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The effect of SARS-CoV-2 virus on resting-state functional connectivity during adolescence: Investigating brain correlates of psychotic-like experiences and SARS-CoV-2 related inflammation response

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ABSTRACT

We first aimed to investigate resting-state functional connectivity (rs-FC) differences between adolescents exposed to SARS-CoV-2 and healthy controls. Secondly, the moderator effect of PLEs on group differences in rs-FC was examined. Thirdly, brain correlates of inflammation response during acute SARS-CoV-2 infection were investigated. Eighty-two participants aged between 14 and 24 years (SARS-CoV-2 (n = 35), controls (n = 47)) were examined using rs-fMRI. Seed-based rs-FC analysis was performed. The positive subscale of Community Assessment of Psychotic Experiences-42 (CAPE-Pos) was used to measure PLEs. The SARS-CoV-2 group had a lesser rs-FC within sensorimotor network (SMN), central executive network (CEN) and language network (LN), but an increased rs-FC within visual network (VN) compared to controls. No significant differences were detected between the groups regarding CAPE-Pos-score. However, including CAPE-Pos as a covariate, we found increased rs-FC within CEN and SN in SARS-CoV-2 compared to controls. Among the SARS-CoV-2 group, neutrophil/lymphocyte and thrombocyte*neutrophil/lymphocyte ratio was correlated with decreased/increased FC within DMN and SN, and increased FC within CEN. Our results showed rs-FC alterations within the SMN, CEN, LN, and VN among adolescents exposed to SARS-CoV-2. Moreover, changes in rs-FC associated with PLEs existed in these adolescents despite the absence of clinical changes. Furthermore, inflammation response was correlated with alterations in FC within the triple network system.

1. Introduction

The novel coronavirus (Severe acute respiratory syndrome-2 (SARS-CoV-2)) which caused the coronavirus disease 2019 (COVID-19) pandemic led to 757 million confirmed cases and 6.8 million deaths world-wild by February 2023 ("WHO Coronavirus (COVID-19) Dashboard," 2023). A recent meta-analysis showed that approximately one in two survivors of SARS-CoV-2 suffer from physical and mental sequelae for up to 12 months after infection (Zeng et al., 2023). The pooled prevalence of neuropsychiatric symptoms among SARS-CoV-2 survivors within 12 months was reported as 41.2 % mild/moderate anxiety, 6 % severe/very severe anxiety, 18.3 % depression, 17.9 % post-traumatic stress disorders, 13.5 % sleep disturbance, 17.5 % memory impairment, and 15.7 % lost of taste or smell infection (Zeng et al., 2023).

In addition, concerns have been raised regarding a possible link between SARS-CoV-2 and new-onset psychosis, though the validity of

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this association is still questioned (Moccia et al., 2023). Although the annual incidence of first-episode psychosis ranges from 24.6 to 40.9 per 100.000 inhabitants (Fearon et al., 2006; Kirkbride et al., 2012), its estimated incidence in SARS-CoV-2 survivors over six months reported as 0.42 % in a recent retrospective cohort study (Taquet et al., 2021). Moreover, Oh et al. (2021) found that the risk of first-episode psychosis in the SARS-CoV-2 group (0.17 %) was 2.49 times higher than that in the control group (0.04 %) within six months. However, this observed increase in the incidence of psychosis could also be attributed to the possible confounders such as misdiagnosis of delirium, undocumented previous mental illness, iatrogenic factors (e.g., steroids), or stress related to the pandemic (e.g., quarantine, uncertainty regarding SARS-CoV-2 infection) (Moccia et al., 2023).

Several shared risk factors, including genetic risk, migration, adverse childhood experiences, peer bullying, substance use, perinatal events, neuroanatomical and neurocognitive changes, depressive/anxiety symptoms and self-harm/suicide have been reported between psychosis and psychotic-like experiences (PLEs) (Staines et al., 2022; van Os and Reininghaus, 2016). In addition, peripheral inflammation as a result of infections or auto-immune diseases may trigger PLEs (Khandaker et al., 2014) and psychosis (Fraguas et al., 2017). Thus, because of the assumption of a clinical continuum and several shared risk factors, especially peripheral inflammation, between PLEs and psychotic disorder, several studies have also begun to examine whether PLEs are associated with SARS-CoV-2 infection (Fraguas et al., 2017; Khandaker et al., 2014; van Os and Reininghaus, 2016). A large-scale epidemiological study confirmed that COVID-19 infection was associated with significantly greater odds of having PLEs (Oh et al., 2021). Yilmaz Kafali et al. (2022) also showed that PLEs were more frequently and severely experienced by SARS-CoV-2 adolescent survivors than controls. Moreover, the authors showed an association between the severity of SARS-CoV-2 infection and PLE frequency, which was fully mediated by anxiety/depressive symptoms (Yilmaz Kafali et al., 2022). Despite the possible association between SARS-CoV-2 and PLEs, to our knowledge, the neural correlates of PLEs among adolescents exposed to SARS-CoV-2 have not been investigated yet.

