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Dynamic recovery of piriform cortex function and its impact on cognitive processing speed following mild COVID-19

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Abstract

Background Although the neurological sequelae of severe COVID-19 are increasingly recognized, the long-term neural impact of uncomplicated mild SARS-CoV-2 infection remains insufficiently characterized. This study investigated post-infection alterations in piriform cortex activity, a region central to olfactory processing and integrative cognitive-emotional networks, and their associations with cognitive outcomes in adults.

Methods Fifty adults with pre- and post-SARS-CoV-2 magnetic resonance imaging (MRI) and clinical/neuropsychological data were analyzed. A demographically matched control group of 50 individuals without prior COVID-19 or vaccination was included. Resting-state functional MRI assessed amplitude of low-frequency fluctuations (ALFF) within the piriform cortex as an index of regional neural activity.

Results Baseline piriform ALFF did not differ between the two groups ($p = 0.421$). Following infection, piriform ALFF exhibited a significant quadratic trajectory ($p = 0.003$), characterized by early elevation relative to baseline, a decline to a nadir at approximately three months, and subsequent recovery toward baseline levels by six months. Greater acute COVID-19 symptom burden correlated with higher piriform ALFF ($\beta = 0.34$, $p = 0.017$). Elevated ALFF was associated with reduced processing speed ($\beta = -0.52$, $p = 0.001$). Mediation analysis demonstrated that piriform ALFF significantly mediated the relationship between symptom burden and processing speed (indirect effect $b = -0.081$, $p = 0.037$).

Conclusions Piriform cortex function demonstrated a dynamic, nonlinear pattern within six months after mild COVID-19, marked by early hyperactivity, later downregulation, and gradual normalization. Altered piriform activity mediated the association between symptom burden and processing speed deficits, suggesting transient post-infection neurophysiological disruption with potential relevance to cognitive symptoms. Longitudinal follow-up is warranted to clarify underlying mechanisms and long-term implications.

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Keywords COVID-19, Piriform cortex, Amplitude of low-frequency fluctuations, Functional magnetic resonance imaging, Neuroplasticity, Processing speed

Background

Coronavirus disease 2019 (COVID-19) is increasingly recognized to cause central nervous system sequelae, including brain deficits and olfactory dysfunction, beyond its respiratory manifestations [1]. Cognitive impairment, particularly slowed processing speed, and emotional symptoms are also frequently reported after infection, including among non-hospitalized individuals [2–4].

Neuroimaging studies have documented subtle abnormalities in brain structure and function among COVID-19 survivors [2, 5]. Longitudinal investigations further suggest dynamic and often nonlinear region-specific brain changes following COVID-19 infection, with some alterations resolving over time and others persisting or worsening despite clinical recovery [6–8]. These heterogeneous trajectories highlight the complexity of post-COVID-19 neurobiological processes and underscore the need for focused examination of brain regions implicated in both pathophysiology and clinical presentation..

The piriform cortex, also referred to as the primary olfactory cortex, is the principal cortical target of olfactory bulb projections and plays a central role in processing odor identity and quality, supported by prominent synaptic plasticity [9]. Emerging evidence indicates that the piriform cortex is not restricted to unimodal olfactory processing, but instead participates in broader networks involved in emotion and cognition through extensive reciprocal connections with limbic and cortical regions [10]. During odor processing, piriform activity contributes to attentional modulation, task performance speed, and anxiety [11–13]. Furthermore, patients with late-onset depression exhibit lower functional connectivity in the piriform cortex compared with those with early-onset depression and healthy controls, with this reduction correlating with impaired cognition, particularly processing speed [14]. This region is of particular interest in COVID-19 because it is the primary cortical target of olfactory input from a sensory system frequently affected by SARS-CoV-2 infection [9], while also maintaining reciprocal connections with limbic and cortical networks relevant to cognition and emotion [10].

Although neuroimaging studies have identified structural and functional abnormalities in the olfactory bulb and broader olfactory networks after COVID-19 [2, 15], research focusing specifically on the piriform cortex remains limited. A small number of cross-sectional studies have reported higher resting-state functional connectivity in this region after infection [16, 17], and a case report described increased piriform activation to odor stimuli in a patient with persistent cacosmia and cacogeusia [18]. However, the evolution of piriform cortex function during the recovery period following COVID-19 infection requires further clarification.

To address this gap, the present study investigated the trajectory of piriform cortex function during the post-COVID-19 recovery period in non-hospitalized patients with mild symptoms using the amplitude of low-frequency fluctuations (ALFF), a well-established resting-state functional magnetic resonance imaging (fMRI) metric that indexes local neural activity by quantifying the strength of spontaneous neural oscillations [19]. Additionally, we examined associations of piriform ALFF with emotional symptoms, processing speed, and COVID-19 symptom burden to evaluate the potential contribution of this region to changes in neuropsychological function during recovery.

