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SHORT COMMUNICATION

Impact of long-COVID on the local and global efficiency of brain networks

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Abstract

Background and purpose: Subjective cognitive complaints post-COVID-19, known as long-COVID, have unclear effects on neural activity. This study explores the neural basis of these cognitive impairments by comparing resting-state functional networks of long-COVID individuals to a control group.

Methods: Forty-two individuals with cognitive complaints persisting 24 weeks post COVID-19 infection and 43 age-, sex- and education-matched healthy controls without a history of infection were studied using resting-state functional MRI (rs-fMRI) and the Uniform Data Set (UDS-3) neurocognitive test battery (NCT). Neuropsychological scores were adjusted to the mean and grouped into seven cognitive composites. The rs-fMRI data were partitioned into seven distinct functional neural networks—Salience/Ventral Attention, Dorsal Attention, Default, Frontoparietal, Visual, Somatomotor, and Limbic—and their efficiency, largest connected component, and modularity (Q) were studied.

Results: The NCT scores yielded statistically significant differences in long-COVID subjects compared to controls at attention, language, memory, executive, and global composites. We observed significant differences ($p < .001$) in the global and mean local efficiency of the Salience/Ventral Attention and Global networks, and to a lesser extent ($p < .005$ and $p < .01$) in the Default and Dorsal Attention networks.

Conclusions: Our findings reveal significant group-level differences in executive, attentional, language, and memory outcomes, alongside less efficient and organized connections among Salience/Ventral Attention and Global networks.

KEYWORDS
cognitive impact, functional network analysis, long-COVID, network efficiency, rs-fMRI

INTRODUCTION

With a prevalence that ranges from 6.8% to 87.9% across various countries,[1] long-COVID presents itself as a constellation of symptoms that can arise between 4 and 12 weeks following the onset of infection from COVID-19, persisting for a minimum of 2 months without an alternative explanation.[1–3] Patients frequently report difficulties with memory, attention, and executive functions, severely impacting their

	Control	Long-COVID
Age	59 (+/- 9.9)	56 (+/- 12.2)
Sex	25 females; 18 males	30 females; 12 males
Years of education	15 (+/- 3.1)	16 (+/- 2.1)
Time to study (since infection) (y)	N/A	1.15 (+/- 0.65)
Hospital admission (n)	N/A	10
Critical care unit admission (n)	N/A	3

	Mean and interquartile range of NCTs		Estimate	ΔAIC
Memory	-0.08 [-0.56; 0.47]	-1.12 [-1.78; -0.32]	-1.20 [-2.09; -0.30]	14.45
Language	0.18 [-0.18; 0.52]	-0.43 [-0.82; 0.25]	-1.63 [-2.67; -0.59]	10.99
Attention	-0.16 [-0.41; 0.26]	-1.21 [-1.80; -0.40]	-1.61 [-2.48; -0.74]	17.59
Executive	-0.16 [-0.45; 0.06]	-0.82 [-1.37; -0.12]	-1.56 [-2.75; -0.37]	12.28
Visuospatial	0.21 [0.0; 0.43]	0.02 [-0.17; 0.33]	-0.88 [-1.94; 0.18]	0.82
Global	0.09 [-0.09; 0.33]	-0.87 [-1.36; -0.25]	-3.91 [-7.20; -0.62]	34.70

FIGURE 1 Sociodemographics and NCTs' results. Sociodemographics (top panel) and composites in each cognitive domain (mean and interquartile range; bottom panel). GLMM (group ~ age + sex + education_level + composite + (one|participant)) was used (right columns) to assess the impact of the composite on the group (estimate and 95% confidence interval), its significance (color scale) and improvement of the model. GLMM, generalized linear mixed-effects model; NCT, neurocognitive test.

quality of life. Some studies have shown widespread cortical volume reduction following a COVID-19 infection, with key brain regions (like the parahippocampal gyrus and the insula) affected.[4,5] Potential contributors point to sustained systemic inflammation and disruptions in the blood–brain barrier.[6,7]

Functionally, prior research on long-COVID mainly addressed olfactory dysfunction shortly after infection,[5,8,9] and only recently prolonged effects on brain function have been examined.[10–13] By leveraging graph theoretical analysis of resting-state functional MRI (rs-fMRI),[14,15] we aim to reveal patterns and alterations that may underlie the cognitive difficulties seen in long-COVID, thereby enhancing our understanding of its impact on the brain.