Various studies have examined functional connectivity (FC) changes in the brain among individuals who experience PLEs. Data from 3434 9–11-year-olds in the Adolescent Brain Cognitive Development (ABCD) study demonstrated that children experiencing PLEs had decreased FC in the salience network (SN), default mode network (DMN), and fronto-parietal network (also known as central executive network (CEN)) than controls (Karcher et al., 2019). Similar to Karcher et al.'s study, reduced global efficiency of DMN and SN (Sheffield et al., 2016); higher connectivity within DMN and lower connectivity within CEN (Blain et al., 2020); and hypoconnectivity between dorsal striatum, dorsolateral prefrontal, anterior cingulate, and primary motor cortices (Sabaroedin et al., 2019) were reported. Thus, we assumed that SARS-CoV-2 infection may cause dysconnectivity within DMN, SN, and CEN which may provide a basis for PLEs.

Abnormal FC findings among SARS-CoV-2 survivors without neurological manifestations have been documented since the beginning of the COVID-19 pandemic. A recent resting-state functional magnetic resonance imaging (rs-fMRI) study revealed that SARS-CoV-2 survivors had an increased amplitude of low-frequency fluctuation (ALFF) values in the limbic system, striatum, and left frontal, parietal, and temporal lobes than controls (Du et al., 2022). Hafiz et al. (2022) showed an enhanced FC within basal ganglia and precuneus networks, while a reduced FC in the language network (LN). In addition, an increase in FC was observed in SARS-CoV-2 survivors within DMN and dorsal attention network (DAN) compared to healthy controls (Niroumand Sarvandani et al., 2021) (Fu et al. (2021) reported an increased occurrence of a dynamic FC state with heterogeneous patterns between sensorimotor network (SMN) and visual network (VN) in COVID-19 survivors compared to controls. In a multi-model MRI study, Benedetti et al. (2021) found that the severity of inflammation during the acute phase of SARS-CoV-2 infection was associated with a reduction of resting-state FC between DMN, language network and CEN; and SN and DAN. Despite these abnormal FC findings, little is known regarding the effect of COVID-19 disease on the developing brain.

In the current study, we first aimed to investigate the alterations of the neural circuits of the brain among adolescents exposed to SARS-CoV-2 compared to healthy controls, using rs-fMRI. Considering the possible association between PLEs and the SARS-CoV-2 infection, our second aim was to examine the effect of the Community Assessment of Psychotic Experiences-42 (CAPE-42) score on the group differences in resting-state FC. Moreover, since inflammation markers were found to be related to more severe PLEs (Edmondson-Stait et al., 2022), thirdly, we aimed to investigate the brain correlates associated with SARS-CoV-2-related inflammation response during the acute infection. We considered the following hypothesis: (1) Adolescents who were exposed to SARS-CoV-2 show alterations within DMN, SMN, VN, LN, and DAN compared to controls. (2) When PLEs are included as a covariate, adolescents exposed to SARS-CoV-2 have dysconnectivity within DMN, CEN, and SN compared to controls. (3) The severity of inflammation during the acute infection period is associated with a reduced FC of DMN, SN, CEN, LN, and DAN.

2. Methods

2.1. Participants and study procedure

This cross-sectional case-control study consists of two groups: Participants infected with the SARS-CoV-2 virus (SARS-CoV-2 group) and the control group (CG). The SARS-CoV-2 group was referred by the Ankara City Hospital Department of Child Infectious Diseases and the Department of Infectious Diseases between December 2020 and October 2021. For the CG, we used the data from an earlier study, entitled "Developmental Trajectory of Working Memory Circuits in Adolescent and Young Adult Twins: Cortical maturation, environmental risk, and the implications for schizophrenia and the implications for the vulnerability to psychosis" at Bilkent University (Decision/Meeting No: 2016_08_02_01; Project Number: 119k410, PI Toulopoulou), for which the same protocol of the current study was used. The control data were collected prior to the start of the pandemic between July 2018 and January 2020.

