). To do this, the multi-session temporal concatenation tool in MELODIC and the preprocessing and steps required for group data analysis in this tool were used. Spatial Independent components analysis using 60 independent component maps was used to detect resting-state networks from the control group. The reason for choosing the control group is that experience shows that using a group analysis consisting of both control and patient groups provides maps of the average of the two groups, which reduces the sensitivity of differences between the two groups in the next step, dual regression analysis (Abou Elseoud et al., 2011). Data were also normalized to variance (Variance normalization). IC mappings were then thresholded using a hypothesis test based on the fit of a Gaussian mixed model on the intensity distribution of voxels on spatial mappings and false-discovery rate control at $p < 0.5$ (Abou-Elseoud et al., 2010; Beckmann & Smith, 2004). Twenty-three rest networks were identified as classical anatomical and functional networks based on ocular examination by an experienced neuroradiologist using criteria previously described (Abou-Elseoud et al., 2010; Kiviniemi et al., 2009; Smith et al., 2009). The 23 resting-state networks mentioned above are shown in the supplementary table S1 and Fig. 1.

The analysis was performed to investigate the intergroup differences using the dual regression technique in FMRIB software library, which allows the voxel-like comparison of resting-state fMRI images (Abou-Elseoud et al., 2010; Filippini et al., 2009; Littow et al., 2010). This step includes (a) the use of group Independent components analysis spatial maps to fit a linear model on various fMRI datasets, leading to matrices (time change matrices) that describe temporal dynamics related to (B) Use these time course matrices to estimate the spatial mappings of each individual. Independent components analysis patterns for dual regression were selected from sound control data. Dual regression analysis was performed with both normalization and non-normalization of variance (dual regression command with `des norm-option` variable equal to 1 or 0, respectively) because the results have a different emphasis on the location and amplitude of the BOLD signal depending on the normalization (Allen et al., 2014; Allen, Erhardt, Wei, Eichele, &

Calhoun, 2012). With variance normalization, dual regression shows differences in both resting-state networks activity and spatial dispersion. Without normalization, only spatial changes are reflected.

As a statistical analysis, the maps of different components on different people are integrated into 4D files (one file for each original Independent components analysis mapping) and are tested in a box-by-box manner to examine statistically significant differences between groups. This is done using the non-parametric random permutation test FMRIB software library with 5000 permutations using an enhanced free threshold clustering technique to control multiple comparisons (Nichols & Holmes, 2002). The difference hypothesis between the two groups was calculated using a threshold of $p < 0.05$ by changing the vaccine to vaccine in the randomized FMRIB software library tool. To control the comparison of several detected differences between different components of Independent components analysis, the inter-IC concatenation technique was used (Abou Elseoud et al., 2014). After 5000 times permutation, the resulting datasets were separated using the `fsROI` command and the threshold of $p < 0.05$ to correct type 1 error for the selected independent components. As a new step, a gray matter regressor image was introduced into the model in the same way so that it was concatenated in the y-direction to control the gray matter differences using the `vx1` and `vx2` options in randomize FMRIB software library.

The Juelich Histological Atlas is embedded in the FMRIB software library, and the Harvard-Oxford cortical and subcortical atlases were used in the FMRIB software library to identify the anatomical features of the probabilistic Independent components analysis maps obtained. Finally, `fsLstats` and `fsLmaths` tools were used to calculate the number of non-zero voxels in the selected difference maps and their t-score values. Fig. 4 showed applied pipeline for rest-fMRI data processing and analysis.

Statistical Analysis

Data from quantitative variables were expressed as mean ($\pm$ SD) and categorical variables as frequency and percentage. Data with normal distribution were compared using a t-test, and data with non-normal distribution with the Mann-Whitney U test in order to compare continuous variables. The correlation between quantitative variables was examined by the Pearson correlation coefficient or non-parametric Spearman test. The association of cognitive indices with MRI

characteristics was assessed using a multiple linear regression model. Data were analyzed in SPSS version 20. The level of significance was <0.05.

Results

Demographics, Neuropsychological Tests, and fMRI

Table 1 shows the demographic, MoCA, and fMRI measures of patients with COVID-19 and healthy controls. Supplementary Table S2 presents more detailed characteristics of COVID-19 patients. The two groups were matched by age, gender, and education level. According to the results of MoCA, the neurocognitive performance was significantly lower in the COV group than healthy controls ($P < 0.001$). The mean ($\pm$ SD) MoCA score of the patients was 20.41 ± 6.07 . Among patients, five (17.2%) were normal and the remaining 24 (82.8%) had mild cognitive impairment. Moreover, patients with COVID-19 had impairments in visual acuity, memory, attention, speech, abstraction, information, and names.

Table 1. Demographic, MoCA, and rsfMRI data.