MATERIALS AND METHODS

Participants

Our study comprised 42 subjects with cognitive complaints after at least 6 months following a confirmed positive SARS-CoV2 RT-PCR result from nasopharyngeal swabs (long-COVID group) with disease severity mild to moderate[16] and 43 subjects matched by age, sex, and years of education with no history of COVID-19 infection (control group) (Figure 1). Hospitalization and vaccination status did not affect eligibility, but participants with prior cognitive decline were excluded. All participants underwent a USD-3 neurocognitive test (NCT)[17] and rs-fMRI protocols.

Neurocognitive tests

The NCTs included: Montreal Cognitive Assessment (MoCA), Craft Story delayed and trail-making test B (TMT-B) as a general (global) assessment; Craft Story immediate and delayed for testing memory; Benson's figure copy and reproduction for testing visuospatial skills; semantic fluencies and Multilingual Naming Test (MINT) for testing language; trail making test A (TMT-A) and direct span to assess attention; TMT-B and indirect span for testing executive functions. A composite was made for each of these domains based on the *z*-scores of their corresponding tests.[17]

We fitted a Generalized Linear Mixed-Effects Model (GLMM) with the group (control or long-COVID) as the dependent variable and the demographics (age, sex, and education level) and the composite score as fixed-effects and participants as a random effect. Data were centered by subtracting the mean before fitting the model. When performing this analysis on the executive, global, and language scores, three subjects from the long-COVID group were left out due to missing values.