The inclusion criteria for the SARS-CoV-2 group were: (1) aged between 14 and 24 years, (2) reverse transcriptase polymerase chain reaction test (RT-PCR) positivity for the SARS-CoV-2 virus, (3) participants who were willing and able to give informed consent (If a participant was under 18 years of age, verbal and written consent from parents or legal guardians were obtained), (4) at least two and maximum four months after recovery from SARS-CoV-2 virus (Confirmed with RT-PCR test negativity), and (5) being a Turkish citizen and speaking Turkish as the native language. The inclusion criteria for the CG were as follows: (1) aged between 14 and 24 years, (2) participants who were willing and able to give informed consent (If a participant was under 18 years of age, verbal and written consent from parents or legal guardians were obtained), and (3) being a Turkish citizen and speaking Turkish as the native language. Exclusion criteria for both groups were: (1) intellectual disabilities, (2) history of head trauma, (3) history of loss of consciousness, (4) having a neuropsychiatric disease or active medical condition, (5) serious visual impairment, and (6) contraindication for MRI or presence of foreign material such as screws, pins, shrapnel remnants, braces to degrade image quality.

For the SARS-CoV-2 group, 230 participants were evaluated in terms of inclusion and exclusion criteria. Thirty-five participants were recruited for the SARS-CoV-2 group. Reasons for exclusions for the SARS-CoV-2 group were: (a) Age not appropriate (n = 82), (b) not reachable by phone (n = 27), not appropriate for MRI (n = 52), and declined to participate (n = 34). The data of the 47 participants were used for the CG.

All the assessments were completed at Aysel Sabuncu Brain Research Center (UMRAM) at Bilkent University. rs-fMRI of the brain was collected from all participants.

This study was approved by the clinical research ethics review committee of Bilkent University (Decision/Meeting No: 2020_10_19_01, PI Toulopoulou). The study procedure adhered to the principles of the Declaration of Helsinki.

2.2. Cognitive battery and questionnaires

2.2.1. Wechsler abbreviated scale of intelligence-2 (WASI-II)

WASI-II is a general measure of intelligence and evaluates the overall cognitive abilities of individuals (Wechsler, 2018). The WASI-II scale consists of 4 subtests: Block Design, Vocabulary, Matrix Reasoning, and Similarities. Only Block-Design (13 items) and Matrix Reasoning (30 items) were used among the subtests. The Vocabulary and Similarities subtests were not included due to the lack of valid equivalents in Turkish. Depending on the age of the participants, the raw scores for Block Design and Matrix Reasoning were calculated and then converted into individual T scores. The sum of T scores was then converted into a composite score. Block Design and Matrix Reasoning subtests were combined to form the Perceptual Reasoning Index. WASI-II was used to ensure that groups were matched regarding performance intelligence quotient (IQ) scores.

2.2.2. Community assessment of psychic experiences-42 (CAPE)

CAPE is a 42-item self-report questionnaire that measures lifelong psychotic experiences and psychosis tendencies in emotional and non-emotional areas (Mark and Toulopoulou, 2015). CAPE measures the frequency and distress associated with psychotic experiences. It has three subscales: Positive, negative, and depression. Each subscale has frequency and distress subdimensions. The validity and reliability of the CAPE were conducted by Konings et al. (2006). Only the positive subscale of CAPE was used for the current study.

2.3. Brain image acquisition and processing

2.3.1. rs-fMRI acquisition

All MRIs were performed at National Magnetic Resonance Research Center (UMRAM, Bilkent University, Turkiye) using a 3-T scanner (Siemens Trio, Germany) magnet equipped with a 32-channel phased array head coil. Subjects were instructed to rest with closed eyes, and not to fall asleep. rs-fMRI was applied with Echo Planar Imaging (EPI) sequence in the axial plane through anterior and posterior commissure with the following parameters: TR: 2000 ms, TE: 35 ms, FA: 75, FOV: 192 mm, slices: 28, matrix: 64 × 64, slice thickness: 3 mm, 150 images with voxel size: $3 \times 3 \times 3\ mm^3$. High-resolution anatomical images were collected using 3D T1-weighted, magnetization-prepared rapid gradient-recalled echo (MPRAGE) sequence with TR: 2600 ms, TE: 3.02 ms, FA: 8, FOV: 256 mm, slices: 176, matrix: 64 × 64, slice thickness: 1 mm, voxel size: $1 \times 1 \times 1\ mm^3$.