Methods

Participants

This observational study included 50 non-hospitalized middle-aged adults who had recovered from mild COVID-19 within the preceding six months, with or without persistent symptoms at the time of evaluation (hereafter referred to as the "patient group"). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was confirmed using reverse-transcription polymerase chain reaction (RT-PCR) testing. Each patient underwent one pre-infection baseline MRI/clinical assessment and one post-infection assessment performed at a variable time point within six months following confirmed infection. Pre-infection baseline data were obtained from existing MRI scans and clinical assessments acquired a mean of 21.7 months (SD = 16.6) before infection. The control group, included as a baseline reference group, consisted of 50 healthy individuals who were matched for demographic characteristics and who had no documented history of COVID-19 infection or vaccination. The control group underwent a single MRI and clinical assessment and was not followed longitudinally.

Exclusion criteria for both groups included current neurological or psychiatric disorders, clinically significant abnormalities on structural brain magnetic resonance imaging (MRI), current use of psychotropic medication, and contraindications to MRI.

The study received approval from the Institutional Review Board of Ewha Womans University, and written informed consent was obtained from all participants.

Clinical and cognitive assessment

Acute COVID-19 symptom burden was quantified by assessing the types and total number of symptoms experienced during the first month following confirmed SARS-CoV-2 infection. This evaluation was conducted using a semi-structured interview based on World Health Organization (WHO) criteria for COVID-19 symptomatology [20].

Emotional symptoms were assessed using established psychometric instruments. Depressive symptoms and anxiety symptoms were assessed using the Hamilton Depression Rating Scale (HDRS) and the Hamilton Anxiety Rating Scale (HARS), respectively [21, 22]. To generate a unified index of emotional distress, individual HDRS and HARS scores were adjusted for age and sex using linear regression and then standardized to z-scores based on the baseline mean and SD across all participants. A composite emotional symptom score was calculated as the mean of the standardized z-scores from these two scales.

Cognitive function was assessed with a focus on processing speed. Processing speed was evaluated using the Grooved Pegboard Test (GPT; completion time for dominant and nondominant hands) and the Trail Making Test (TMT) Part A (completion time), both established indicators of psychomotor and visual processing speed [23, 24]. Each measure was adjusted for age, sex, and education using linear regression, standardized to z-scores based on the baseline distribution, and inverted so that higher scores reflected better performance. For the GPT, z-scores for dominant and nondominant hands were averaged. A composite processing speed score was computed as the mean of the standardized z-scores from both measures. Follow-up neuropsychological assessments were available for 39 of the 50 patients.

Medical history was assessed at both baseline and follow-up visits to identify medical events that could potentially affect brain function. Broader pandemic-related impact at the post-infection visit was additionally assessed using the Coronavirus Impact Scale (CIS), a self-report measure of the overall impact of the COVID-19 pandemic on daily life, with higher total scores indicating greater pandemic-related impact [25].

MRI data acquisition

Brain MRI scans were conducted using a 3.0 Tesla Philips MR scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. High-resolution three-dimensional T1-weighted images were acquired using a turbo field echo sequence with the following parameters: repetition time (TR) = 7.4 ms, echo time (TE) = 3.4 ms, flip angle (FA) = 8°, field of view (FOV) = 224 × 224 mm^2, voxel size = 1 × 1 × 1 mm^3, and 180 sagittal slices. Resting-state fMRI data were collected using a T2*-weighted gradient-echo echo-planar imaging sequence with TR = 800 ms, TE = 30 ms, FA = 76°, FOV = 208 × 208 mm^2, voxel size = 2.6 × 2.6 × 2.6 mm^3, 55 axial slices, multiband SENSE factor = 5, in-plane SENSE factor = 1.1, 600 volumes, yielding a total acquisition time of 8 min 6 s. Participants were instructed to keep their eyes closed, remain awake, refrain from intentional thought, and allow spontaneous mind-wandering during the resting-state session. T2-fluid-attenuated inversion recovery (FLAIR) images were also obtained for screening using the following parameters: TR = 4,800 ms, TE = shortest, inversion time = 1,650 ms, FOV = 240 × 240 mm^2, matrix = 216 × 216. Structural images were reviewed by radiologists for clinically significant abnormalities.