Variables N (%)	COV (n=29)	CON (n=20)	Sig.
Demographic Features			
Age (mean $\pm$ SD)	51.62 $\pm$ 15.99	50.7 $\pm$ 13.42	0.83
Sex (Male)	20(69%)	12(60%)	0.52
Educational status			
Elementary school	19(65.5%)	9(45%)	
Diploma degree	9(45%)	4(20%)	0.29
University degree	28(57.1%)	9(18.4%)	
MoCA			
MoCA (total)	20.41 $\pm$ 6.07	28.31 $\pm$ 3.42	<0.001*
Normal	5(17.2%)	16(80%)	<0.001*
Visual	2.07 $\pm$ 2.05	4.3 $\pm$ 1.22	<0.001*
Memory	3.52 $\pm$ 1.9	4.5 $\pm$ 0.51	0.02*
Attention	2.37 $\pm$ 1.68	5.8 $\pm$ 0.52	<0.001*
Speech	1.14 $\pm$ 0.83	1.6 $\pm$ 0.68	0.046*
Abstraction	1 $\pm$ 0.92	1.75 $\pm$ 0.64	0.003*

Information	5.44±0.74	5.95±0.22	0.005*
Name	2.38±0.73	2.9±0.31	0.004*
fMRI			
DMNpcc (IC00)	0.85±0.5	2.29±0.59	<0.001*
DAN (IC08)	1.2±0.79	2.9±1.12	<0.001*
V1 dorsal L (IC14)	1.29±0.37	0.48±0.28	<0.001*
BA25 (IC38)	0.87±0.34	0.05±0.31	<0.001*

* Significant, COV: COVID-19 group; CON: Control group; IC: independent components; MoCA: Montreal cognitive assessment; rsfMRI: resting state functional MRI.

The whole-brain functional connectivity was detected by rs-fMRI in all the 29 patients using data obtained from functional MRI. Then, the 23 brain regions of each patient were compared to obtain functional connectivity. The normal resting-state networks of the classical RNS groups identified anatomically and functionally are shown in a red-yellow color FSL, based on the $2.5 < z\text{-score} < 8$ thresholds (Fig. 1). Table 2 shows a significant increase in the functional connectivity of patients with COVID-19 compared with controls in terms of DMN and DAN, based on IC results.

Table 2. Functional brain regions showing increased functional connectivity in patients with COVID-19 compared to healthy controls.

IC	RSN	Voxels	max			max	mean	SD
			<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i> -score	<i>T</i> -score	
IC00	DMNpcc	267	40	33	57	6.86	4.12	0.69
IC08	DAN	53	52	35	58	5.69	4.44	0.53

IC: independent components; RSN: Resting State Networks; DAN: dorsal attention network; DMN: default mode network; SD: standard deviation.

Table 3 shows the results of ICs with a significant decrease in functional connectivity in V1 dorsal L and BA25 of patients with COVID-19 (Fig. 2).

Table 3. Functional brain regions showing decreased functional connectivity in patients with COVID-19 compared to healthy controls.

IC	RSN	Voxels	max			max	mean	SD
			<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i> -score	<i>T</i> -score	
IC14	V1 dorsal L	10299	73	23	37	5.38	2.44	0.49
IC38	BA25	7617	42	27	48	5.6	2.67	0.49

IC: independent components; RSN: Resting State Networks; DAN: dorsal attention network; DMN: default mode network; SD: standard deviation.

Correlations between Functional Connectivity, Neuropsychological Variables, and Paraclinical assessments

The detailed information about the comparison of paraclinical data of participants with normal and abnormal MoCA scores, such as their association with rs-fMRI data, as well as Hb, ESR, CRP, and blood oxygen levels, is shown in tables 4, 5 and 6.

Table 4. The comparison of rsfMRI data in participants with normal and abnormal MoCA.

	COV		CON	
	MoCA(<26)	MoCA (≥26)	MoCA(<26)	MoCA (≥26)
DMNpcc (IC00)	0.87±0.5	0.75±0.54	2.44±1.03	2.25±0.55
P-Value	0.11		0.18	
DAN (IC08)	1.29±0.81	0.69±0.46	2.68±0.08	3.02±1.16
P-Value	0.17		0.62	
V1 dorsal L (IC14)	1.32±0.38	1.13±0.23	0.21±0.36	0.52±0.26
P-Value	0.35		0.09	
BA25 (IC38)	0.89±0.36	0.77±0.14	-0.05±0.25	0.03±0.26
P-Value	0.53		0.61	

COV: COVID-19 group; CON: Control group; IC: independent components; MoCA: Montreal cognitive assessment; rsfMRI: resting state functional MRI.

Table 5. The comparison of paraclinic data in all participants with normal and abnormal MoCA.