2.3.2. rs-fMRI data preprocessing

All pre-processing steps were performed using SPM12 (*Statistical Parametric Mapping 12, Welcome centre for Human Neuroimaging*, n.d.) and CONN software (Nieto-Castanon, 2021) implemented in Matlab2020 (The MathWorks, Inc., Natick, Massachusetts, USA). The first step of pre-processing was discarding the first three images from the data to reach a steady state of magnetization. Slice time correction, motion correction, which will be used later as regressors, co-registration (co-registered to the structural images), segmentation (into gray matter, white matter, and cerebrospinal fluid), normalization to the Montreal Neurological Institute (MNI), smoothing (full width at half maximum: FWHM: 8 mm), and a band-pass filter [0.008–0.09 Hz] were applied to the data to focus on slow frequency fluctuations.

A *component-based noise correction* (CompCor) method was applied to reduce noise in images especially to estimate subject-motion parameters, and to identify outlier scans (Power et al., 2014).

The CONN toolbox includes 164 predefined Region of Interests (ROIs) which are contained in the networks using the Harvard-Oxford Cortical atlas with the CONN toolbox cortical and subcortical areas. In our study, seven networks including DMN, SN, CEN, LN, DAN, SMN, and VN were selected and examined.

2.3.3. Inflammation markers

To analyze the inflammation response, neutrophil/lymphocyte ratio ($N = 14$) and thrombocyte*neutrophil/lymphocyte ratio ($N = 14$)) ratios were used. Since the control samples were recruited from an earlier study, there was no inflammation data for the control group. The inflammation markers were obtained, when the participants had admitted to the hospital during the acute phase of the SARS-Cov-2 infection, while they were experiencing the symptoms of COVID-19.

2.3.4. Neuroimaging data analysis

Before analyzing the data, structural MRI images were examined by K.K.O. There was no brain lesions among the SARS-CoV-2 group. Then, seed based connectivity (SBC) analysis was applied to the data. SBC refers to the average connectivity between the specified ROI with each voxel across the brain. Thus, SBC characterizes the level of FC between a pre-defined seed/ROI and every voxel. Connectivity analysis was performed between the networks (DMN, SN, CEN, LN, DAN, SMN, and VN) and every voxel in the brain and between groups (SARS-CoV-2 group and healthy group).

Resting-state FC maps were assessed using SBC analysis which is based on the time series of a seed voxel (or ROI) for all subjects and groups, connectivity is calculated as the correlation of time series for all other voxels in the brain. Total connectivity maps were computed as the Fisher-transformed bivariate correlation coefficients between an ROI BOLD time series and each individual voxel BOLD time series.

SBC was performed at single-subject level and group level. Group comparisons were performed using a two-sample *t*-test. One-way ANCOVA analysis was applied to data to evaluate the association between clinical measures and connectivity. The association between the CAPE-positive and FC was analyzed among the whole sample. Moreover, among the SARS-CoV-2 group, the association of FC with inflammation markers during the acute infection was calculated.

Significant clusters were marked and given with k in the tables for each network. A $p < 0.001$ uncorrected value statistical threshold was set at the voxel level across the whole brain. For multiple comparisons, we used FDR-corrected $P < 0.05$ at the cluster-level (Nieto-Castanon, 2020).

3. Results

3.1. Socio-demographic and behavioral characteristics of the participants

The groups were matched in terms of age ($U = 747.000$, $p = 0.22$), education level ($t\ (75) = 0.602$, $p = 0.27$), and Perceptual Reasoning Index of the Intelligence Coefficient score (SARS-CoV-2 group: 98.8 ± 13 and CG 98.6 ± 12.6; $t\ (76) = -0.063$, $p = 0.4$). The groups did not differ significantly for gender ($X^2 = 3.545$, $p = 0.06$). The mean age was 17 ± 3 years in the SARS-CoV-2 group and 17.4 ± 2.1 years in the CG. The mean education year was 11.5 ± 2.5 in the SARS-CoV-2 group and 11.8 ± 2.2 in the CG. 34.3 % ($n = 12$) of the SARS-CoV-2 group and 61.7 % ($n = 29$) of the CG were female. No significant difference was found between the groups in terms of CAPE-Positive symptoms ($t\ (76) = 0.708$, $p = 0.24$).