MRI data analysis

MRI data were preprocessed using the CONN toolbox (release 22.v2407) [26] in conjunction with Statistical Parametric Mapping 12. After realignment, potential outlier volumes were identified using the Artifact Detection Tools (ART) when framewise displacement exceeded 0.9 mm or when global blood-oxygen-level–dependent (BOLD) signal change exceeded 5 standard deviations [27]. The number of identified outlier volumes did not differ significantly between the patient group (mean = 0.74, SD = 1.58, range = 0–6) and the control group at baseline (mean = 1.68, SD = 3.21, range = 0–17; $p = 0.066$). At the post-infection assessment, the patient group exhibited a mean of 1.58 outlier volumes (SD = 6.45, range = 0–45). Participants with more than 20% outlier volumes were excluded [28]; no participants met this criterion.

Functional and structural imaging data were spatially normalized to Montreal Neurological Institute (MNI) space and resampled into 2 mm isotropic voxels using the unified segmentation and normalization algorithm in SPM [29].

For denoising, confounding effects including white matter and cerebrospinal fluid signals, subject motion parameters and their first-order derivatives, outlier volumes, and mean and linear trends in the BOLD signal were regressed out using a CompCor approach [30]. Bandpass filtering between 0.008 and 0.09 Hz was then applied.

Voxel-wise ALFF maps were computed in the CONN toolbox using its default implementation, in which ALFF is defined as the root mean square of the denoised, detrended, and filtered BOLD signal [19]. ALFF values were z-standardized across voxels within each participant. Piriform ALFF values were extracted from bilateral spherical seeds with a radius of 6 mm centered on established MNI coordinates (left = – 22, 0, – 14; right = 22, 2, – 12; Fig. 1) [31] and adjusted for age and sex using linear regression for statistical analysis.

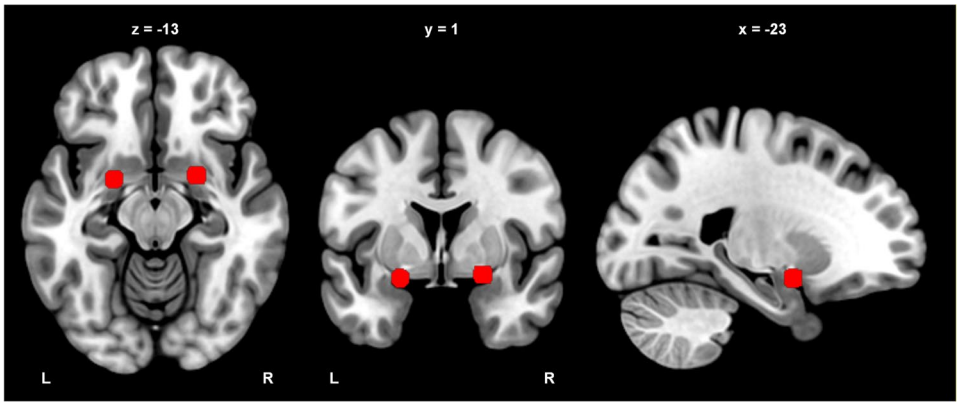


Fig. 1 Seed regions of the piriform cortex. Bilateral spherical seed masks with a 6 mm radius were generated based on previously established standard coordinates [31]. L, left; R, right

Statistical analysis

Baseline demographic and clinical characteristics were compared between the two groups using independent t-tests or chi-square tests.

The post-infection temporal dynamics of clinical and neuroimaging outcomes were examined using regression models, with time elapsed since confirmed SARS-CoV-2 infection specified as the independent variable.

The trajectories of all standardized post-infection measures, including the composite emotional symptom score, the processing speed score, and piriform cortex ALFF values, were evaluated by fitting both linear and quadratic regression models, in which time since infection was entered as a mean-centered linear term and, in the quadratic model, an additional squared term. The nested linear and quadratic models were then compared using likelihood ratio tests.

Associations between acute COVID-19 symptom burden, defined as the total count of COVID-19 symptoms, and post-infection clinical and neuroimaging outcomes (emotional symptoms, processing speed, and piriform cortex ALFF) were evaluated using linear regression analysis.

To examine the effect of symptom burden on ALFF, linear regression was performed using the total number of COVID-19 symptoms as the independent variable and adjusted piriform ALFF as the dependent variable in the patient group.

To assess the relationship between regional brain activity and clinical outcomes, linear regression analyses were conducted with piriform cortex ALFF as the independent variable and emotional symptoms or processing speed as the dependent variables. As a supplementary analysis, separate linear regression models were performed in the patient group with piriform cortex ALFF as the independent variable and either the GPT composite z-score or the TMT Part A z-score as the dependent variable.