	MoCA (≥ 26)	MoCA (< 26)	Sig.
rsfMRI			
DMNpcc (IC00)	1.05 $\pm$ 0.75	1.95 $\pm$ 0.82	$<0.001^*$
DAN (IC08)	1.46 $\pm$ 0.88	2.56 $\pm$ 1.4	0.002*
V1 dorsal L (IC14)	1.2 $\pm$ 0.52	0.64 $\pm$ 0.35	$<0.001^*$
BA25 (IC38)	0.78 $\pm$ 0.46	0.18 $\pm$ 0.38	$<0.001^*$
Hb			
Normal	19(50%)	19(50%)	0.27
Abnormal	5(71.4%)	2(28.6%)	
ESR			
Normal	9(33.3%)	18(66.7%)	0.001*
Abnormal	11(91.7%)	1(8.3%)	
CRP			
Normal	11(39.3%)	17(60.7%)	0.04*
Abnormal	9(75%)	3(25%)	
O ₂ Sat.			
Normal	24(53.3%)	21(46.7%)	0.11
Abnormal	3(100%)	0	

* Significant, IC: independent components; MoCA: Montreal cognitive assessment; rsfMRI: resting state functional MRI; Hb: hemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive Protein; O₂ Sat.: oxygen saturation. Normal range: O₂ Sat., 95–100%; Hb, 14–18 mg/dl; ESR, Up to 15 mm/hr; CRP, <6 mg/dl.

Table 6. The correlation between functional brain regions showing alternation in functional connectivity and paraclinical data.

Variables	DMNpcc (IC00)	DAN (IC08)	V1 dorsal L BA25 (IC38) (IC14)	
Hb				
Normal	1.62±0.88	2.17±1.22	0.91±0.56	0.45±0.54
Abnormal	0.76±0.58	0.99±1.04	1.1±0.21	0.75±0.17
P-Value	0.03*	0.03*	0.4	0.18
ESR				
Normal	1.83±0.93	2.37±1.33	0.66±0.39	0.23±0.41
Abnormal	0.93±0.38	1.43±0.97	1.37±0.36	0.87±0.35
P-Value	0.004*	0.04*	<0.001*	<0.001*
CRP				
Normal	1.85±0.86	2.37±1.32	0.71±0.46	0.3±0.5
Abnormal	0.78±0.53	1.24±0.73	1.41±0.36	0.86±0.38
P-Value	<0.001*	0.008*	<0.001*	0.002*
O₂ Sat.				
Normal	1.49±0.9	1.99±1.28	0.93±0.53	0.49±0.52
Abnormal	0.67±0.36	1.1±0.5	1.35±1.96	0.93±0.01
P-Value	0.12	0.24	0.18	0.15

* Significant, IC: independent components; Hb: hemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive Protein; O₂ Sat.: oxygen saturation. Normal range: O₂ Sat., 95–100%; Hb, 14–18 mg/dl; ESR, Up to 15 mm/hr; CRP, <6 mg/dl.

According to the obtained results, a significant correlation was found between the rs-fMRI data and MoCA subdomains, except memory and speech. Table 7 on the correlation between functional brain regions shows alternations in functional connectivity and scores of MoCA subdomains.

Table 7. The correlation between functional brain regions showing alternation in functional connectivity and subcriteria of MoCA in patients with COVID-19.

MoCA	DMNpcc (IC00)	DAN (IC08)	V1 dorsal L (IC14)	BA25 (IC38)
Total	R=0.47	R=0.3	R= -0.49	R= - 0.54
P-Value	0.001*	0.04*	0.001*	<0.001*
Visual	R=0.53	R=0.43	R= - 0.38	R= - 0.51
P-Value	0.001*	0.003*	0.004*	<0.001*
Memory	R=0.25	R=0.2	R= - 0.14	R= - 0.23
P-Value	0.09	0.19	0.36	0.12
Attention	R=0.74	R=0.62	R= -0.59	R= - 0.66
P-Value	<0.001*	<0.001*	<0.001*	<0.001*
Speech	R=0.27	R=0.28	R= - 0.26	R= - 0.25
P-Value	0.07	0.06	0.08	0.09
Abstraction	R=0.39	R=0.3	R= -0.3	R=0.4
P-Value	0.008*	0.04*	0.04*	0.006*
Information	R=0.43	R=0.36	R= - 0.29	R = - 0.3
P-Value	0.003*	0.01*	0.04*	0.04*
Name	R=0.29	R=0.3	R= - 0.25	R=0.34
P-Value	0.049*	0.04*	0.08	0.01*

* Significant, IC: independent components; MoCA: Montreal cognitive assessment.

