

SARS-CoV-2 Disrupts Functional Network Connectivity in Older APOE ϵ 4 Carriers: A CLSA COVID-19 Brain Health Study

P2-07

Hsu CL, Boa Sorte Silva NC, Stein RG, Hernández Gamboa R, Gu Y, Zou J, Dimri V, Tam RC, Salluzzi M, McCreary CR, Anderson L, Cossette B, Davidson P, Griffith LE, Hogan DB, McMillan JM, O'Connell ME, Wolfson C, Raina P, Smith E, Taler V, Liu-Ambrose T

INTRODUCTION

- SARS-CoV-2 is associated with acute respiratory effects and long-term neurological sequelae
- APOE ϵ 4 carriers have increased susceptibility to neuroinflammation and cerebrovascular complications post-infection
- Study Aim 1: Assess whether APOE ϵ 4 carriers show greater network disruption following SARS-CoV-2 infection
- Study Aim 2: Examine associations between network changes and cognitive/physical decline

METHODS

- 24-month longitudinal rs-fMRI data from 393 participants from the COVID-19 Brain Health Study of the Canadian Longitudinal Study on Aging (CLSA)
- Assessments: baseline, 12-month, 24-month behavioral; MRI at baseline and 24-month
- APOE ϵ 4 genotype: heterozygotes (n = 104), non-carriers (n = 289)
- SARS-CoV-2 status: cases (n = 81), controls (n = 312)
- Multi-site MRI acquisition: Vancouver, Sherbrooke, Calgary, Hamilton; harmonized protocol was utilized
- T1-weighted MRI, resting-state fMRI:
- 2 $\times$ 2 mixed ANCOVA: APOE ϵ 4 $\times$ SARS-CoV-2

RESULTS

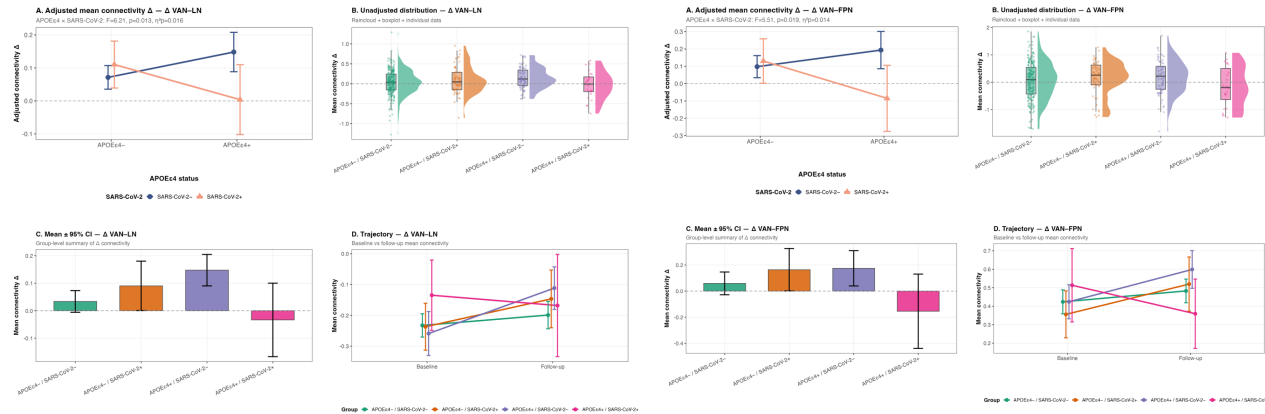


Figure 2. APOE ϵ 4 $\times$ SARS-CoV-2 Interaction on VAN-FPN Connectivity
Panel A shows covariate-adjusted estimated marginal means of VAN-FPN connectivity Δ by APOE ϵ 4 status and SARS-CoV-2 infection. APOE ϵ 4 carriers without prior infection display the highest positive Δ , whereas APOE ϵ 4 carriers with prior SARS-CoV-2 infection show reduced Δ , indicating that infection dampens the APOE ϵ 4-related increase in VAN-FPN coupling.
Panel B presents unadjusted raincloud plots of VAN-FPN connectivity Δ , with relatively narrow, near-zero distributions in APOE ϵ 4- / SARS-CoV-2- and broader, positively shifted distributions in APOE ϵ 4+ / SARS-CoV-2+, alongside more variable and attenuated changes in APOE ϵ 4+ / SARS-CoV-2-.
Panel C summarizes mean VAN-FPN Δ with 95% confidence intervals, demonstrating that APOE ϵ 4+ / SARS-CoV-2+ show greater mean increases than APOE ϵ 4+ / SARS-CoV-2-, whereas APOE ϵ 4+ / SARS-CoV-2- do not show comparable increases, consistent with the significant interaction.
Panel D displays baseline and follow-up trajectories, with steeper increases in VAN-FPN connectivity among APOE ϵ 4+ controls and smaller or reversed changes in infected APOE ϵ 4 carriers.

