

Sex Differences in Altered Functional Connectivity Following SARS-CoV-2 Infection: A CLSA COVID-19 Brain Health Study

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

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INTRODUCTION

- Sex differences are well-established in large-scale functional brain organization and may persist or amplify with aging
- Females and males show differential vulnerability to neuroinflammation, vascular dysfunction, and network-level disruption
- Study objective: determine whether sex moderates longitudinal changes in functional connectivity following SARS-CoV-2 infection

METHODS

- 24-month longitudinal rs-fMRI dataset from 393 older adults from the CLSA COVID-19 Brain Health Study
- Sex: female (n = 218), male (n = 175)
- SARS-CoV-2 status: cases (n = 81), controls (n = 312)
- Network-level connectivity derived from Yeo 7-network parcellation
- Longitudinal change computed as follow-up minus baseline
- 2 × 2 MANCOVA (sex × SARS-CoV-2 status)
- Covariates: age, site

RESULTS

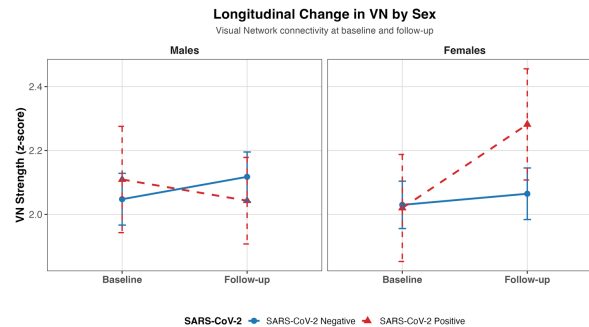


Figure 1. Longitudinal trajectories of visual network (VN) connectivity (z-scores) from baseline to follow-up, stratified by sex and SARS-CoV-2 status. In males, VN connectivity showed minimal change over time with overlapping 95% confidence intervals. In females, VN connectivity increased more in the SARS-CoV-2-positive group than in the SARS-CoV-2-negative group by follow-up. Blue solid circles/lines denote SARS-CoV-2 negative and red dashed triangles/lines denote SARS-CoV-2 positive; error bars represent 95% confidence intervals

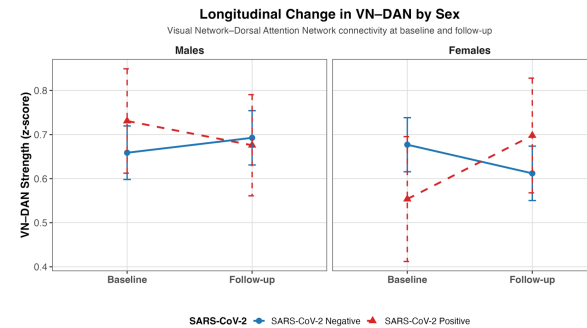


Figure 2. Longitudinal trajectories of within-network VN connectivity (z-scores) by sex and SARS-CoV-2 status. In males, VN connectivity remained relatively stable over time in both groups. In females, VN connectivity increased modestly in SARS-CoV-2-negative participants and more prominently in SARS-CoV-2-positive participants, resulting in higher VN connectivity in the positive group at follow-up. Blue solid circles/lines denote SARS-CoV-2 negative and red dashed triangles/lines denote SARS-CoV-2 positive; error bars represent 95% confidence intervals

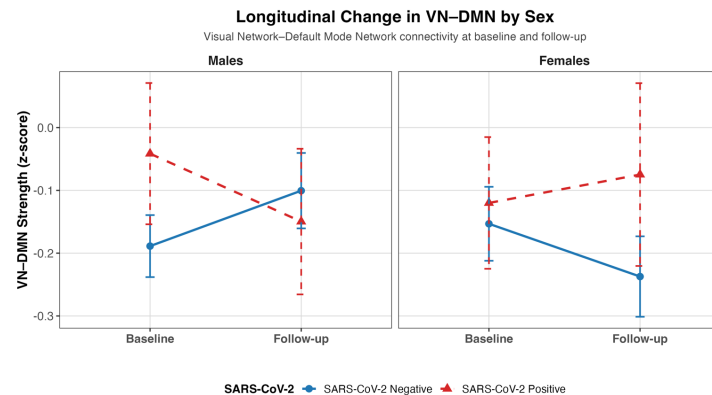


Figure 3. Longitudinal trajectories of VN-DMN connectivity (z-scores) by sex and SARS-CoV-2 status. In males, VN-DMN connectivity increased over time in SARS-CoV-2-negative participants but decreased slightly in SARS-CoV-2-positive participants. In females, trajectories also differed by infection status, with declining values in SARS-CoV-2-negative participants and increasing values in SARS-CoV-2-positive participants. Blue solid circles/lines denote SARS-CoV-2 negative and red dashed triangles/lines denote SARS-CoV-2 positive; error bars represent 95% confidence intervals

CONCLUSIONS

- SARS-CoV-2 preferentially altered connectivity of the Visual Network (VN) and its interactions with attentional (DAN) and default mode (DMN) systems
- Females with SARS-CoV-2 infection showed increased within-network VN connectivity and increased VN-DAN connectivity, consistent with hyperconnectivity in visual-attention networks
- Males with SARS-CoV-2 infection showed decreased VN-DMN connectivity, indicating reduced integration between sensory and default mode networks
- Among SARS-CoV-2 cases, females exhibited greater VN connectivity than males, whereas among controls, females showed lower VN-DMN connectivity than males
- Overall, SARS-CoV-2 infection was associated with female-predominant hyperconnectivity and male-predominant hypoconnectivity in visual-network connectivity
- These findings suggest sex-dependent reorganization of visual-system connectivity following SARS-CoV-2 infection, with potential implications for sex differences in post-COVID neurological symptom profiles.

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