Discussion

To our knowledge this is the first study aimed at assessing cognitive impairments and investigating the whole-brain functional connectivity using rs-fMRI in patients with COVID-19 compared with healthy controls. The COV group obtained a lower score in the MoCA test, increased functional connectivity in the DMN (IC00) and DAN (IC08), and decreased functional connectivity in the V1 dorsal L (IC14) and BA25 (IC38) at the baseline compared with healthy controls (Fig. 3). Cognitive impairment was mainly manifested in visual acuity, attention, abstraction, information, and name domains, while speech and memory had no deficits based on the MoCA results. Finally,

the functional connectivity of these brain regions showed a correlation with the total score of MoCA. It should be noted specific factors that may affect the final analysis results include the mental status of the subject, the physiology of the BOLD signal, and the methodology of the analysis approach. A study about pattern of cognitive deficits during the post-critical acute stage of severe COVID-19 reported mild to severe deficits at MoCA with extensive cognitive impairment in memory, attention, executive, and visuospatial functions, but relatively preserved language and orientation dysfunction (Beaud et al., 2021). Blazhenets et al. assessed MoCA and PET scans in 8 COVID-19 patients at the subacute and chronic stages found a residual impairment still measurable in some patients six months after the infection of COVID-19 (Blazhenets et al., 2021).

DMN contributes to internal psychological processing. There is a correlation between external environmental monitoring and internally directed cognition (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner, Andrews-Hanna, & Schacter, 2008); its activity decreases during a variety of cognitive tasks requiring external perceptual attention (Greicius, Krasnow, Reiss, & Menon, 2003). In contrast, DAN contributes to controls that are goal- and attention-oriented (Scaif, Ahn, Beck, & Lleras, 2014). It has a significant correlation with externally directed cognition (Corbetta & Shulman, 2002) and its activity increases during cognitive tasks focusing on external visuospatial attention (Miller & Buschman, 2013). DMN and DAN show an anticorrelated activity pattern in resting and task (internal and external cues) state studies. In addition, when the system works properly, they show a competitive relationship that represents a cerebral mechanism supporting cognitive functions, switching focus between internal (supported by DMN) and external cues (supported by DAN) (Esposito et al., 2018b; Franzmeier, Götter, et al., 2017). The details of how the DMN and DAN interact remain unknown. However, the current study results showed that both DMN and DAN increased functional connectivity. Therefore, there were no anticorrelations between them. It seems that a decrease in DMN-DAN anticorrelation is part of the normal process of aging (Esposito et al., 2018a); hence, any abnormality in this process can be associated with cognitive dysfunction and increase the risk of Alzheimer's disease (28) and mild cognitive impairment (Franzmeier, Buerger, et al., 2017; Zhu et al., 2016). As previously mentioned, in patients with COVID-19, the activity of the DAN network increased, whereas due

to the cognitive deficit based on MoCA results, it was expected to decrease. The patterns of DAN and DMN activity may be related to a compensatory mechanism against cognitive impairment in patients with COVID-19.

Both CRP and ESR, as markers of inflammation, increased in patients with COVID-19. Also, evidence showing that the excessive immune response was reported following the induction of cytokine storm by the virus (Nile et al., 2020). These patterns were also observed in ARDS as a systemic inflammatory disease that some of its symptoms are similar to those of the COVID-19.

As several studies reported (35-37), in the current study, the MoCA score was also negatively correlated with ESR and CRP levels. Marsland et al., (2017) showed an association between interleukin-6, a systemic inflammation indicator, and alterations in the DMN activity. Moreover, the DMN may contribute to the incidence of psychiatric and neurological disorders correlating with systemic inflammations-eg, anxiety, and mood disorders, characterized by emotion regulation impairments and raised systemic inflammation (Labrenz et al., 2019; Rabany et al., 2017). Cognitive impairments are reported in survivors of ARDS even several years after discharge (Hopkins et al., 2005). Patients with ARDS may experience prolonged hypotension, metabolic abnormalities, and hypoxemia, which predispose them to injuries in the peripheral and central nervous systems, followed by neurologic and cognitive impairments (Hopkins, Gale, & Weaver, 2006; Hopkins, Weaver, Chan, & ORME, 2004). In contrast, no significant association was found between blood oxygen levels, MoCA scores, and rs-fMRI data in the current study. One possible explanation for inconsistent finding is our small sample size. On the other hand, ARDS survivors experience prolonged psychiatric symptoms after discharge. Systematic reviews reported 17% to 43% depression, 23% to 48% anxiety, and 8% to 35% post-traumatic stress disorder (PTSD) symptoms in ARDS survivors. The several studies examine the impact of stress related to COVID-19. Patients with COVID-19 experience prolonged stress because of fear of death. So, COVID-19 has already led to various stress-related disorders, including anxiety and posttraumatic stress disorder (Tucker & Czapla, 2020). Our data in line with previous studies, show that the DMN activity may contribute to the incidence of psychiatric disorders correlating with anxiety (Vicentini et al., 2017).