A mediation analysis was conducted to evaluate the hypothesis that piriform ALFF mediates the relationship between COVID-19 symptom burden and emotional symptoms or processing speed. In this model, the number of COVID-19 symptoms served as the independent variable (X), piriform cortex ALFF as the mediator (M), and the composite emotional symptom score or processing speed score as the dependent variable (Y). The significance of the indirect effect, representing the pathway from X to Y through M, was tested using bootstrapping with 5,000 resamples.

As sensitivity analyses addressing potential confounding by vaccination-related factors and broader pandemic-related influences, the interval from the last vaccination to infection and the CIS total score were separately included as covariates in the piriform ALFF regression models examining associations with time since infection and acute COVID-19 symptom burden, as well as in the mediation model. In addition, the key regression and mediation analyses were repeated after excluding the participant who had a non-COVID-related medical event between baseline and follow-up that could potentially affect brain function. For the mediation analysis, a time-adjusted sensitivity model was performed to account for follow-up timing, with centered linear and quadratic terms for time since infection included in the mediator equation and a centered linear term included in the outcome equation, consistent with the temporal patterns observed in the main analyses.

Statistical significance was defined as two-tailed $p < 0.05$. All analyses were performed using Stata 19 (StataCorp, College Station, TX, USA).

Results

Participant characteristics

The demographic and clinical characteristics are summarized in Table 1. The patient and control groups did not

Table 1 Demographic and clinical characteristics

Characteristics	COVID-19 patients ($n=50$)	Non-infected controls ($n=50$)	Test
Baseline characteristics			
Age (year)	43.4 (13.0)	43.8 (11.0)	t = -0.15, $p=0.883$
Male	29 (58.0%)	28 (56.0%)	$\chi^2=0.04$, $p=0.840$
Higher education[a]	41 (82.0%)	42 (84.0%)	$\chi^2=0.07$, $p=0.790$
Emotional symptoms (z)	-0.06 (0.66)	0.06 (1.23)	t = -0.65, $p=0.515$
Processing speed (z)	-0.04 (0.91)	0.04 (0.60)	t = -0.58, $p=0.562$
COVID-19-related characteristics at follow-up			
Age at follow-up visit (year)	45.4 (12.5)	-	
Vaccination prior to infection	48 (96.0%)	-	
Hospitalization	0 (0.0%)	-	
Post-infection period (month)	2.7 (1.7)	-	
Mean number of symptoms	2.8 (2.1)		
Individuals with any symptoms	44 (88.0%)	-	
Sore throat	30 (60.0%)	-	
Fever	27 (54.0%)	-	
Cough	23 (46.0%)	-	
Myalgia	18 (36.0%)	-	
Rhinorrhea	16 (32.0%)	-	
Headache	8 (16.0%)	-	
Fatigue	5 (10.0%)	-	
Olfactory symptom	2 (4.0%)	-	
Gustatory symptom	2 (4.0%)	-	
CIS[b]	4.2 (2.9)	-	

Data are presented as mean (standard deviation) or *n* (%)

CIS Coronavirus Impact Scale

[a] College or higher education. [b] $n = 46$

differ significantly in age ($p=0.883$), sex ($p=0.840$), or education level ($p=0.790$).

In the patient group, the mean follow-up interval from the time of infection to the post-infection assessment was 2.7 months (SD = 1.7), with a range of 0.2 to 5.3 months. A large majority of patients (96.0%) had received a SARS-CoV-2 vaccine prior to infection. Detailed pre-infection vaccination characteristics, including the number of vaccine doses, the manufacturer of the last vaccine dose, and the interval from the last vaccination to infection, are presented in Supplementary Table 1. All patients were managed in an outpatient setting and treated with over-the-counter or prescribed medications, consistent with non-hospitalized status. The mean number of acute COVID-19 symptoms was 2.8 (SD = 2.1), and 88% of patients reported at least one symptom. The mean CIS total score was 4.2 (SD = 2.9; $n=46$).

Trajectory of clinical and neuroimaging outcomes following COVID-19 infection

At baseline, before SARS-CoV-2 infection, the patient and control groups exhibited no significant differences in composite emotional symptom scores (t = -0.65, $p=0.515$), processing speed composite scores (t = -0.58, $p=0.562$), or piriform cortex ALFF ($t=0.81$, $p=0.421$).