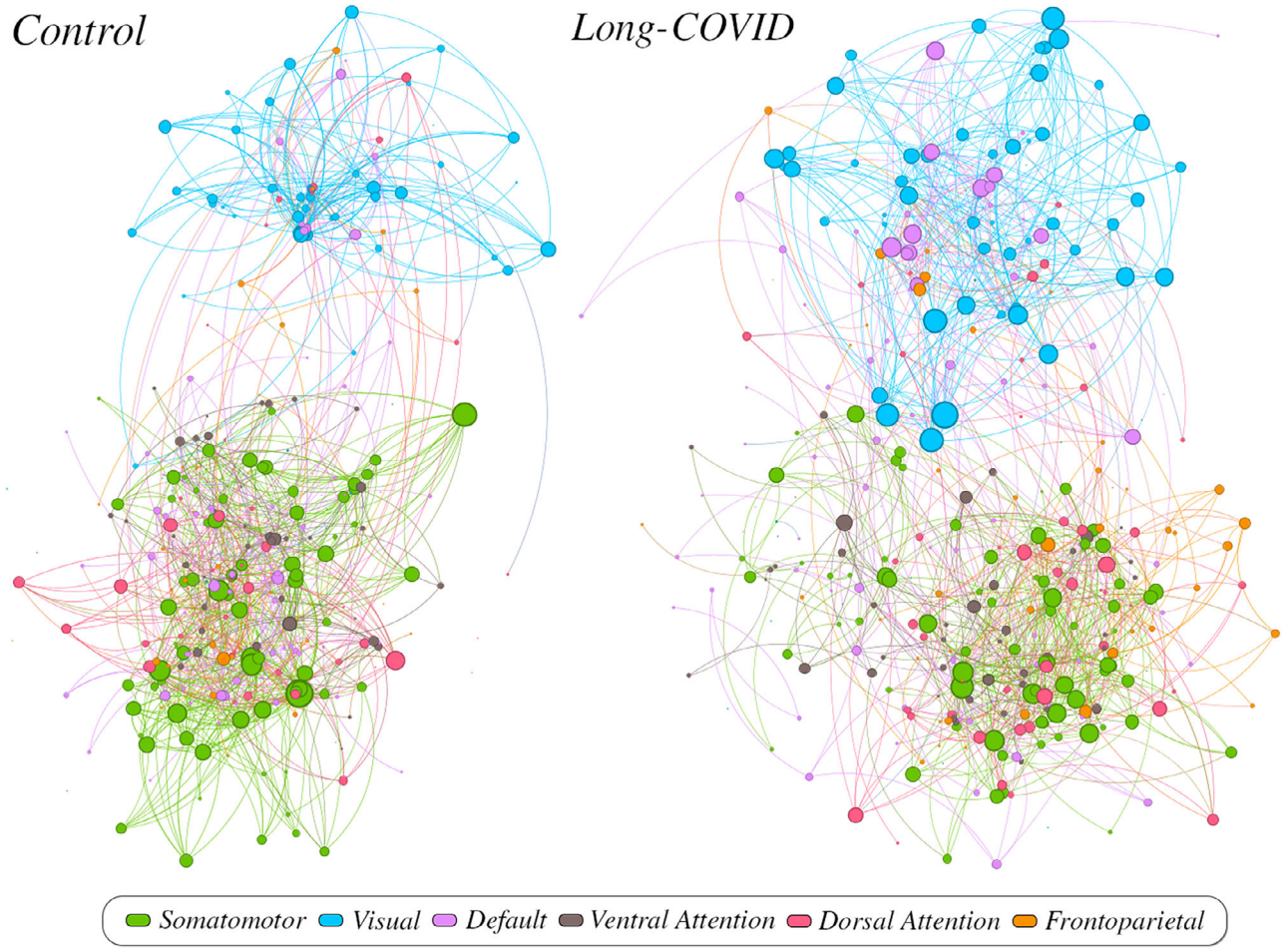

FIGURE 2 Mean global networks. Groups' mean global network at $\delta = 40\%$ (top 1% edges) using OpenOrd in Gephi (v0.10, Gephi Developers, https://gephi.org/). Each node corresponds to a brain region. Their size depicts their average weighted degree their color and the functional network they belong to. δ, connection density.

Functional MRI

Each participant underwent MRI (T1-weighted; 1 mm^3 resolution) and rs-fMRI scans (3 mm^3 resolution; 7-min sessions; 2 s repetition time) with a GE Discovery 750 3T. These were preprocessed with fMRIPrep (v23.2, NiPreps Developers, https://fmriprep.org/) with default parameters and slice-timing correction. Preprocessing involved head-motion correction, white matter and cerebrospinal fluid, high-pass filtering confounds, spatial smoothing with an FWHM kernel of size six, and a 0.08 Hz low-pass filter.

Parcellation was done with Schaefer's atlas (400 regions of interest),[18] using the Nilearn library (v0.10.1, Nilearn contributors, https://nilearn.github.io/). fMRI data were split into seven functional neural networks (Salience/Ventral Attention, Dorsal Attention, Default, Frontoparietal, Visual, Somatomotor, and Limbic)[19] in addition to the complete (global) network (Figure 2).

We proceeded to study the structure of these networks through global topological measures with the tool NetworkX (v3.3, NetworkX Developers, https://networkx.org/). As some measures require shortest-path calculations, we converted the networks' weights (correlation coefficients) to their absolute values before analysis. A global thresholding strategy was applied to enhance statistical power, extracting the greatest edge weights from each network. Inter-group differences' significance was assessed at each connection density (δ) using the Wilcoxon rank-sum test.