Based on the obtained results, a decrease of functional connectivity in patients with COVID-19 was observed in the occipital cortex, including bilateral lingual gyri and left middle occipital gyrus

located in the visual network, which contributes to visual memory and visuospatial function processing (Cai et al., 2017). The potential brain bases for the impaired multiple cognitive domains were determined based on the findings of COVID-19 that were consistent with those of a study reporting the neurological symptoms in patients with COVID-19 (Li et al., 2020). There was a significant correlation between the occipital lobe activities and functional connectivity, and visual hallucination, visual memory, and visuospatial function (Yao et al., 2016). Hence, the occipital cortex functional impairments may play a role in damage to multiple cognitive domains, especially in terms of visual cognition, in patients with COVID-19.

In terms of the study limitations, first, the sample size was small. Second, because of the high infectivity and fatality of COVID-19 and its psychosocial impacts, both the patients and researchers experienced a huge amount of stress. Third, the brain function impairments and recovery should be investigated in patients with COVID-19 through longitudinal studies.

Conclusions

In conclusion, the study results indicated significant clinical changes in resting-state functional connectivity of patients with COVID-19. In such patients, functional connectivity within different cognitive networks decreased and cognitive impairments occurred, according to MoCA results. Further longitudinal studies with larger sample sizes are required to obtain more conclusive results and understand the rsfMRI of cognitive networks and changes in neural circuits.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interests.

Funding This research was funded by a specific project grant of Shahrood University of Medical Sciences (Grant No: 98133). This paper was not extracted from a thesis. The present study complies with contemporary laws and regulations in Iran. The funding organization had no role in the design and conduct of the study; in the collection, analysis and interpretation of the data; or in the preparation, review, or approval of the manuscript and the decision to submit the paper for publication.

Ethical approval The present study was completed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health research established by ministry of Health and

Medical Education and Ministry of Science, Research and Technology, Iran. We obtained the approval by the Ethics Review Committee of Shahroud Medical University Iran (IR.SHMU.REC.1398.174).

Informed consent All subjects provided their informed written consent for participation in the present study.

Availability of data and material The authors declare that all data supporting the findings of this study are available within this article.

Acknowledgements The authors wish to thank all the participants in this project. Also they thank the manager of Imam Hossein Hospital of Shahroud for their sincere cooperation.

Author Contributions

Conceptualization, M.N.S. and J.Sh.K.; Methodology, R.R., and M.S.; Formal Analysis, R.R. and J. Sh. K.; Investigation, H.Gh., S.M.S.T.; Writing – Original Draft, R.R. and M.N.S.; Writing – Review & Editing, H.Sh. and M.S.; Funding Acquisition, H.Sh.; Resources, H.Sh. and M.S.; Supervision, H.Sh.

References

- Abou-Elseoud, Ahmed, Starck, Tuomo, Remes, Jukka, Nikkinen, Juha, Tervonen, Osmo, & Kiviniemi, Vesa. (2010). The effect of model order selection in group PICA. *Hum. Brain Mapp.*, 31(8), 1207-1216. doi: 10.1002/hbm.20929.
- Abou Elseoud, Ahmed, Littow, Harri, Remes, Jukka, Starck, Tuomo, Nikkinen, Juha, Nissilä, Juuso, . . . Kiviniemi, Vesa J. (2011). Group-ICA model order highlights patterns of functional brain connectivity. *Front. Syst. Neurosci.*, 5, 37. doi: <https://doi.org/10.3389/fnsys.2011.00037>
- Abou Elseoud, Ahmed, Nissilä, Juuso, Liettu, Anu, Remes, Jukka, Jokelainen, Jari, Takala, Timo, . . . Koponen, Hannu. (2014). Altered resting-state activity in seasonal affective disorder. *Hum. Brain Mapp.*, 35(1), 161-172. doi: 10.1002/hbm.22164
- Al-Sarraj, Safa, Troakes, Claire, Hanley, Brian, Osborn, Michael, Richardson, Mark P, Hotopf, Matthew, . . . Everall, IP. (2021). Invited Review: The spectrum of neuropathology in COVID-19. *Neuropathology and applied neurobiology*, 47(1), 3-16.
- Allen, Elena A, Damaraju, Eswar, Plis, Sergey M, Erhardt, Erik B, Eichele, Tom, & Calhoun, Vince D. (2014). Tracking whole-brain connectivity dynamics in the resting state. *Cereb cortex*, 24(3), 663-676. doi: 10.1093/cercor/bhs352
- Allen, Elena A, Erhardt, Erik B, Wei, Yonghua, Eichele, Tom, & Calhoun, Vince D. (2012). Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study. *Neuroimage*, 59(4), 4141-4159. doi: 10.1016/j.neuroimage.2011.10.010
- Andrews-Hanna, Jessica R, Reidler, Jay S, Sepulcre, Jorge, Poulin, Renee, & Buckner, Randy L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron*, 65(4), 550-562. doi: 10.1016/j.neuron.2010.02.005
- Beaud, Valérie, Crottaz-Herbette, Sonia, Dunet, Vincent, Vaucher, Julien, Bernard-Valnet, Raphaël, Du Pasquier, Renaud, . . . Clarke, Stephanie. (2021). Pattern of cognitive deficits in severe COVID-19. *Journal of Neurology, Neurosurgery & Psychiatry*, 92(5), 567-568.
- Beckmann, Christian F, & Smith, Stephen M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging*, 23(2), 137-152. doi: 10.1109/TMI.2003.822821.