In the patient group, comparison of linear and quadratic regression models of time since infection showed that both emotional symptoms and processing speed followed primarily linear trajectories over the post-infection period. Emotional symptoms significantly decreased with increasing time since infection ($n=50$, β = −0.32, $p=0.024$; Fig. 2A), consistent with gradual improvement in depressive and anxiety symptomatology. Processing speed demonstrated a marginally significant linear improvement ($n=39$, $\beta=0.31$, $p=0.053$; Fig. 2B). Both emotional symptoms (quadratic term $p=0.343$; likelihood ratio test favoring the linear model, $p=0.325$) and processing speed (quadratic term $p=0.859$; likelihood ratio test favoring the linear model, $p=0.852$) exhibited no evidence supporting a nonlinear pattern.

Piriform cortex ALFF, however, displayed a significant nonlinear trajectory in the quadratic regression model. The linear model alone showed only a trend-level association with post-infection period (β = −0.25, $p=0.081$). Incorporating the quadratic term significantly improved model fit ($F_{(2,47)}=6.67$, $p=0.003$, adjusted $R^2=0.19$; likelihood ratio test versus linear model $p=0.002$). Both the quadratic term ($p=0.003$) and the linear term ($p=0.015$) were significant, revealing a U-shaped trajectory in which ALFF values were initially elevated relative to

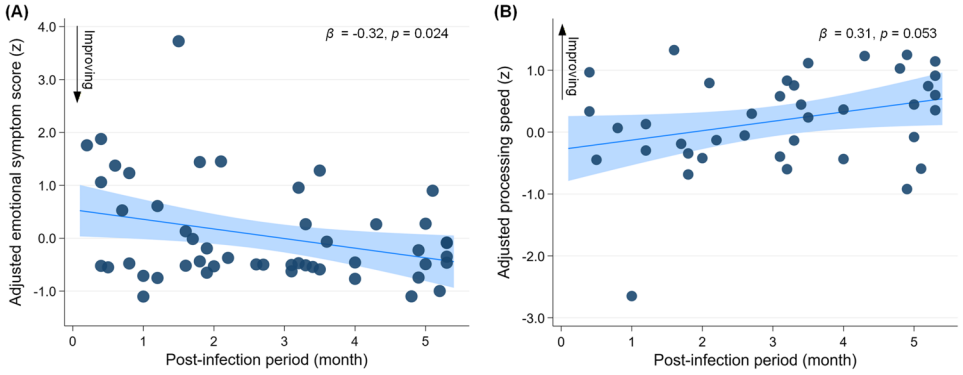


Fig. 2 Associations between post-infection period and (**A**) emotional symptom levels and (**B**) processing speed. Lower emotional symptom scores indicate fewer depressive and anxiety symptoms, whereas higher processing speed scores reflect better function. The solid lines show fitted regression functions, and shaded areas represent 95% confidence intervals

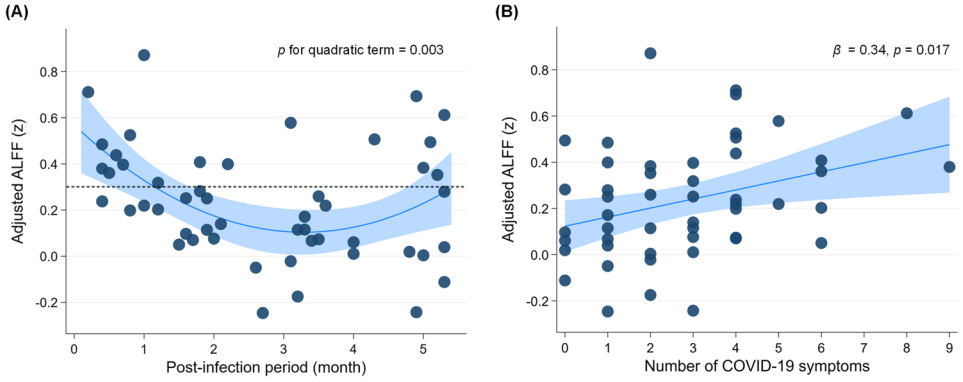


Fig. 3 Piriform ALFF as a function of (**A**) post-infection period and (**B**) the number of COVID-19 symptoms. The solid lines indicate fitted regression functions, and shaded areas represent 95% confidence intervals. The horizontal dotted line in panel (**A**) marks the group baseline mean ALFF. ALFF, amplitude of low-frequency fluctuations

pre-infection baseline, declined to a nadir at approximately 3.3 months post-infection, and subsequently returned toward baseline levels by 6 months (Fig. 3A).

Piriform function as a potential mediator between COVID-19 and impaired processing speed

We first examined the relationship between acute illness severity, piriform ALFF, and clinical outcomes. The total count of acute COVID-19 symptoms, reflecting symptom burden, showed a positive linear correlation with higher post-infection piriform ALFF ($\beta = 0.34$, $p = 0.017$; Fig. 3B) and greater emotional symptoms ($\beta = 0.35$, $p = 0.014$). However, symptom burden was not significantly associated with the processing speed score (β = -0.07, $p = 0.684$).

