

# Is Neurodegeneration Accelerated? Investigating COVID-19's Impact on Dementia via Functional Connectivity

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## ABSTRACT

**Introduction:** COVID-19 has been associated with various neurological complications, including cognitive impairments such as memory deficits, attention difficulties, and executive dysfunction. These symptoms raise concerns about potential long-term effects, particularly in individuals with preexisting neurodegenerative conditions. Emerging evidence suggests that systemic inflammation, blood-brain barrier (BBB) dysfunction, and neuroinflammation may contribute to cognitive decline in COVID-19 patients. However, the impact of COVID-19 on functional brain connectivity, particularly in dementia patients, remains unclear.

This study aims to investigate the differences in functional connectivity across different frequency bands (delta, theta, alpha, beta, and gamma) in dementia patients with and without a history of COVID-19 (D-COVID and D-nCOVID) compared to a healthy control (HC) group. The study explores whether COVID-19 accelerates neurodegenerative processes by disrupting functional brain networks.

**Methods:** Functional connectivity was assessed using electroencephalography (EEG)-based network analysis in three groups: D-COVID, D-nCOVID, and HC. Connectivity metrics were compared across frequency bands, with a focus on local efficiency (LE) and

global network alterations. The Kruskal-Wallis test assessed statistical significance, while the Dunn test was used for post-hoc analysis.

**Results:** Findings indicate a significant reduction in functional connectivity across multiple brain regions in dementia patients, with the D-COVID group exhibiting more pronounced declines. The observed decrease in connectivity suggests that COVID-19 may accelerate neurodegenerative processes. Additionally, the HC group demonstrated stronger connectivity and higher LE metrics, highlighting the widespread impact of dementia on brain networks.

**Conclusion:** These findings support the hypothesis that COVID-19 contributes to cognitive decline by exacerbating neurodegenerative mechanisms. The disruption of functional brain connectivity observed in D-COVID patients aligns with previous studies suggesting that SARS-CoV-2 may indirectly promote neuronal degeneration. Further longitudinal studies are needed to determine the long-term cognitive consequences of COVID-19 and potential therapeutic interventions to mitigate these effects.

**Keywords:** COVID-19, dementia, electroencephalography, functional connectivity, neurodegeneration

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of COVID-19, has primarily been associated with respiratory complications. However, growing evidence suggests that the virus may also affect the central nervous system (CNS) and lead to various neurological symptoms. Cognitive impairments such as memory loss, attention deficits, and executive dysfunction have been reported in COVID-19 patients, a condition frequently referred to as “brain fog” (1). These cognitive disturbances raise significant concerns regarding the long-term effects of COVID-19 on brain function, particularly in individuals with neurodegenerative diseases such as dementia.

The observation of neurological symptoms in COVID-19 patients has led to speculation that SARS-CoV-2 may infect brain endothelial cells.

## Highlights

- Cognitive decline post-COVID-19 was examined using functional connectivity analysis.
- The impact of COVID-19 on the rate of neurodegeneration in dementia was investigated.
- Functional connectivity shows a decline in dementia patients after COVID-19.
- EEG functional connectivity analysis is useful in monitoring neurodegeneration.

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Studies have shown that systemic cytokine imbalances observed during COVID-19 can trigger immune responses, lead to blood-brain barrier (BBB) disruption, and ultimately result in neuroinflammation (2,3). Moreover, this process has been shown to impact cognitive functions (4). Additionally, it may enhance microglial activation and potentially accelerate neurodegenerative processes (5). Furthermore, disruptions in functional brain connectivity have been observed in COVID-19 patients, supporting the hypothesis that the disease may contribute to cognitive decline (6).

Given these concerns, it is of great importance to investigate the effects of COVID-19 on functional brain networks, particularly in individuals with neurodegenerative diseases such as dementia. This study aims to examine the differences in functional connectivity across different frequency bands (delta, theta, alpha, beta, and gamma) among dementia patients with a history of COVID-19 (D-COVID), dementia patients without COVID-19 (D-nCOVID), and a healthy control (HC) group. By analyzing connectivity patterns, this study seeks to determine whether COVID-19 worsens cognitive decline and accelerates neurodegenerative processes.