3.2. Group differences in resting-state FC

Group comparisons demonstrated that the SARS-CoV-2 group had less connectivity in the left precentral gyrus than the controls within SMN (Fig. 1, Table 1). Conversely, the left superior and middle frontal

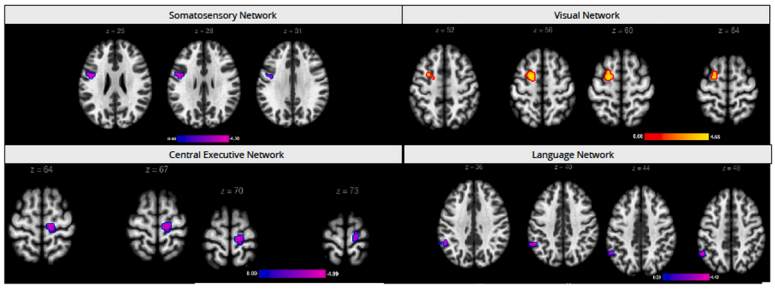

Fig. 1. Significant resting state functional connectivity differences between groups (SARS-CoV-2 and control group) ($n = 82$).
Legend: Color bar indicates the t-value. The enhanced and decreased functional connectivity is depicted in red and blue, respectively. The SARS-CoV-2 group had a lesser resting-state functional connectivity (rs-FC) within the sensorimotor, central executive, language networks and across the brain but an increased rs-FC within visual network compared to controls.

Table 1
Significant resting state functional connectivity differences between the groups ($n = 82$).

Cluster (x, y, z)	Regions	Size (k)	Size p-FDR	Peak uncorrected	T
Sensorimotor Network (SMN)					
−42 00 25	Left Precentral Gyrus	128	0.019447	0.000036	−4.18[a]
Visual Network (VN)					
−18 −04 56	Left Superior Frontal Gyrus Left Middle Frontal Gyrus	197	0.003911	0.000013	4.51[b]
Central Executive Network (CEN)					
12 −24 66	Right Precentral Gyrus	186	0.003064	0.000003	−4.60[c]
Language Network (LN)					
−54 −54 50	Posterior division left Supramarginal Gyrus Left Angular Gyrus	213	0.000954	0.00003	−4.38[d]

Results are given in clusters with MNI coordinates.
[a] $k \geq 128$, FDR: False Discovery Rate.
[b] $k \geq 197$, FDR: False Discovery Rate.
[c] $k \geq 186$, FDR: False Discovery Rate.
[d] $k \geq 213$, FDR: False Discovery Rate.

gyrus showed increased connectivity in the SARS-CoV-2 group compared to the controls within VN (Fig. 1, Table 1). The right precentral gyrus joined the CEN with decreased connectivity in the SARS-CoV-2 group (Fig. 1, Table 1). Within LN, a decreased connectivity in the left posterior division of the supramarginal gyrus and the left angular gyrus was found in the SARS-CoV-2 group compared to the controls (Fig. 1, Table 1). Resting-state FC did not significantly differ between the groups within DMN, SN, and DAN.

3.3. *Effects of CAPE-Positive score on group differences in resting-state FC*

When the CAPE-positive score was included as a covariate, there was increased connectivity in the SARS-CoV-2 group in the right and left supplementary motor cortex, the right superior frontal gyrus, the right paracingulate gyrus, and the right caudate, the right putamen, the right accumbens within CEN; and in the right precentral gyrus within SN (Table 2, Fig. 2).

3.4. *Effects of inflammation markers on resting-state FC among the SARS-CoV-2 group*

Neutrophil/lymphocyte ratio was correlated with an increased connectivity in regions of the DMN (Table 2, Fig. 3). Thrombocyte* neutrophil/lymphocyte ratio was correlated with a decreased connectivity in regions of DMN but an increased connectivity in regions of the SN and CEN (Table 2, Fig. 3).

3.5. *Effects of age on group differences in resting-state FC*

When the age was included as a covariate, there was decreased connectivity in the SARS-CoV-2 group in the Precentral Gyrus Right within CEN (Table 2).

4. Discussion

This cross-sectional study investigated FC differences within brain circuits between adolescents exposed to SARS-CoV-2 and healthy controls. Secondly, the moderator effect of the CAPE-positive score on group differences in resting-state FC was examined. Thirdly, we investigated the brain correlates of inflammation response during the acute phase of the infection among adolescents exposed to SARS-CoV-2.

The current study found decreased connectivity in the left precentral gyrus within SMN and the right precentral gyrus within CEN in the SARS-CoV-2 group compared to the controls. Consistent with our finding, functional and anatomical abnormalities in the precentral gyrus, which is part of the somatosensory cortex, have been reported in COVID-19 survivors (Banker and Tadi, 2023; Guedj et al., 2022; Park et al., 2022; Parsons et al., 2021). In a recent review, the largest number of gray matter events (i.e., radiologically visible lesions) in COVID-19 survivors with small neurological events were found in the precentral gyrus, and bilateral superior temporal and lateral occipital cortices (Parsons et al., 2021). Furthermore, lower metabolism and higher fractional anisotropy in the left precentral gyrus were detected in patients with persistent post-COVID-19 fatigue compared to those without (Park et al., 2022). Moreover, Guedj et al. (2022), found a negative correlation between the duration of the lockdown during the COVID-19 pandemic and the metabolism of the left precentral gyrus. Thus, abnormalities in the precentral gyrus may be related to both SARS-CoV-2 infection, small neurological events, and the effects of prolonged lockdown period during the pandemic.