Higher piriform ALFF was significantly associated with lower processing speed in patients with COVID-19 (β = −0.52, $p = 0.001$; Fig. 4A), whereas no such association was observed in healthy controls (β = −0.10, $p = 0.506$). In supplementary analyses of the individual component tests, higher piriform ALFF showed significant associations with poorer performance on both the GPT and TMT Part A (Supplementary Table 2). Associations between piriform ALFF and emotional symptoms were non-significant in both patients ($\beta = 0.13$, $p = 0.372$) and controls (β = −0.003, $p = 0.982$).

A mediation analysis was performed to determine whether piriform ALFF accounted for the relationship between COVID-19 symptom burden and processing speed. Although the total effect of symptom burden on processing speed was not significant (b = − 0.027, $p = 0.631$, bootstrapped 95% confidence interval [CI] = − 0.137 to 0.083), the indirect effect through piriform ALFF was statistically significant (b = − 0.081, $p = 0.037$, bootstrapped 95% CI = − 0.157 to − 0.005; Fig. 4B). These results support an indirect-only mediation pattern, indicating that greater acute symptom burden is associated with reduced processing speed through its influence on piriform cortical activity.

Sensitivity analyses adjusting for potential confounding factors

Additional sensitivity analyses adjusting for the interval from the last vaccination to infection or CIS total score showed similar results for the associations of piriform

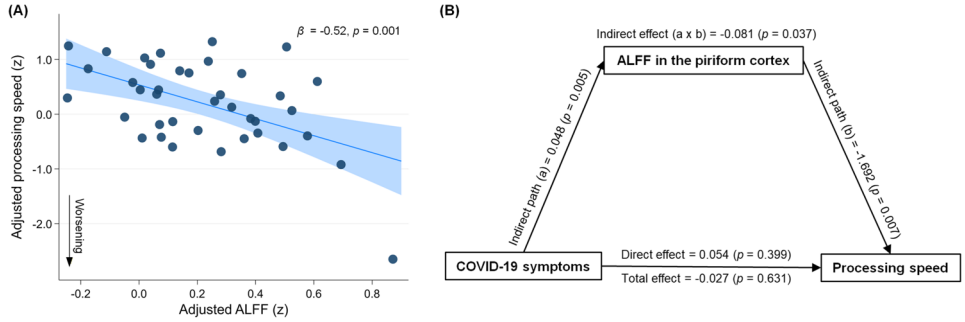


Fig. 4 Piriform ALFF as a mediator of the association between COVID-19 symptom severity and processing speed. **A** Scatterplot showing the relationship between amplitude of low-frequency fluctuations (ALFF) in the piriform cortex and processing speed. Lower processing speed scores indicate poorer performance. The solid line shows the fitted regression function, and the shaded area denotes the 95% confidence interval. **B** Mediation model demonstrating a significant indirect effect of COVID-19 symptom severity on processing speed via ALFF in the piriform cortex. Coefficients and corresponding *p*-values estimated using bootstrapping are shown for all model paths. ALFF, amplitude of low-frequency fluctuations

ALFF with time since infection and acute COVID-19 symptom burden (Supplementary Tables 3 and 4). In the mediation analysis, the results remained largely consistent with the main findings after adjusting for the interval from the last vaccination to infection or CIS total score (Supplementary Table 5). In a sensitivity analysis additionally adjusting the mediation model for time since infection, the indirect effect remained directionally similar but was no longer statistically significant (Supplementary Table 5).

Review of medical history at baseline and follow-up identified one participant who had experienced a traffic accident with mild concussion but had recovered by the follow-up assessment without ongoing symptoms of mild traumatic brain injury. The main results remained significant in sensitivity analyses excluding this participant (Supplementary Tables 3–5).

Discussion

This study provides new insights into the temporal dynamics of piriform cortex function following mild COVID-19 infection in non-hospitalized middle-aged adults. Three principal findings emerged. First, piriform cortex ALFF exhibited a distinctive U-shaped nonlinear pattern across the six-month post-infection period, with values initially elevated relative to pre-infection baseline, decreasing to a nadir at approximately three months post-infection, and then returning toward baseline by six months. Second, greater acute COVID-19 symptom burden, defined as the total number of symptoms experienced during the first month after confirmed infection, was associated with higher piriform cortex ALFF during recovery. Third, piriform cortex ALFF significantly mediated the association between symptom burden and reduced processing speed, indicating a potential mechanistic pathway through which acute illness severity may influence cognitive outcomes.

