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LETTER

# Neuroanatomical substrates of generalized brain dysfunction in COVID-19

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Dear Editor,

Central nervous system involvement is common in coronavirus disease 2019 (COVID-19), and may be driven by many mechanisms [1]. Reports of brain X-ray computed tomography [2] or magnetic resonance imaging (MRI) [3] findings in individual patients or small case series have generally focused on discrete pathologies such as stroke or focal abnormalities. However, these reports do not elucidate more generalized abnormalities of central nervous function, such as the alteration of mental status in a third of patients [4], or quantitative imaging correlates of reported brainstem pathology [5].

We report MRI findings in six patients with severe COVID-19-related respiratory failure (WHO Ordinal Scale 7), imaged 19 days (range 16–26) post admission, using conventional MRI and diffusion tensor imaging (DTI, Supplementary Table 1). The scans were performed for clinical reasons while the patients were in the intensive care unit with data prospectively collected. Indications included: persistent unresponsiveness after washout of sedative agents ($n=4$); severe delirium ($n=1$); or generalized myoclonus ($n=1$). Three patients had small acute ischemic lesions in the frontal deep white matter and two of these also had subarachnoid, intraventricular, or small parenchymal hemorrhage. However, none of the patients had abnormalities on conventional MRI that explained their clinical presentation or indicated hypoxic-ischemic injury.

DTI characterizes the diffusion of water molecules in tissue environments which are influenced by the microstructural organization of tissues. The diffusion tensor can be used to represent the magnitude of water diffusion (quantified as mean diffusivity (MD), which quantifies overall diffusion of water in tissue compartments), describe whether such diffusion is directionally non-uniform (fractional anisotropy, which classically changes with white matter pathology), and characterize the orientation of that direction (eigenvectors/eigenvalues, used for tractography; a modeling technique was used to map out white matter tracts, see Supplementary Tables 3, 4 and 5 for tract names).

All of the COVID-19 patients showed pervasive abnormalities on quantitative DTI compared to controls (Fig. 1A–B, Supplementary Tables 2–5), with increased mean diffusivity (MD) in frontal, temporal, parietal, and occipital cortices and hippocampi, consistent with vasogenic edema. In contrast, the mesencephalic and pontine reticular formations showed significant MD reductions, suggesting cytotoxic edema. No significant differences were seen in the basal ganglia or thalami. COVID-19 patients had significantly lower fractional anisotropy in several white matter tracts (Fig. 1B), suggesting microstructural disruption (e.g. edema, inflammation). All reported differences remained significant after stringent correction for multiple comparisons ($p<0.05$, Bonferroni corrected).

These findings suggest pervasive vasogenic edema in cortical gray and white matter tracts, recapitulating post-mortem findings in sepsis-associated encephalopathy [6]. The presence of edema in brainstem regions, however,

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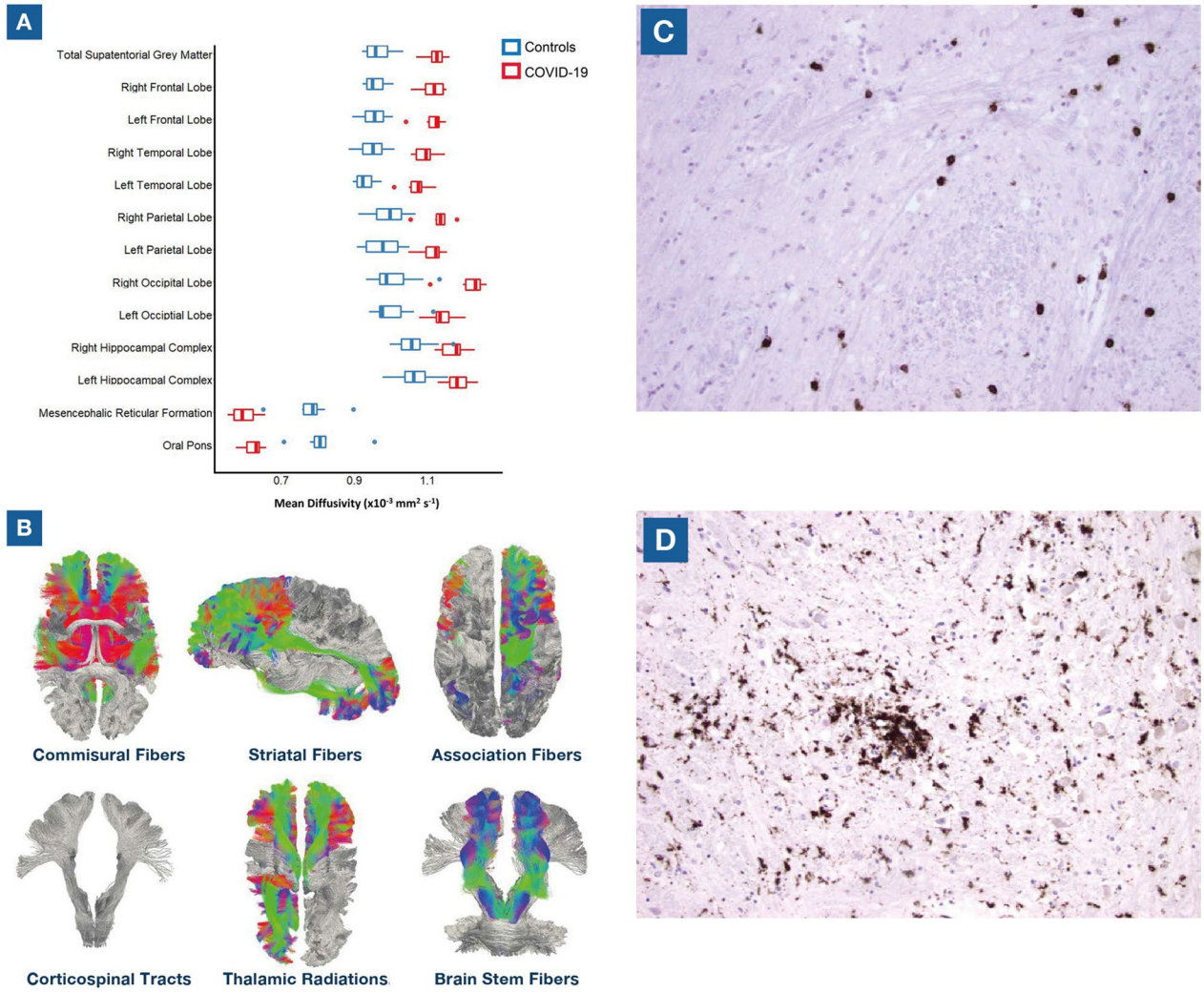