- Blazhenets, Ganna, Schröter, Nils, Bormann, Tobias, Thurow, Johannes, Wagner, Dirk, Frings, Lars, . . . Hosp, Jonas A. (2021). Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients. *Journal of Nuclear Medicine*.
- Bostancıoğlu, Mehmet. (2020). SARS-CoV2 entry and spread in the lymphatic drainage system of the brain. *Brain Behav Immun*, S0889-1591(0820)30695-30694. doi: 10.1016/j.bbi.2020.04.080
- Buckner, Randy L, Andrews-Hanna, Jessica R, & Schacter, Daniel L. (2008). The brain's default network: anatomy, function, and relevance to disease. doi: 10.1196/annals.1440.011
- Cai, Suping, Chong, Tao, Peng, Yanlin, Shen, Wenyue, Li, Jun, von Deneen, Karen M, . . . Initiative, Alzheimer's Disease Neuroimaging. (2017). Altered functional brain networks in amnesic mild cognitive impairment: a resting-state fMRI study. *Brain imaging and behavior*, 11(3), 619-631.
- Chen, Rongrong, Wang, Keer, Yu, Jie, Howard, Derek, French, Leon, Chen, Zhong, . . . Xu, Zhenghao. (2021). The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Frontiers in neurology*, 11, 1860.
- Chen, Rongrong, Yu, Jie, Wang, Keer, Howard, Derek, French, Leon, Chen, Zhong, . . . Xu, Zhenghao. (2020). The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *bioRxiv*.
- Corbetta, Maurizio, & Shulman, Gordon L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience*, 3(3), 201-215.
- Emsaki, Golita, Molavi, Hussein, Chitsaz, Ahmad, Abtahi, Mahsa Movahed, & Asgari, Karim. (2011). Psychometric Properties of the Montreal Cognitive Assessment (MoCA) in Parkinson's Disease Patients in Isfahan. *Journal of Isfahan Medical School*, 29(158).
- Esposito, Roberto, Cieri, Filippo, Chiacchiarretta, Piero, Cera, Nicoletta, Lauriola, Mariella, Di Giannantonio, Massimo, . . . Ferretti, Antonio. (2018a). Modifications in resting state functional anticorrelation between default mode network and dorsal attention network: comparison among young adults, healthy elders and mild cognitive impairment patients. *Brain imaging and behavior*, 12(1), 127-141.
- Esposito, Roberto, Cieri, Filippo, Chiacchiarretta, Piero, Cera, Nicoletta, Lauriola, Mariella, Di Giannantonio, Massimo, . . . Ferretti, Antonio. (2018b). Modifications in resting state

- functional anticorrelation between default mode network and dorsal attention network: comparison among young adults, healthy elders and mild cognitive impairment patients. *Brain Imaging Behav.*, 12(1), 127-141. doi: 10.1007/s11682-017-9686-y
- Filippini, Nicola, MacIntosh, Bradley J, Hough, Morgan G, Goodwin, Guy M, Frisoni, Giovanni B, Smith, Stephen M, . . . Mackay, Clare E. (2009). Distinct patterns of brain activity in young carriers of the APOE- ϵ 4 allele. *Proc. Natl. Acad. Sci.*, 106(17), 7209-7214. doi: <https://doi.org/10.1073/pnas.0811879106>
- Fox, Michael, & Greicius, Michael. (2010). Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience*, 4(19). doi: 10.3389/fnsys.2010.00019
- Franzmeier, Nicolai, Buerger, Katharina, Teipel, Stefan, Stern, Yaakov, Dichgans, Martin, Ewers, Michael, & Initiative, Alzheimer's Disease Neuroimaging. (2017). Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI. *Neurobiol Aging*, 50, 152-162. doi: 10.1016/j.neurobiolaging.2016.11.013
- Franzmeier, Nicolai, Göttler, Jens, Grimmer, Timo, Drzezga, Alexander, Áraque-Caballero, Miguel A, Simon-Vermot, Lee, . . . Janowitz, Daniel. (2017). Resting-state connectivity of the left frontal cortex to the default mode and dorsal attention network supports reserve in mild cognitive impairment. *Frontiers in aging neuroscience*, 9, 264.
- Greicius, Michael D, Krasnow, Ben, Reiss, Allan L, & Menon, Vinod. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, 100(1), 253-258.
- Guimond, Marie-Odile, & Gallo-Payet, Nicole. (2012). The Angiotensin II Type 2 Receptor in Brain Functions: An Update. *Int. J. Hypertens.*, 2012, 351758. doi: 10.1155/2012/351758
- Hopkins, Ramona O, Gale, Shawn D, & Weaver, Lindell K. (2006). Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. *Brain Injury*, 20(3), 263-271.
- Hopkins, Ramona O, Weaver, Lindell K, Chan, Karen J, & ORME, JAMES F. (2004). Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J. Int. Neuropsychol. Soc.*, 10(7), 1005-1017.
- Hopkins, Ramona O, Weaver, Lindell K, Collingridge, Dave, Parkinson, R Bruce, Chan, Karen J, & Orme Jr, James F. (2005). Two-year cognitive, emotional, and quality-of-life outcomes