These findings build on the expanding evidence that COVID-19 can exert neurobiological effects even in the absence of hospitalization or severe clinical presentation. Importantly, the mediation effect is particularly noteworthy as it suggests that altered piriform cortex activity is not merely a secondary consequence of infection but may represent a functionally relevant intermediate process linking acute symptom burden to persistent cognitive difficulty.

The observed six-month trajectory of piriform cortex function can be interpreted within the broader context of post-COVID-19 neurobiological change. The first three months after infection are frequently characterized by structural and functional abnormalities, including cortical thinning, white matter microstructural disruption, and hypoperfusion, which have been associated with cognitive impairment, emotional symptoms, fatigue, and ongoing COVID-19 symptoms, whereas the six-month time point is often accompanied by partial recovery of neural structure and function [7, 8].

The elevated piriform ALFF observed early after infection, which was associated with both greater acute symptom burden and slower processing speed, may reflect inflammatory mechanisms that increase spontaneous neural activity. Peripheral and central immune responses drive microglial activation and pro-inflammatory cytokine release, which can heighten neuronal excitability and glutamatergic signaling, thereby amplifying spontaneous fluctuations in the BOLD signal [32]. Consistent with this interpretation, a longitudinal study of hospitalized COVID-19 survivors demonstrated elevated ALFF across widespread cortical regions at one-year follow-up, with associations to insomnia symptoms and acute-phase neutrophil counts, suggesting that increased ALFF may reflect pathological processes rather than beneficial compensation [33]. In individuals with COVID-19-related hyposmia, increased piriform functional connectivity was paired with reduced local efficiency, indicating that

elevated activity does not necessarily support efficient information processing [16]. A case report describing persistent cacosmia and cacogeusia after COVID-19 also showed increased piriform activation to odor stimuli [18]. Taken together, convergent evidence suggests that elevated piriform activity following COVID-19 may reflect inefficient or dysregulated neural responses rather than adaptive functional enhancement.

Recent studies across a range of acute brain injuries and early-stage neurodegenerative diseases have indicated that early-phase hyperactivation and hyperconnectivity may, in some situations, represent direct consequences of pathology rather than adaptive compensation [34, 35]. Supporting this interpretation, an elevated perioperative ratio of interleukin (IL)-6 to IL-10, an indicator of systemic inflammation, was associated with increased cortical ALFF after metabolic-bariatric surgery, followed by subsequent reductions in ALFF as inflammatory profiles improved [36]. Patients with allergic rhinitis have also demonstrated significantly elevated ALFF in the anterior cingulate cortex that correlates with symptom severity [37]. Furthermore, in amnestic mild cognitive impairment, suppression of hippocampal hyperactivity with levetiracetam improved memory performance, indicating that increased neural activity can impair rather than enhance function [38]. Collectively, these observations support the interpretation that initial piriform hyperactivity in our cohort may reflect inflammation-related neuronal hyperexcitability, pathological neural noise, and inefficient recruitment.

However, sustained short-term hyperactivation can impose substantial metabolic costs and overload neural networks, increasing susceptibility to functional exhaustion and neurodegenerative processes over time [35, 39]. The observed decline of piriform ALFF to below-baseline levels at approximately three months post-infection, followed by recovery toward baseline, may reflect homeostatic downregulation in which neural circuits suppress excessive activity and restore firing-rate set-points following acute insult. During the post-inflammatory transition period, increasing anti-inflammatory signaling and reductions in pro-inflammatory cytokines may facilitate synaptic downscaling and network rebalancing [40]. A temporal lag between the suppression of hyperactivation and complete stabilization can produce transient undershoot, a recognized feature of biological homeostatic systems [41, 42]. Consistent with this interpretation, a sepsis-associated encephalopathy animal model demonstrated elevated hippocampal ALFF at seven days post-injury that declined by day 14, with both elevated and reduced ALFF phases showing negative associations with cognitive performance [43]. Thus, the reduction of ALFF toward baseline may reflect restoration of excitation–inhibition balance through coordinated mechanisms that include global synaptic downscaling and strengthened inhibitory control, resulting in improved signal-to-noise ratio and functional efficiency [41, 42]. Nevertheless, this remains speculative, and future work including molecular and cellular assessments will be necessary to investigate the underlying mechanisms.