Our results showed an enhanced FC of the VN among the SARS-CoV-2 group compared to controls with regions from the left superior and middle frontal gyrus. The prefrontal cortex, which includes the superior, middle, and inferior frontal gyrus, regulates the neuronal responses of the posterior visual areas, thus contributing to the employment of visual attention (Paneri and Gregoriou, 2017). Do Carmo Filho et al. (2022) reported that COVID-19 survivors showed greater reaction time, variability of reaction time, and omission errors compared to controls in the Continuous Visual Attention Test. Problems in visual attention among COVID-19 survivors have also been demonstrated by Hampshire et al. (2021) and Tolentino et al. (2021). Although we did not directly administer a visual attention test in the current study, abnormalities in PFC within VN may be the neural basis of visual attentional difficulties among adolescents exposed to SARS-CoV-2. Future research is needed to confirm this hypothesis.

Table 2
Brain correlates of psychotic-like experiences (SARS-CoV-2 and control) and inflammation markers during the acute SARS-CoV-2 infection (Only SARS-CoV-2 group).

Cluster (x, y, z)	Regions		Size (k)	Size p-FDR	Peak uncorrected	T
CAPE-POS (n=82)						
Central Executive Network (CEN)						
10 06 56	Right and left Supplementary Motor Cortex	114		0.005074	0.000061	−4.48
	Right Superior Frontal Gyrus					
	Right Paracingulate Gyrus					
18 14 −04	Right Caudate	82		0.011925	0.000034	−4.86
	Right Putamen					
	Right Accumbens					
Salience Network (SN)						
−48 −24 54	Left Postcentral Gyrus	99		0.021595	0.000023	−4.48
Neutrophil/Lymphocyte (n = 14)						
Default Mode Network (DMN)						
	Right Precentral Gyrus					
4 −22 48	Posterior division Cingulate Gyrus		151	0.001777	0.000017	6.33[a]
18 62 −22	Right Frontal Pole		93	0.12814	0.000004	−7.75 [a]
	Left precentral Gyrus					
−14 −30 50	Posterior division Cingulate Gyrus		62	0.04479	0.000095	5.79 [a]
Thrombocyte*Neutrophil/Lymphocyte (n = 14)						
Default Mode Network (DMN)						
24 −92 32	Right Occipital Pole					
	Right Superior Division of the Lateral Occipital Cortex		145	0.002226	0.000014	−7.51 [b]
−08 −80 54	Left Superior Division of the Lateral Occipital Cortex					
	Precuneus Cortex		67	0.046660	0.000004	−6.56 [b]
Salience Network (SN)						
−38 08 08	Left Frontal Operculum Cortex					
	Left Central Operculum cortex		143	0.002510	0.000009	7.38 [b]
	Pars opercularis Left Inferior Frontal Gyrus					
	Insular Cortex					
−66 −16 00	Left Central Operculum Cortex					
	Left Planum Temporale		133	0.002510	0.000040	−7.23 [b]
	Left Posterior Division of the Superior Temporal Gyrus					
	Left Postcentral Gyrus					
54 −04 36	Right Precentral Gyrus		121	0.002902	0.000055	−5.89 [b]
	Left Postcentral Gyrus					
Central Executive Network						
	Left Precentral Gyrus					
−06 −30 48	Posterior Division of the Cingulate Gyrus		202	0.000170	0.000017	6.81 [b]
	Right Precentral Gyrus					
	Precuneous cortex					
12 −16 18	White Matter		66	0.037215	0.000022	5.53 [b]
	Thalamus					
Age (n=82)						
12 −24 66	Precentral Gyrus Right		204	0.002584	0.000002	4.65

Results are given in clusters with MNI coordinates. [a] $k \geq 62$, FDR: False Discovery Rate. [b] $k \geq 67$, FDR: False Discovery Rate.