- in acute respiratory distress syndrome. *American journal of respiratory and critical care medicine*, 171(4), 340-347.
- Jenkinson, Mark, Bannister, Peter, Brady, Michael, & Smith, Stephen. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, 17(2), 825-841. doi: 10.1016/s1053-8119(02)91132-8.
- Kang, Jae Myeong, Cho, Young-Sung, Park, Soowon, Lee, Byung Ho, Sohn, Bo Kyung, Choi, Chi Hyun, . . . Lee, Jun-Young. (2018). Montreal cognitive assessment reflects cognitive reserve. *BMC geriatrics*, 18(1), 261-261. doi: 10.1186/s12877-018-0951-8
- Karuppan, Mohan Kumar Muthu, Devadoss, Dinesh, Nair, Madhavan, Chand, Hitendra S, & Lakshmana, Madepalli K. (2021). SARS-CoV-2 infection in the central and peripheral nervous system-associated morbidities and their potential mechanism. *Molecular neurobiology*, 1-16.
- Kiviniemi, Vesa, Starck, Tuomo, Remes, Jukka, Long, Xiangyu, Nikkinen, Juha, Haapea, Marianne, . . . Zang, Yu-Feng. (2009). Functional segmentation of the brain cortex using high model order group PICA. *Hum brain mapp*, 30(12), 3865-3886. doi: 10.1002/hbm.20813
- Labrenz, Franziska, Ferri, Francesca, Wrede, Karsten, Forsting, Michael, Schedlowski, Manfred, Engler, Harald, . . . Costantini, Marcello. (2019). Altered temporal variance and functional connectivity of BOLD signal is associated with state anxiety during acute systemic inflammation. *NeuroImage*, 184, 916-924. doi: 10.1016/j.neuroimage.2018.09.056
- Li, Zhengqian, Liu, Taotao, Yang, Ning, Han, Dengyang, Mi, Xinning, Li, Yue, . . . Guo, Xiangyang. (2020). Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. *Front Med*, 1-9. doi: 10.1007/s11684-020-0786-5
- Littow, Harri, Abou Elseoud, Ahmed, Haapea, Marianne, Isohanni, Matti, Moilanen, Irma, Mankinen, Katariina, . . . Remes, Jukka. (2010). Age-related differences in functional nodes of the brain cortex—a high model order group ICA study. *Front syst neurosci*, 4, 32. doi: 10.3389/fnsys.2010.00032. eCollection 2010
- Ma, Di, Chen, Chong-Bo, Jhanji, Vishal, Xu, Ciyan, Yuan, Xiang-Ling, Liang, Jia-Jian, . . . Ng, Tsz Kin. (2020). Expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in human