METHODS

Participant Selection

This study aimed to ensure comparable living conditions among participants by including 26 elderly individuals residing in Istanbul Metropolitan Municipality Senior Center, which is managed by the Darülaceze Elderly Care Center (Istanbul, Türkiye). The cohort consisted of 20 dementia patients and 6 healthy controls (HC). To minimize infection risks during the pandemic, the center implemented a staggered work schedule with 2-week shifts. Residents' COVID-19 status was closely monitored through polymerase chain reaction (PCR) testing.

Participants were categorized into three groups: the D-COVID group (10 dementia patients with a history of COVID-19 before vaccination), the D-nCOVID group (10 dementia patients with no known history of COVID-19), and the HC group (6 healthy controls). Detailed demographic and clinical data for all participants are provided in Table 1.

Vaccination data revealed that all participants had received at least one dose of either the Sinovac or BioNTech vaccine. In the non-COVID group, the average number of doses was 1.89±1.27 for Sinovac and 1.78±1.30 for BioNTech. In contrast, the COVID group, which had a history of infection before vaccination, received a higher number of doses, averaging 3.5±0.85 for Sinovac and 1.3±0.82 for BioNTech.

The diagnosis of dementia was established by neurologists and psychiatrists at the admitting institution, following the rigorous criteria set by the International Classification of Diseases, 10th Revision (ICD-

10) (7). Only individuals aged 65 years or older were included in the study. To ensure the validity of cognitive assessments, participants with conditions that could significantly impact cognitive function such as epilepsy, cardiovascular disease, diabetes, cancer, major psychiatric disorders, neurodegenerative diseases, a history of head trauma or stroke, hydrocephalus, or tumors were excluded.

All participants were enrolled with informed consent obtained from their legal guardians, who signed forms confirming their understanding and agreement with the study's objectives. The study protocol strictly adhered to the ethical guidelines of the Declaration of Helsinki and was formally approved by the Ethical Committee of Istanbul Nişantaşı University (2023/42-2023).

Data Acquisition Procedure

Electroencephalography (EEG) recordings were obtained using the ANT Neuro eego sports mobile EEG system (EE-222, eemagine Medical Imaging Solution GmbH, Berlin, Germany), adhering to the 10–20 electrode system. Waveguard gel-based cap electrodes (eemagine GmbH, Berlin, Germany) were used as sensors. The sampling frequency was 500 Hz, and a finite impulse response (FIR) band-pass filter was applied to the range from 1 to 45 Hz to capture relevant neural activity while minimizing noise interference. All recordings were conducted in a dimly lit environment with participants in an eyes-closed resting state.

Since recordings were conducted at the patients' location, frequency analysis was performed immediately after each session to assess noise levels. If necessary, the recording was repeated. A minimum of 30 minutes of recording was conducted to ensure sufficient data collection. The mastoid electrodes were chosen for their adaptability to various reference configurations and their widespread clinical use.

For functional connectivity analysis, the recordings were re-referenced using the surface Laplacian method, which employed the New Orleans configuration, a technique known for reducing volume conduction effects in coherence analysis (8). This re-referencing was implemented with a MATLAB function developed by Cohen (9), specifically designed for functional connectivity computations.

Preprocessing

The EEG data underwent additional preprocessing steps to enhance signal quality. First, the Artifact Subspace Reconstruction (ASR) method, integrated into the EEGLAB toolbox (10), was applied to eliminate noisy segments from the recordings. Next, the Wavelet-enhanced Independent Component Analysis (wICA) (11) method was employed to identify and suppress noise-related components within the EEG data automatically.

This technique, implemented using a MATLAB toolbox, is well-regarded for its effectiveness in isolating neural signals from various noise sources. As a result of the combined ASR and wICA preprocessing steps, high-quality EEG signals with a minimum duration of 20 minutes were obtained, ensuring reliable data for further analysis.

Functional Connectivity Analysis

In this study, Imaginary Part of Coherence (iCOH) was employed due to its efficacy in mitigating the confounding effects of volume conduction compared to standard coherency (12) for functional connectivity analysis. A Hanning window of 1-second length with a 50% segment shift was used for iCOH calculations. Calculations are repeated for seven frequency bands, which are Delta (1–3 Hz), Theta (3–7 Hz), Alpha (7–12 Hz), Beta I (12–18 Hz), Beta II (18–24 Hz), Beta III (24–30 Hz), and Gamma (30–45 Hz), and full spectrum (1–45 Hz). Consequently, 210 iCOH values were calculated to explain the relation between the 21 electrodes.