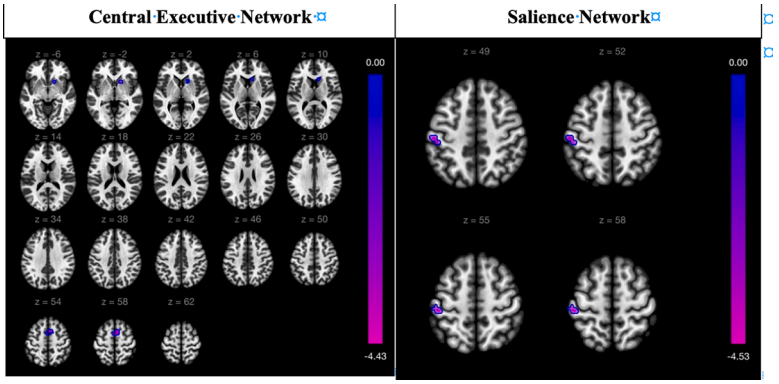

Fig. 2. The effect of positive subscale of the Community Assessment of Psychic Experiences (CAPE) scores on group differences between the SARS-CoV-2 and healthy control groups in functional connectivity.
Legend: Color bar indicates the t-value. The enhanced and decreased functional connectivity is depicted in red and blue, respectively. When the CAPE-positive score was included as a covariate, there was an increased connectivity in the SARS-CoV-2 group within central executive and salience networks.

The current study showed that the SARS-CoV-2 group demonstrated decreased FC of LN with regions from the supramarginal gyrus and left angular gyrus compared to controls. The angular gyrus is associated with complex language functions, spatial cognition, memory retrieval, attention, and arithmetic ability (Seghier, 2013). The supramarginal gyrus is involved in language perception and processing (Stoeckel et al., 2009). Consistent with our finding, reduced regional homogeneity in the left angular gyrus (Cattarinussi et al., 2022) and increased amplitude of

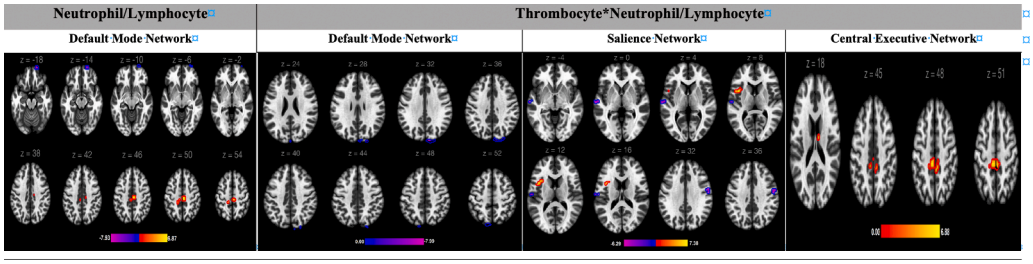

Fig. 3. Brain correlates of inflammatory markers during the acute infection among adolescents exposed to SARS-CoV-2 ($n = 14$).
Legend: Color bar indicates the t-value. The enhanced and decreased functional connectivity is depicted in red and blue, respective. Neutrophil/lymphocyte ratio was correlated with an increased and decreased functional connectivity (FC) within default mode network (DMN). Thrombocyte* neutrophil/lymphocyte ratio was correlated with a decreased FC within DMN; increased and decreased FC within salience; and increased FC within central executive network.

low-frequency fluctuation values in both angular gyrus and supramarginal gyrus (Du et al., 2022) were reported among SARS-CoV-2 survivors. Moreover, both the angular and supramarginal gyrus and the superior and middle frontal gyrus are involved in semantic verbal fluency (Arrigo et al., 2023; Birn et al., 2010). Semantic verbal fluency has been reported as one of the most affected cognitive domains in COVID-19 survivors after hospital discharge (Almeria et al., 2020; Méndez et al., 2022, 2021). Hence, FC abnormalities in the angular gyrus, supramarginal gyrus, and superior and middle frontal gyrus in our study may be the underlying mechanism of semantic verbal fluency difficulties among COVID-19 survivors.

Including CAPE positive subscale score as a covariate, we found an increased FC of CEN with regions located in the right superior frontal gyrus, the left and right supplementary motor cortex, ventral striatum (nucleus accumbens), and dorsal striatum (the right caudate and putamen) and an increased FC of SN with the regions located in the right precentral gyrus in the SARS-CoV-2 group compared to controls. Sabaroedin et al. (2019) reported hypoconnectivity between the dorsal striatum, dorsolateral prefrontal, anterior cingulate, and primary motor cortices in individuals who experience PLEs. Decoupling between the dorsal striatum and prefrontal cortex demonstrated in individuals with PLEs, high risk for psychosis, at-risk mental state for psychosis, patients with first-episode psychosis, and schizophrenia (Anticevic et al., 2015, 2014; Dandash et al., 2014; Pani et al., 2021; Woodward and Heckers, 2016). Moreover, hypoconnectivity within the motor network (primary motor cortices and precentral gyrus) was claimed as a sign of neural inefficiency among individuals at-risk for psychosis and related to the transition to psychosis (Anticevic et al., 2015). Although our results showed changes in the FC of brain circuits associated with PLEs including CEN and SN among adolescents exposed to SARS-CoV-2 compared to controls, future research is needed to elucidate whether alterations in the FC of these brain regions increase the tendency for PLEs among these adolescents.