The negative association between piriform ALFF and processing speed observed only in the patient group suggests a COVID-19-specific context. The combination of linear improvement in processing speed over six months, a quadratic ALFF trajectory, and a negative group-level correlation may reflect heterogeneous individual recovery patterns in which normalization of ALFF can precede or evolve in parallel with cognitive improvement. The mediation analysis further indicates that the association between COVID-19 symptom burden and slower processing speed may partially operate through piriform ALFF. However, given the cross-sectional nature of the mediation analysis, causal inferences cannot be determined. While processing speed impairments are commonly reported following COVID-19 [4], prior piriform evidence related to attention and processing speed has primarily been limited to olfactory tasks [12, 13]. Although direct evidence linking piriform neural function to domain-general processing speed remains limited, plausible pathways include indirect influences through olfactory–limbic–prefrontal networks [10]. Therefore, the observed piriform–processing speed association should be considered preliminary and hypothesis-generating. The association between piriform ALFF and processing speed (β = –0.52) was of moderate magnitude and therefore unlikely to be trivial. However, because processing speed was defined as a study-specific age-, sex-, and education-adjusted standardized composite score, the clinical significance of this effect should be interpreted cautiously.

Sensitivity analyses indicated that the nonlinear post-infection trajectory of piriform ALFF and its positive association with acute COVID-19 symptom burden were broadly similar after adjustment for the interval from the last vaccination to infection, CIS total score, or exclusion of the participant with a non-COVID-related medical event. In the mediation model, the indirect effect of acute COVID-19 symptom burden on processing speed through piriform ALFF remained largely consistent after adjustment for vaccination interval or CIS total score and after exclusion of the participant with a non-COVID-related medical event. When time since infection was additionally included, the indirect effect was attenuated and no longer statistically significant. This may be understood in the context of the present findings, as the temporal dynamics of piriform ALFF are closely intertwined with the infection-related process under investigation, making it difficult to fully separate time-dependent and

infection-driven components of ALFF variance. Our findings should therefore be interpreted with caution, as potential influences of these factors on piriform function and its relationship with processing speed cannot be fully excluded.

Several limitations should be acknowledged. First, although baseline data indicated no pre-existing piriform dysfunction, the interval between the pre-infection baseline and SARS-CoV-2 infection was relatively long (mean 21.7 months), and influences of aging, intervening life events, or broader pandemic effects cannot be fully excluded. Notably, age and sex were adjusted for in all analyses, and the nonlinear U-shaped trajectory of piriform ALFF, anatomically specific and correlated with acute symptom burden, is difficult to attribute to monotonic aging or generalized stressors. Because the control group was not followed longitudinally, nonspecific temporal influences unrelated to infection could not be directly evaluated. Our cross-sectional design yielded group-averaged rather than individual trajectories, and longitudinal within-subject tracking will be essential for more definitively disentangling infection-specific effects from time-dependent confounds. Second, objective olfactory testing was not conducted to directly examine associations between piriform ALFF and olfactory function. Subclinical olfactory dysfunction may occur even in the absence of self-reported symptoms among individuals with COVID-19. Third, the sample consisted exclusively of non-hospitalized individuals with mild COVID-19. Thus, generalizability to hospitalized or more severely affected cases, long-COVID phenotypes, or cohorts with persistent anosmia remains uncertain, and future studies should recruit participants spanning a broader range of disease severity. Finally, explicit susceptibility-distortion correction was not performed. Given that the piriform cortex lies in a region vulnerable to susceptibility-related signal loss and geometric distortion, this may have reduced anatomical precision and BOLD sensitivity in the region of interest.

Conclusions

In summary, we observed a U-shaped trajectory of piriform cortex ALFF in non-hospitalized adults with mild COVID-19, with values elevated relative to baseline early after infection, declining to below-baseline levels by approximately three months, and recovering toward baseline by six months. Elevated ALFF was associated with greater acute symptom burden and slower processing speed. These findings suggest temporally dynamic changes in piriform cortex function, potentially reflecting a transient window of neural vulnerability during recovery from COVID-19. Future investigations should incorporate within-subject longitudinal designs and multimodal biomarker assessments to elucidate underlying mechanisms and inform development of targeted therapeutic strategies.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
HJ: Conceptualization, Formal analysis, Funding acquisition, Writing – original draft, Writing – review and editing; YS: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review and editing; YJoo: Data curation, Investigation, Writing – review and editing; YK: Data curation, Investigation, Writing – review and editing; CS: Data curation, Investigation, Writing – review and editing; YJin: Data curation, Investigation, Writing – review and editing; HS: Data curation, Investigation, Writing – review and editing; IKL: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review and editing; SY: Conceptualization, Funding acquisition, Project administration, Supervision, Formal analysis, Writing – review and editing.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Board of Ewha Womans University. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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