Table 1. Demographic and clinical characteristics of study participants

	D-COVID	D-nCOVID	HC
Subject number	10	10	6
Laterality	80% Right-handed	70% Right-handed	100% Right-handed
Age (Mean ± SD)	86.5±8.1	88.1±9.0	75.9±9.9
Gender	50% women	50% women	50% women
Literacy rate	40%	80%	83%

D-COVID: dementia patients with COVID-19 history; D-nCOVID: dementia patients without COVID-19 history; HC: healthy control; SD: standard deviation.

Additionally, to the coherence metric, Global Efficiency (GE), Local Efficiency (LE), and Transitivity (T) were employed in the analysis. Global Efficiency (GE) quantifies functional integration in graph theory, providing insights into the overall efficiency of information transfer and communication within the brain network (13,14). Local Efficiency (LE) measures the average efficiency of information transfer across the neighboring nodes, offering insights into the network's local processing capabilities (15). T measures the likelihood of interconnectedness between indirectly linked nodes in a network (16).

The metrics were calculated for all frequency bands. Then Kruskal-Wallis test was employed to assess because the groups didn't have a normal distribution. The Kruskal-Wallis test was conducted for inter-group comparisons among the dementia with a history of COVID-19 (D-COVID) group, the dementia without a history of COVID-19 (D-nCOVID) group, and the healthy control (HC) group, followed by Dunn's test as a post-hoc analysis. All analyses were performed in MATLAB.

## RESULTS

In the delta frequency band (1–4 Hz), the Kruskal-Wallis test revealed significant differences in connectivity between the regions shown in Figure 1B ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the D-nCOVID group compared to the D-COVID group.

For the theta frequency band (4–8 Hz), significant differences in connectivity were observed between the regions shown in Figure 1C ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the HC group compared to the D-nCOVID and D-COVID groups.

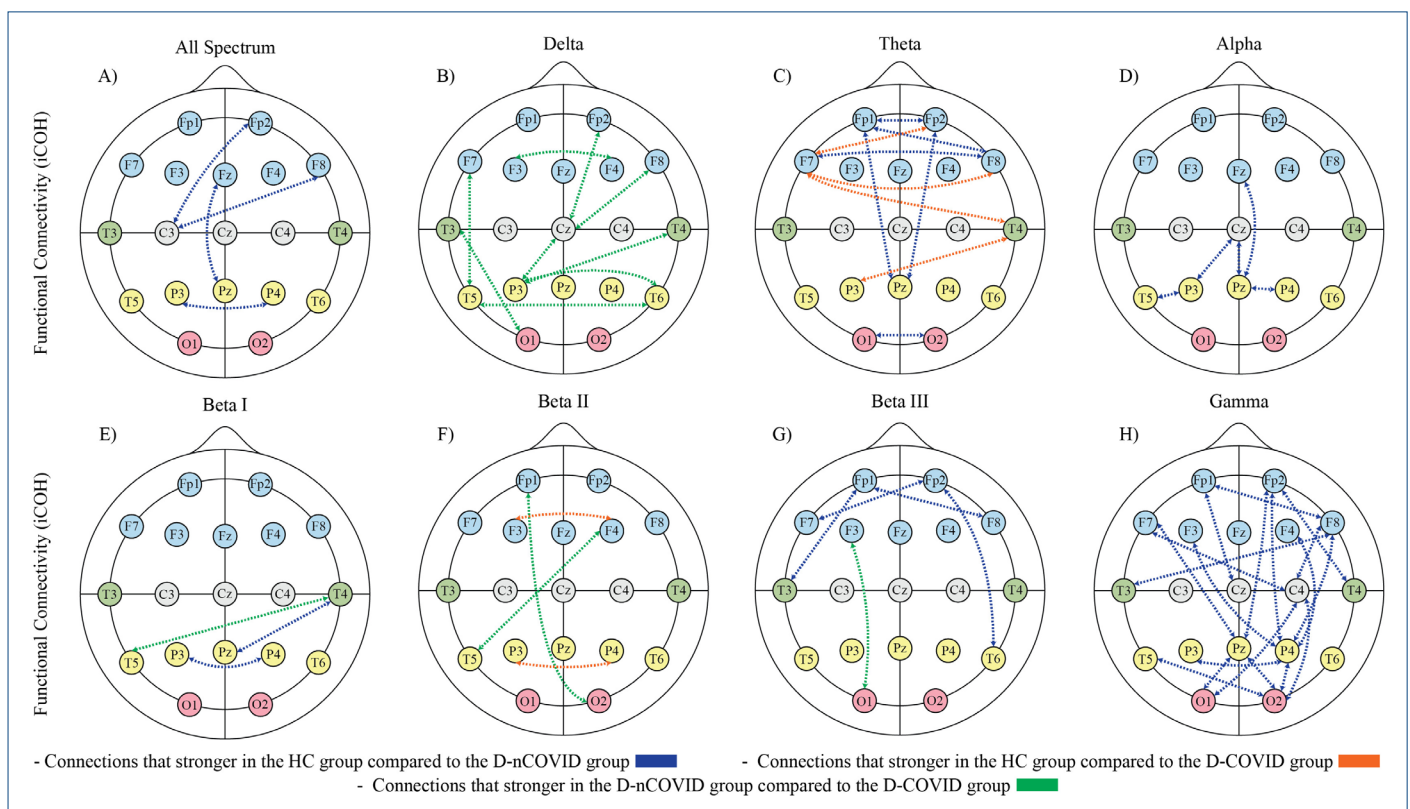
In the alpha frequency band (8–12 Hz), significant differences in connectivity were observed between the regions shown in Figure 1D ( $p < 0.05$ ). Post-hoc analysis revealed that the HC group exhibited stronger connectivity than the DnCOVID group in these regions.

