P - 2149

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Brain Microstructural Disorganization as a Potential Mechanism of post-COVID-19 Condition and the Onset-suppressive Effects of Ensitrelvir Revealed by Advanced Diffusion MRI

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Introduction

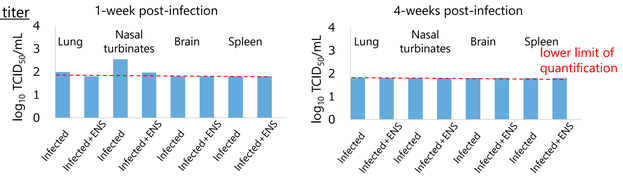
- **Post-COVID-19 condition (PCC)**
  - characterised by long-term sequalae (fatigue, smell and taste disorders, and cognitive impairment) whilst effective treatment options remain limited owing to unclear pathophysiology.
    →Early antiviral treatment in acute phase is crucial
- **Ensitrelvir (ENS)**
  - an oral antiviral drug approved in Japan for the treatment and post-exposure prophylaxis of COVID-19 and in US and EU for post-exposure prophylaxis[1,2]
- **diffusion MRI (dMRI)**
  - detect brain microstructural alterations underlying cognitive dysfunction
  - Fractional anisotropy (FA) is widely used and varies with fatigue scale in PCC patients[3], but it reflects composite tissue properties

This study characterizes persistent brain microstructural alterations following SARS-CoV-2 infection and evaluates the effects of early ensitrelvir treatment in a hamster model using advanced diffusion MRI.
(Neurite Orientation Dispersion and Density Imaging (NODDI) and Tractography).

Methods

~Animal model~
Syrian hamsters infected with SARS-CoV-2 were used.
ENS (50 mg/kg) was orally administered twice daily for five days starting one day post-infection (simulate exposure in humans).
Brain tissues were dissected at 4 weeks post-infection.

Viral titer



~Ex vivo whole-brain MRI study~
7T MRI System (Bruker BioSpin) was used.
A 3D diffusion weighted echo-planar-imaging (EPI) sequence was used with TR/TE = 2000/22.5 ms, FOV = 18 × 12 × 12 mm^3,
spatial resolution = 150 µm isotropic, b-value = 1000, 3000 s/mm^2,
diffusion directions = 30 (b = 1000 s/mm^2), 42 (b = 3000 s/mm^2).
Diffusion Tensor Imaging analysis was performed with MRtrix3 and FSL on Infected + ENS (infected and received ensitrelvir, n=14 (FA and NODDI) or 13 (Tractography)), Infected (infected but received vehicle only, n=13), and Non-infected (non-infected and received vehicle only, n=10) groups.
Statistical significance was assessed by ANOVA followed by Dunnett's test.

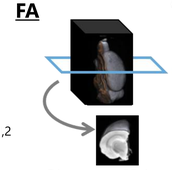


~Transmission electron microscopy (TEM) study~
Ultrathin sections were obtained from fixed brain samples (Non-infected (n=5), Infected (n=5), and Infected + ENS (n=5) groups).
JEOL JEM1400Flash was used to assess ultrastructural tissue integrity.

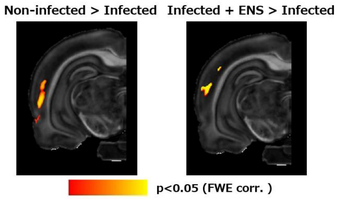
Results

MRI study

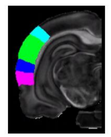
FA



A Whole-brain voxel-based analysis of FA



B Regions of interest (ROI) of post-infectious chronic fatigue syndrome (PI-CFS)-associated regions[4]



C ROI-based analysis of FA in PI-CFS–associated regions

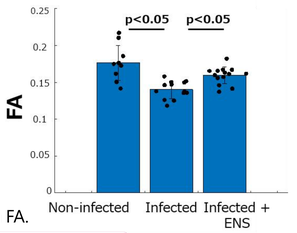
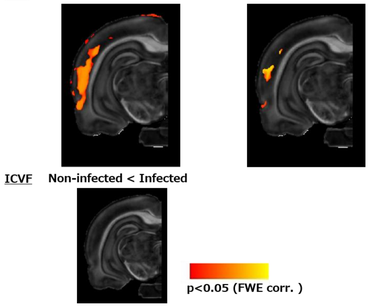


Figure1. Early ENS treatment mitigates SARS-CoV-2–associated reductions in brain FA.

Significant FA reductions following infection and attenuated by early ENS treatment.

NODDI

A Whole-brain voxel-based analysis of NODDI (ODI, ICVF)



B ROI-based analysis of ODI in PI-CFS–associated regions

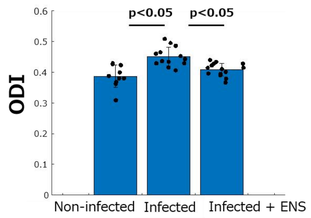
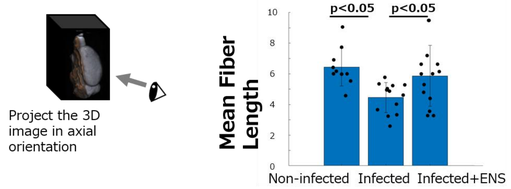


Figure2.
SARS-CoV-2 infection induces neurite orientation disorganization without density loss, attenuated by early ENS treatment revealed by NODDI analysis.

Increased orientation dispersion index (ODI) without changes in intracellular volume fraction (ICVF) indicating microstructural disorganization rather than neurite loss; these alterations were attenuated by ENS.

Tractography

A ROI-based analysis of mean fiber length connecting a PI-CFS–associated region and striatum (associated with motor function)



B 3D tractogram

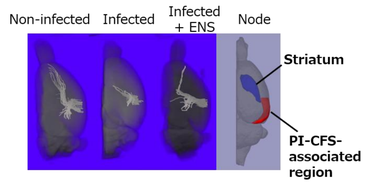


Figure3. SARS-CoV-2 infection disrupts fatigue-associated brain networks, preserved by early ENS treatment.

Reduced mean fiber length in PI-CFS–related regions in infected group, which was preserved by ENS.

TEM study

Representative TEM images in the MRI varying area with fatigue scale in PCC patients (corpus callosum)

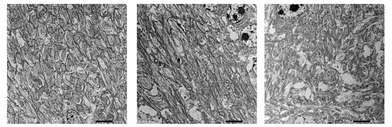


Figure4.
SARS-CoV-2 infection doesn't induce overt structural changes.

No overt structural damage among groups, supporting NODDI findings.

Summary

Our translational MRI approach revealed brain microstructural disorganization without neurite loss in a PCC model.

Early ENS treatment mitigated SARS-CoV-2-induced brain microstructural abnormalities in hamsters, potentially through viral load reduction, suggesting that acute antiviral intervention may reduce infection-associated neural alteration

References

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