**Fig. 1** *Quantitative DTI*. Panel **A** shows boxplots of mean difusivity (MD) in gray matter regions where COVID-19 patients show significant diferences compared to age- and sex-matched control subjects. Panel **B** shows the group wise comparison of parcellated white matter tracts. Tracts in color (not gray) have significantly lower fractional anisotropy (FA) in the COVID-19 cases when compared to age and sex-matched controls. The color coding reflects directionality of fibers, with green denoting anterior/posterior, blue superior/inferior, and red right/left directionality. *Histology of the dorsal medulla (patient 2)*. Panel **C**: CD3 (x 200 magnification) immunohistochemistry showing a moderate parenchymal infiltrate of T-cells. Panel **D**: CD68 immunohistochemistry showing micogliosis with microglial nodules

requires alternate explanation. The mesencephalic and pontine reticular formations are key glutamatergic nuclei, suggesting possible excitotoxic injury. Alternatively, restricted diffusion may arise from inflammatory cell infiltration, as described in other viral encephalitides [7]. Such brainstem involvement may reflect direct SARS-CoV-2 infection, perhaps entering the brain through cranial nerves [1].

One patient (Patient 2, Supplementary Table 1) underwent a post-mortem examination. There was no evidence of established hypoxic-ischaemic brain injury and no vascular micro-thrombi were seen. In the dorsal medulla, there was a moderate parenchymal infiltrate of T-lymphocytes ($CD3^+CD8^+$), and activated microglia ($CD68^+$) involving the motor nucleus of the vagus nerve, nucleus ambiguus, solitary tract nucleus and inferior cerebellar peduncle (Fig. 1C–D). The inflammatory infiltrate did not involve ventral medullary structures, such as the pyramidal tracts or olivary nuclear complexes. A mild perivascular infiltrate of T-lymphocytes ($CD3^+CD8^+$) was found in the cerebral and cerebellar leptomeninges, cerebral white matter, and basal ganglia. Both ISH and

RT-PCR for SARS-CoV-2 RNA were negative in paraffin-embedded tissue sampled from the area of encephalitis in the medulla.

These novel findings are important for three reasons. First, we show that quantitative DTI may be abnormal in brain tissue that appears radiologically normal. Second, the widespread cortical and hippocampal abnormalities may explain mental status alterations seen in many patients. Finally, abnormalities in key brainstem arousal nuclei provide plausible neuroanatomical substrates for alteration of the sensorium in our patients. Further work is needed to ascertain whether these features reflect generic sepsis-related encephalopathy or are specific to SARS-CoV-2.

**Electronic supplementary material**
The online version of this article (https://doi.org/10.1007/s00134-020-06241-w) contains supplementary material, which is available to authorized users.

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**Author contributions**
VFJN and DKM designed the study. VFJN, LRBS, SW and EAS analysed the data. TD provided neuroradiology input. KA provided neuropathology input. All authors interpreted the data and contributed to the writing of the letter.

**Compliance with ethical standards**

**Conflicts of interest**
All the authors declare no conflict of interest.

**Ethical approval**
The Local Research Committee approved the use of the data used in this study (NIHR BioResource REC reference; 17/EE/0025, IRAS project ID 220277). Assent was obtained from next of kin. For control data ethical approval was obtained from the Local Research Ethics Committee (LREC 97/290 and 17/EE/0032, IRAS project ID 204052) and written consent was obtained.

## Publisher's Note



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