- primary conjunctival and pterygium cell lines and in mouse cornea. *Eye*, 1-8. doi: <https://doi.org/10.1038/s41433-020-0939-4>
- Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proc. Natl. Acad. Sci.*, 104(32), 13170. doi: 10.1073/pnas.0700668104
- Mao, Ling, Wang, Mengdie, Chen, Shanghai, He, Quanwei, Chang, Jiang, Hong, Candong, . . . Hu, Bo. (2020). Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. *medRxiv*, 2020.2002.2022.20026500. doi: 10.1101/2020.02.22.20026500
- Matías-Guiu, J., Gomez-Pinedo, U., Montero-Escribano, P., Gomez-Iglesias, P., Porta-Etessam, J., & Matias-Guiu, J. A. (2020). Should we expect neurological symptoms in the SARS-CoV-2 epidemic? *Neurología*, 35(3), 170-175. doi: <https://doi.org/10.1016/j.nrleng.2020.03.002>
- Miller, Earl K, & Buschman, Timothy J. (2013). Cortical circuits for the control of attention. *Curr. Opin. Neurobiol.*, 23(2), 216-222. doi: 10.1016/j.conb.2012.11.011
- Nichols, Thomas E, & Holmes, Andrew P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum brain mapp*, 15(1), 1-25. doi: 10.1002/hbm.1058
- Nile, Shivraj Hariram, Nile, Arti, Qiu, Jiayin, Li, Lin, Jia, Xu, & Kai, Guoyin. (2020). COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine Growth Factor Rev*, 53, 66-70. doi: <https://doi.org/10.1016/j.cytogfr.2020.05.002>
- Organization, World Health. (2020). Novel Coronavirus (2019-nCoV): situation report, 3.
- Rabany, Liron, Diefenbach, Gretchen J, Bragdon, Laura B, Pittman, Brian P, Zertuche, Luis, Tolin, David F, . . . Assaf, Michal. (2017). Resting-state functional connectivity in generalized anxiety disorder and social anxiety disorder: evidence for a dimensional approach. *Brain connect*, 7(5), 289-298. doi: 10.1089/brain.2017.0497
- Scalf, Paige E, Ahn, JeeWon, Beck, Diane M, & Lleras, Alejandro. (2014). Trial history effects in the ventral attentional network. *J cogn neurosci*, 26(12), 2789-2797. doi: 10.1162/jocn_a_00678
- Singhal, Tanu. (2020). A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr*, 87(4), 281-286. doi: 10.1007/s12098-020-03263-6

- Smith, Stephen M, Fox, Peter T, Miller, Karla L, Glahn, David C, Fox, P Mickle, Mackay, Clare E, . . . Laird, Angela R. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proc. Natl. Acad. Sci.* , 106(31), 13040-13045. doi: <https://doi.org/10.1073/pnas.0905267106>
- Tucker, P, & Czapla, CS. (2020). Post-COVID stress disorder: another emerging consequence of the global pandemic. *Psychiatric Times*.
- Vicentini, Jéssica Elias, Weiler, Marina, Almeida, Sara Regina Meira, de Campos, Brunno Machado, Valler, Lenise, & Li, Li Min. (2017). Depression and anxiety symptoms are associated to disruption of default mode network in subacute ischemic stroke. *Brain imaging and behavior*, 11(6), 1571-1580.
- Wang, Xiao-Li, Iwanami, Jun, Min, Li-Juan, Tsukuda, Kana, Nakaoka, Hirotomo, Bai, Hui-Yu, . . . Horiuchi, Masatsugu. (2016). Deficiency of angiotensin-converting enzyme 2 causes deterioration of cognitive function. *NPJ Aging Mech. Dis.* , 2, 16024-16024. doi: 10.1038/npjamd.2016.24
- Wu, Yeshun, Xu, Xiaolin, Chen, Zijun, Duan, Jiahao, Hashimoto, Kenji, Yang, Ling, . . . Yang, Chun. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav. Immun.* doi: <https://doi.org/10.1016/j.bbi.2020.03.031>
- Yao, Nailin, Cheung, Charlton, Pang, Shirley, Chang, Richard Shek-kwan, Lau, Kui Kai, Suckling, John, . . . Ho, Shu-Leong. (2016). Multimodal MRI of the hippocampus in Parkinson's disease with visual hallucinations. *Brain Structure and Function*, 221(1), 287-300.
- Zhang, Haibo, Penninger, Josef M, Li, Yimin, Zhong, Nanshan, & Slutsky, Arthur S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med.*, 1-5. doi: 10.1007/s00134-020-05985-9
- Zhou, Fei, Yu, Ting, Du, Ronghui, Fan, Guohui, Liu, Ying, Liu, Zhibo, . . . Cao, Bin. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*, 395(10229), 1054-1062. doi: [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
- Zhu, Haoze, Zhou, Peng, Alcauter, Sarael, Chen, Yuanyuan, Cao, Hongbao, Tian, Miao, . . . Zhao, Xin. (2016). Changes of intranetwork and internetwork functional connectivity in

Alzheimer's disease and mild cognitive impairment. *Journal of Neural Engineering*, 13(4), 046008.

Accepted Manuscript (Uncorrected Proof)

Fig. 1. The normal resting-state networks extracted from the data Melodic toolbox of FSL. The 23 identified networks were post-processed for dual regression analysis. These RSN are shown in FSL red-yellow color using a $2.5 < z\text{-score} < 8$ as thresholds. IC: Independent components.

A

B

Fig. 2. Independent components (IC) with a significant increase (A) and decrease (B) in functional connectivity in patients with COVID-19.

Fig. 3. Brain regions where a significant difference between healthy controls (A) compared with patients with COVID-19 (B) in the level of brain activity. Significant regions are colored in red ($P < 0.001$).

Fig. 4. Applied pipeline for rest-fMRI data processing and analysis.