For the beta I frequency band (12–18 Hz), significant differences in connectivity were observed between the regions shown in Figure 1E ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the HC group compared to the D-nCOVID group. Additionally, the D-nCOVID group exhibited stronger connectivity than the D-COVID group.

In the beta II frequency band (18–24 Hz), significant differences in connectivity were observed between the regions shown in Figure 1F ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the D-nCOVID group compared to the D-COVID group, as well as in the HC group compared to the D-COVID group.

For the beta III frequency band (24–30 Hz), significant differences in connectivity were observed between the regions shown in Figure 1G ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the HC group compared to the D-nCOVID group, whereas the D-nCOVID group exhibited stronger connectivity than the D-COVID group.

In the gamma frequency band (30–45 Hz), significant differences in connectivity were observed between the regions shown in Figure 1H ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the HC group compared to the D-nCOVID group.



**Figure 1.** Functional Connectivity across different frequency bands computed with the imaginary part of coherence (iCOH). Panels (A–H) represent connectivity patterns in distinct EEG frequency bands: A) All Spectrum (overall connectivity across all frequency bands), B) Delta (1–3 Hz), C) Theta (3–7 Hz), D) Alpha (7–12 Hz), E) Beta I (12–18 Hz), F) Beta II (18–24 Hz), G) Beta III (24–30 Hz), and H) Gamma (30–45 Hz).

Activity in the HC group compared to the D-nCOVID group. When examining the entire frequency spectrum (1–45 Hz), significant differences in connectivity were observed between the regions shown in Figure 1A ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by stronger connectivity in the HC group compared to the DnCOVID group.

Connectivity metric analysis revealed no statistically significant differences in GE values across any frequency band ( $p > 0.05$ ). However, significant differences in the T metric were observed in the gamma frequency band, as shown in Figure H ( $p < 0.05$ ). Post-hoc analysis indicated that these differences were primarily driven by higher T values in the HC group compared to the D-nCOVID group. Additionally, LE values were significantly higher in the HC group than in the D-nCOVID group in the left frontal, right frontal, left lateral frontal, right lateral frontal, and right parietal regions.

## DISCUSSION

This study examined the differences in functional connectivity across different frequency bands (delta, theta, alpha, beta, and gamma) in dementia patients (D-nCOVID and D-COVID) and a HC. The findings indicate significantly lower connectivity across multiple brain regions in dementia patients. The significantly lower connectivity observed in the D-COVID group suggests that COVID-19 may accelerate the neurodegenerative process. This finding aligns with previous studies reporting that the virus responsible for COVID-19 may indirectly contribute to neuronal degeneration (17). Additionally, the HC group exhibited stronger connectivity and higher LE metrics in critical brain regions, emphasizing the widespread impact of dementia on brain networks.