Global efficiency[20] is a measure of integration that, together with *local efficiency*, characterizes small-world behavior.[21] Defined as the reciprocal of the harmonic mean of the network's path lengths, it is closely related to the network's characteristic path length, with the advantage that network fragmentation—which could arise from the thresholding—does not pose a problem.

Local efficiency[20] is a node-specific measure that reflects the extent of integration between the immediate neighbors of the given node and can be considered a generalization of the clustering coefficient that explicitly takes into account paths.[22] We report the average across nodes.

The **largest connected component** (LCC), a characterization of the networks' robustness,[23] and the **modularity** (Q) of the Global net-

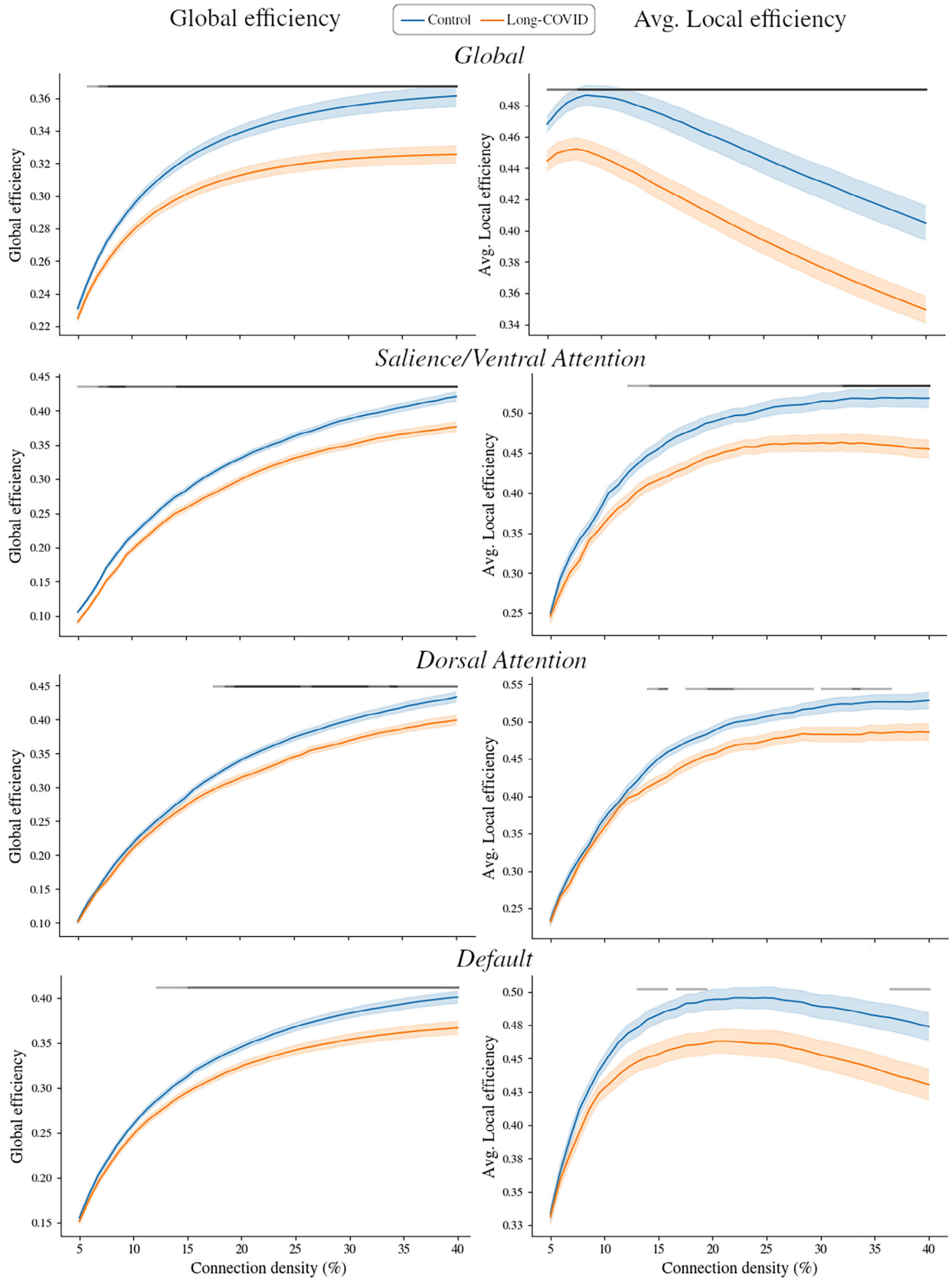

FIGURE 3 Efficiency of functional networks. Group average network efficiency at different δ. Shades of gray describe statistical significance: *black* ($p < .001$), *gray* ($p < .005$), and *light gray* ($p < .01$). δ, connection density.