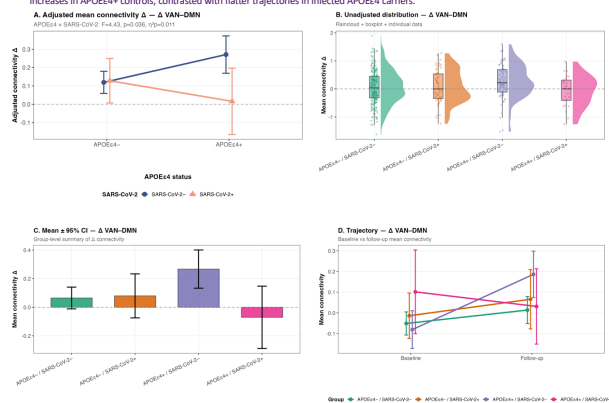


Figure 3. APOE ϵ 4 $\times$ SARS-CoV-2 Interaction on VAN-DMN Connectivity
Panel A shows covariate-adjusted estimated marginal means of VAN-DMN connectivity Δ by APOE ϵ 4 status and SARS-CoV-2 infection. APOE ϵ 4+ / SARS-CoV-2- exhibit the greatest positive Δ , whereas APOE ϵ 4+ / SARS-CoV-2+ show attenuated changes, indicating that SARS-CoV-2 infection reduces the APOE ϵ 4-associated increase in VAN-DMN coupling.
Panel B presents unadjusted raincloud plots of VAN-DMN Δ , with relatively symmetric, near-zero distributions in APOE ϵ 4- / SARS-CoV-2- and more positively shifted distributions in APOE ϵ 4+ / SARS-CoV-2-, and more variable, less strongly shifted distributions in APOE ϵ 4+ / SARS-CoV-2+.
Panel C summarizes mean VAN-DMN Δ with 95% confidence intervals, highlighting elevated Δ in APOE ϵ 4+ controls compared with APOE ϵ 4+ / SARS-CoV-2- and a lack of similar elevation in infected APOE ϵ 4 carriers, reinforcing the interaction effect.
Panel D depicts baseline and follow-up trajectories, showing similar baseline VAN-DMN connectivity across groups but larger follow-up increases in APOE ϵ 4+ controls than in infected APOE ϵ 4 carriers, consistent with infection-related blunting of APOE ϵ 4-associated connectivity changes.

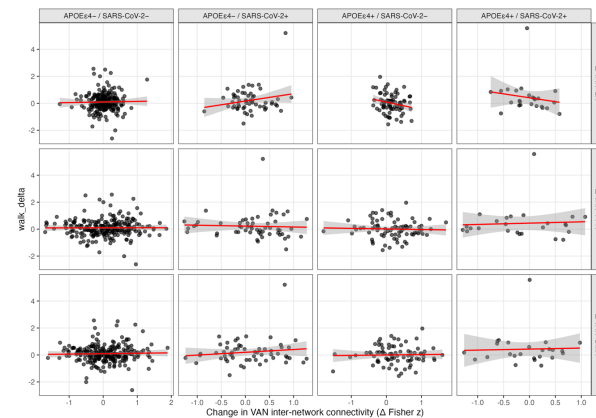


Figure 4. Association between VAN inter-network connectivity Δ and physical performance Δ . Scatterplots show change in gait speed (walk_delta) versus change in VAN inter-network connectivity, with linear fits by APOE $\times$ SARS-CoV-2 group. Regression analyses indicated no overall association between Δ VAN inter-network connectivity and Δ gait speed, but a significant Δ VAN-LN connectivity $\times$ group interaction and, after excluding outliers, a significant negative slope in APOE ϵ 4+ / SARS-CoV-2+ participants ($\beta = -0.89$, $p = 0.008$), with non-significant slopes in the other three groups.

CONCLUSIONS

- Selective alterations in large-scale functional connectivity observed in APOE ϵ 4 carriers following SARS-CoV-2 infection
- 24-month longitudinal decreases identified in: VAN-Limbic Network (LN); VAN-Frontoparietal Network (FPN); VAN-Default Mode Network (DMN)
- Findings suggest an interaction between SARS-CoV-2 infection and APOE ϵ 4 status
- Evidence supports a shift from compensatory hyperconnectivity to pathological hypoconnectivity, particularly across attentional-control networks
- Consistent with a biphasic model of Alzheimer's disease-related network reorganization

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