The GE metric, which reflects overall connectivity effectiveness, did not show a statistically significant difference between groups. This suggests that while global brain connectivity may remain largely preserved, regional impairments may still occur. However, the LE metric was significantly lower in the DnCOVID group compared to the HC group, particularly in the left frontal, right frontal, left lateral frontal, right lateral frontal, and right parietal regions. This finding supports the idea that dementia may lead to regional rather than global connectivity loss. The review of COVID-19 (18) emphasizes that slowed or abnormal electrical activity in the frontal region is the most common finding in resting-state EEG recordings. The observed lower LE in frontal and parietal regions may be associated with executive dysfunction, working memory impairment, and spatial processing deficits.

The T metric, measured in the gamma frequency band, was found to be significantly higher in the HC group compared to the D-nCOVID group, paralleling the findings of (19). Gamma oscillations play a critical role in cognitive processes such as attention, perception, and memory encoding (20). The observed lower T value in the D-nCOVID group suggests deterioration in high-level cognitive functions in dementia. Furthermore, the additional lower T metric observed in the D-COVID group suggests that COVID-19 may exacerbate neural dysfunction through neuroinflammation or vascular damage.

Significant differences were also found in the delta (1–4 Hz) and theta (4–8 Hz) frequency bands across groups. The HC group exhibited stronger theta connectivity, particularly between the frontal, parietal, and occipital regions, compared to both D-nCOVID and D-COVID groups. Theta oscillations represent the “on-line” state of the hippocampus and are associated with memory processes and attentional regulation (21). The observed lower connectivity in theta in dementia patients may indicate disrupted memory networks.

In the alpha band (8–12 Hz), the HC group showed stronger connectivity between the frontal midline and parietal midline regions compared to the D-nCOVID group. Alpha waves are crucial for regulating information flow and sensory integration (22). These lower connections may lead to impairments in attentional control and cognitive coherence.

Connectivity losses in the beta frequency band (12–30 Hz) were particularly observed in the frontal-parietal and frontotemporal pathways, which are important for motor planning, executive functions, and interhemispheric coordination.

The gamma frequency band (30–45 Hz) showed the most pronounced differences between groups. The HC group exhibited significantly stronger connectivity between frontal, parietal, temporal, and occipital regions compared to the DnCOVID group. Gamma oscillations play a critical role in higher-order cognitive processes such as perception, learning, and working memory. The lower gamma connectivity in dementia patients may reflect impaired synaptic synchronization and reduced cognitive flexibility. The more severe connectivity loss observed in the D-COVID group further suggests that COVID-19 may accelerate neurodegenerative processes and impair synaptic function.

The more pronounced connectivity disruptions in the D-COVID group highlight the adverse effects of COVID-19 on the brain. Recent studies indicate that SARS-CoV-2 may enter the central nervous system, triggering neuroinflammation and vascular damage (23). In particular, the lower connection in the beta and gamma frequency bands supports the hypothesis that COVID-19 may impact synaptic transmission and neuronal integrity. The observed lower connectivity in frontal and parietal regions aligns with studies reporting executive dysfunction and attention deficits in post-COVID-19 patients (24). Connectivity disruptions in these regions may contribute to impairments in cognitive control and information integration.

Lower LE values suggest that COVID-19 may introduce disruptions in brain networks, potentially making dementia patients more vulnerable to accelerated cognitive decline.

This study provides important findings for understanding the distinct effects of dementia and COVID-19 on brain connectivity. However, the integration of additional biological measures, such as neuroinflammation markers or cerebrospinal fluid (CSF) biomarkers, could further enhance our understanding of the mechanisms underlying COVID-19-induced neurodegeneration.

As a result, this study highlights functional connectivity losses in dementia patients and suggests that COVID-19 may accelerate this process. Our findings indicate that COVID-19 can lead to significant disruptions in brain networks and exacerbate neurodegenerative processes. The observed lower LE in frontal and parietal regions, along with lower gamma connectivity, suggests that dementia patients may become more vulnerable to cognitive flexibility impairments.

Moving forward, preventive measures should focus on cognitive rehabilitation and neuroprotective strategies to mitigate the impact of COVID-19 on dementia patients. These findings provide valuable insights for future research investigating the long-term effects of COVID-19 on brain connectivity dynamics and cognitive health.

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**Ethics Committee Approval:** The study was formally approved by the Ethical Committee of Istanbul Nişantaşı University (2023/42-2023).

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**Conflict of Interest:** The authors declared that there is no conflict of interest.

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