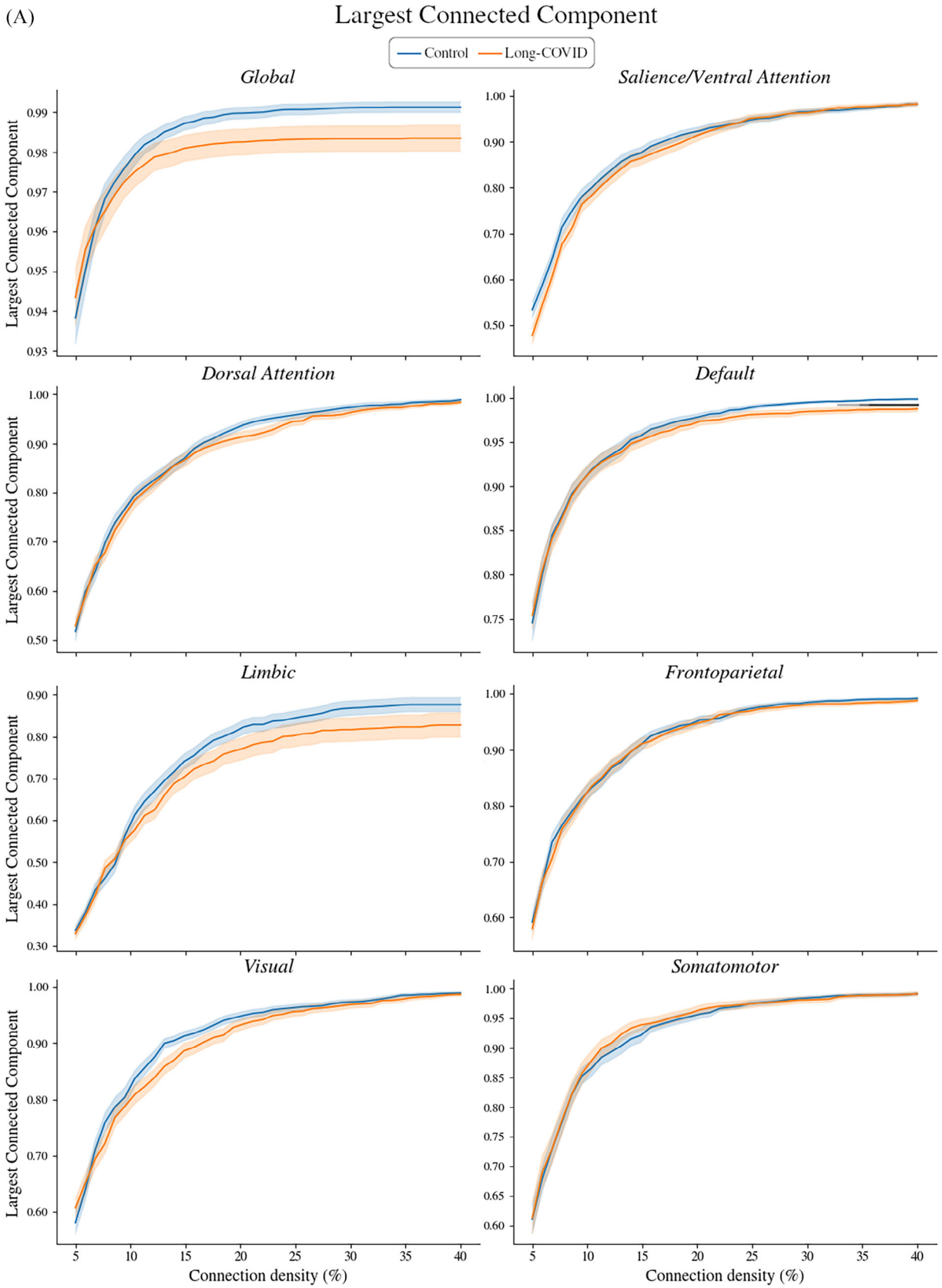

FIGURE 4 LCC and Q of functional networks. (A) LCC as a ratio of the number of nodes across increasing δ. (B) Q measured across different δ for the Global network. LCC, largest connected component; Q, Modularity; δ, connection density.

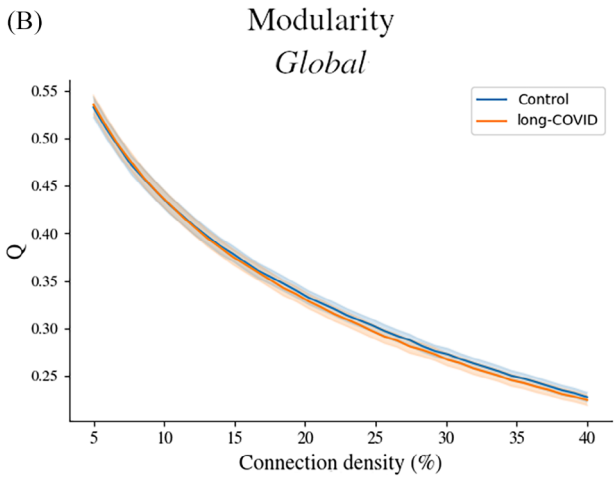

FIGURE 4 Continued

work, an estimation of the node's division into aggregations of densely connected subgroups,[24] were also studied.

RESULTS

The GLMMs ran on the groups yielded statistical significance and a high ΔAIC for the composite variable in attention ($p < .0001$), memory, language ($p < .001$), executive, and global ($p < .01$), with no significant effect in visuospatial ($p > .1$) (Figure 1).

We observe significant differences ($p < .001$) in the global and local efficiency of the Salience/Ventral Attention and Global networks and to a lesser extent ($p < .005$ and $p < .01$) in the Default and Dorsal Attention networks across a wide range of connection densities (with the exception of the local efficiency in the Default network) (Figure 3). No significant differences were found in other functional networks nor the LCC and Q metrics (Figure 4). This notable disparity in network efficiency is reflected by the structural variations visible in Figure 2, and might also be partly responsible for the results behind the NCTs, although no significant correlation was found.

DISCUSSION

This study explored both the cognitive and functional implications behind the subjective complaints following a COVID-19 infection in individuals without a history of cognitive decline before infection. Our clinical study suggests an impact on a broad spectrum of cognitive functions.[5] Additionally, we found alterations in the efficiency of networks that involved brain regions previously reported to be affected by long-COVID.[4,7] While no significant differences were observed in other functional networks, nor the LCC and Q, these disparities in network efficiency suggest that long-COVID may lead to a less resilient and more fragmented architecture. This hypothesis could explain the variety of cognitive impairments observed and aligns with the notion of COVID-19 affecting brain structure and connectivity, expanding upon previous findings in the literature.[10–13]

Our study's limitations include the cross-sectional design, which does not allow for the determination of causality. Future research should consider longitudinal studies to capture the trajectory of these changes over time and their direct impact on cognitive performance.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The authors elect to not share data.