Another finding was that inflammation markers influenced resting-state FC. Higher peripheral inflammation was associated with hypo/hyperconnectivity of the DMN, hypoconnectivity of the SN, and hyperconnectivity of the CEN. SN facilitates switching between DMN and CEN (Zhou et al., 2018). Therefore, it may be assumed that the severity of the COVID-19 inflammation is related to a deterioration in the triple-network system. Consistent with our results, Benedetti et al. (2021) found that peripheral inflammation status is associated with alterations in the DMN, SN, CEN, and LN. Abnormal FC within DMN, SN, and CEN was consistently associated with psychopathological conditions such as depression, post-traumatic stress disorder, anxiety disorder, and PLEs (Karcher et al., 2019; Koch et al., 2016; Xu et al., 2019; Yan et al., 2019). Moreover, the severity of inflammation response during the acute SARS-CoV-2 infection positively related to scores of depression and anxiety at follow-up (Mazza et al., 2020). On the other hand, Francesconi et al. (2020) reported that a high level of internalizing symptoms mediated the association between inflammation during childhood and the future onset of PLEs. It can be assumed that higher inflammation response during acute SARS-CoV-2 infection may cause dysconnectivity within DMN, CEN, and SN, thus facilitating the emergence of depression or anxiety among these patients and eventually making some of them more vulnerable to PLEs. Hence, the possible mediator effect of dysconnectivity of the triple-network system on the association between inflammation response, internalizing symptoms, and PLEs should be investigated.

Our results should be viewed in the light of methodological limitations. Firstly, the relatively small sample size limited the generalizability of our findings. Secondly, although our findings revealed that the SARS-CoV-2 group had alterations in FC compared to controls, it is impossible to attribute all of these changes to SARS-CoV-2 infection. We confirmed RT-PCR positivity for SARS-CoV-2 in the SARS-CoV-2 group, however, the effect of the pandemic including social isolation, sleep problems, uncertainty, stress, anxiety, and depression may also have affected the brains of these adolescents (Casagrande et al., 2021; Hawes et al., 2021; Salari et al., 2020). As aforementioned before, Guedj et al. (2022) found that the length of the 'lockdown' is correlated to changes in left precentral gyrus. Since we did not collect data regarding the length of the lockdown period, we could not investigate the moderator effect of lockdown period on our results. It is also important to note that there was a considerable amount of variability in pubertal development among the sample population. As a result, it is possible that the outcomes reflected this variability. Unfortunately, we were not able to investigate the impact of the difference between the participants' biological and chronological ages on the results. However, we included age as a covariate and found that there was decreased connectivity in the SARS-CoV-2 group in the Precentral Gyrus Right within CEN. FC differences within SMN, VN, and LN between the groups could not be found, when we controlled the age. Thus, it could be inferred that age could be an important factor that may have impacted our results. Additional research is required to shed light on this matter. Moreover, since the control samples were recruited as part of another study prior to the pandemic, there was no inflammation data for the controls, making our third aim more exploratory nature. However, this situation also provided a strength to our study by ensuring that the control samples were not exposed to SARS-CoV-2. Another strength of the current study was that groups were matched in terms of age, education, gender, and performance IQ score. Despite limitations, to our knowledge, this is the first study investigating the effect of SARS-CoV-2 infection on the developing brain using rs-fMRI and the mediator effect of PLEs and peripheral inflammation on group differences in resting-state FC.

In conclusion, this cross-sectional study showed that adolescents exposed to SARS-CoV-2 had a lesser FC within SMN, CEN, and LN, but an increased FC within VN compared to controls. When the CAPE-Positive score was included as a covariate, the SARS-CoV-2 group showed a greater FC within SN and CEN compared to controls, in spite of the absence of clinical changes in CAPE-Positive score. Moreover, among the SARS-CoV-2 group, inflammation markers were correlated with a decreased/increased FC within DMN and SN, but an increased FC within CEN. Further research is needed to confirm our results.

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Declaration of Competing Interest

None declared.

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