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REFERENCES

1. Woodrow M, Carey C, Ziauddeen N, Thomas R, Akrami A, Lutje V, et al. Systematic review of the prevalence of long COVID. Open Forum Infect Dis. 2023;10:ofad233.
2. Davis HE, Mccorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Micro. 2023;21:133–46.
3. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. J Infect Dis. 2022;226:1593–607.
4. Zhou S, Wei T, Liu X, Liu Y, Song W, Que X, et al. Causal effects of COVID-19 on structural changes in specific brain regions: a Mendelian randomization study. BMC Med. 2023;21:261.

5. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, Mccarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 2022;604:697–707./bib>
6. Reiss AB, Greene C, Dayaramani C, Rauchman SH, Stecker MM, De Leon J, et al. Long COVID, the brain, nerves, and cognitive function. Neurol Int. 2023;15:821–41.
7. Greene C, Connolly R, Brennan D, Laffan A, O'Keeffe E, Zaporojan L, et al. Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. Nat Neurosci. 2024;27:421–32.
8. Muccioli L, Sighinolfi G, Mitolo M, Ferri L, Jane Rochat M, Pensato U, et al. Cognitive and functional connectivity impairment in post-COVID-19 olfactory dysfunction. NeuroImage Clin. 2023;38:103410.
9. Esposito F, Cirillo M, De Micco R, Caiazzo G, Siciliano M, Russo AG, et al. Olfactory loss and brain connectivity after COVID-19. Hum Brain Mapp. 2022;43:1548–60.
10. Zhang H, Chung TW-H, Wong FK-C, Hung IF-N, Mak HK-F. Changes in the intranetwork and internetwork connectivity of the default mode network and olfactory network in patients with COVID-19 and olfactory dysfunction. Brain Sci. 2022;12:511.
11. Li R, Liu G, Zhang X, Zhang M, Lu J, Li H. Altered intrinsic brain activity and functional connectivity in COVID-19 hospitalized patients at 6-month follow-up. BMC Infect Dis. 2023;23:521.
12. Jin P, Cui F, Xu M, Ren Y, Zhang L. Altered brain function and structure pre- and post- COVID-19 infection: a longitudinal study. Neurol Sci. 2024;45:1–9.[
13. Churchill NW, Roudaia E, Chen JJ, Gilboa A, Sekuler A, Ji X, et al. Effects of post-acute COVID-19 syndrome on the functional brain networks of non-hospitalized individuals. Front Neurol. 2023;14:1136408.
14. Bungenberg J, Hohenfeld C, Costa AS, Heine J, Schwichtenberg K, Hartung T, et al. Characteristic functional connectome related to Post-COVID-19 syndrome. Sci Rep. 2024;14:4997.
15. Xia M, He Y. Magnetic resonance imaging and graph theoretical analysis of complex brain networks in neuropsychiatric disorders. Brain Connect. 2011;1:349–65.
16. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:e192–97.
17. Dodge HH, Goldstein FC, Wakim NI, Gefen T, Teylan M, Chan KCG, et al. Differentiating among stages of cognitive impairment in aging: version 3 of the uniform data set (UDS) neuropsychological test battery and MoCA index scores. Alzheimers Dement. 2020;6:e12103.
18. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, et al. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb Cortex 2018;28:3095–114.
19. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011;106:1125–65.
20. Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett. 2001;87:198701.
21. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLOS Comput Biol. 2007;3:e17.
22. Fornito A, Zalesky A, Bullmore E. Fundamentals of Brain Network Analysis. Amsterdam: Academic Press; 2016.
23. Albert R, Jeong H, Barabási A-L. Error and attack tolerance of complex networks. Nature 2000;406:378–82.
24. Newman MEJ. Modularity and community structure in networks. Proc Natl Acad Sci USA. 2006;103:8577–82.

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