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Corresponding author(s): Frank L. Heppner

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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	We did not use a software for clinical data collection.
Data analysis	Data were analyzed using Graph Pad Prism, version 8.0 (GraphPad Software, La Jolla, CA, USA). For post-acquisition image processing the image analysis software FIJI (version 1.53e) was used. For data handling of whole slides images an OME-TIFF workflow was used.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Two electronmicroscopy datasets of Supplementary Figure 2 are available at www.nanotomy.org.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	all COVID-19 patients that died and recieved an autopsy were analyzed (N=33)
Data exclusions	no data was excluded
Replication	The SARS-CoV-2 qRT-PCR analysis was replicated at least once for each positive sample. All attemps were successful. SARS-spike protein immunostaining replicated once for all PCR positive samples (olfactory mucosa n= 10; CNS n= 8). All attemps were successful. In situ hybridisation was replicated once. All attemps were successful. Histological stainings, immunochistochemistry, and immunofluorescence, in-situ hybridisation were replicated once. All attemps were successful. Electronmicroscopy was replicated once. All attemps were successful. Histology, immunohistochemistry, immunofluorescence, and in-situ hybridization were analyzed independently by various neuropathologists in two distinct neuropathological institutions (Berlin and Göttingen) for each patient, region and specific staining/method.
Randomization	We determined an infection with SARS-CoV2 by qRT-PCR. The patients were not randomized but assigned to either the SARS-CoV2 positive or negative group.
Blinding	The investigators who performed SARS-CoV2 qRT-PCR and the histological/immunohistochemical/in-situ hybridizytion studies were blinded for the SARS-CoV-2 status of the patient.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

The following primary antibodies were used:
- polyclonal rabbit anti-S100 (Supplier: Dako, Catalog: Z0311, Target: Protein S100-A1, 1:3000)
- monoclonal mouse anti-AE1/AE3 (Supplier: DAKO, Catalog: M3515, Clone: AE1/AE3, 1:200)
- monoclonal mouse anti-MRP14 (Supplier: Acris, Catalog: BM4026B, Clone: S36.48, 1:500)
- monoclonal mouse anti-CD56 (Supplier: Serotec, Catalog: MCA 591, Clone: ERIC-1, 1:200)
- mouse monoclonal anti-SARS spike glycoprotein antibody (Supplier: Abcam, Catalog: ab272420, Clone: 3A2, 1:100)
- polyclonal goat anti-olfactory marker protein (OMP) (Supplier: Wako Chemicals USA, Catalog: 019-22291)
- rabbit monoclonal anti-beta III tubulin (Supplier: Abcam, Catalog: ab215037, Clone: EPR19591)
- rabbit polyclonal anti-neurofilament 200 (NF200) (Supplier: Sigma, Catalog: N4142)
- rabbit polyclonal anti ACE2 (Supplier: Proteintech, Catalog: 21115-1-AP)
- rabbit polyclonal anti-OLIG2 (Supplier: IBL America, Catalog: 18953, 1:150).

Briefly, primary antibodies were applied and developed either using the iVIEW DAB Detection Kit (Supplier: Ventana Medical Systems, Catalog Number: 760-091) and the ultraView Universal Alkaline Phosphatase Red Detection Kit (Ventana Medical Systems, Catalog Number: 760-501) or by manual application of biotinylated secondary antibodies (biotinylated donkey anti-sheep/goat (1:200 Company: Amersham, Catalog: RPN 1025), biotinylated donkey anti-rabbit (1:200), biotinylated sheep anti-mouse (1:200, Company: Amersham, Catalog: RPN 1001), rabbit Ig (Company: Amersham, Catalog: RPN1004), peroxidase-conjugated avidin, and diaminobenzidine (DAB, Company: Sigma, Catalog: D5637) or 3-Amino-9-Ethylcarbazol (AEC).

Validation	To biologically validate all immunohistological stainings, control tissues with known expression pattern harboring or lacking the expected antigens were used (Supplemantary Figure 3). Immunohistochemical staining for S100 protein within normal (non-diseased) autopsy brain tissue depicts glial cells such as astrocytes and neurons, while endothelial cells are spared. The positive control tissue for Olig2, which is known to show nuclear immunoreactivity in glioma tumor cells, while endothelial cells are not reactive to Olig2. HLA-DR immunoreactivity in the brain even under non-pathologic conditions is typically found on CNS-intrinsic myeloid cells, namely microglia, while e.g. neural/neuronal cells show no positivity for HLA-DR. All neuroepithelial cells in the CNS demonstrate a strong immunoreactivity for CD56, which cannot be found on endothelial cells. Tonsils were used to serve as positive control tissue for the general leukocyte marker CD45, while connective tissue of the capsula is not stained. The epithelium in a non-diseased skin sample shows strong immunoreactivity for the pan-cytokeratin marker AE1/3 in contrast to the surrounding connective tissue. The nasal respiratory mucosa of a non-COVID-19 autopsy case – in contrast to the olfactory mucosa - lacks Tuj1+ and OMP+ neural/neuronal cells; In Supplementary Figure 5 we show validation of mouse monoclonal anti-SARS spike glycoprotein antibody we used as positive control SARS-CoV-2-PCR+ mucosa, negative control was mucosa of SARS-CoV-2-PCR-negative cases. In Supplementary Figure 1 we show valdiation of rabbit polyclonal anti ACE2 (Proteintech, 21115-1-AP) the positive control proximal tubulus in kidney and negative control was brain parenchyma. All antibodies were checked for reproducability and integrety of the assay three times in independent staining experiments and in at least three different positive samples and compared to expected staining patterns in the controls regarding published expression of the antigens were applicable. Furthermore, an additional secondary-only antibody control (i.e. omission of first antibody) was performed for every setup.

Human research participants

Policy information about studies involving human research participants

Population characteristics	The median age at death was 71.6 years (IQR: 67 - 79, range: 30 to 98 years), and the time from onset of COVID-19 symptoms to death ranged from 4 to 79 days, with a median of 31 days. Cases were not preselected with regard to clinical and/or neurological symptoms, which due to the pandemic situation in some instances were not fully documented or not possible to retrieve. Clinically documented COVID-19-associated neurologic alterations were impaired consciousness (N=5 patients), intraventricular hemorrhage (N=2), headache (N=2) and behavioral changes (N=2); acute cerebral ischemia was reported for 2 patients, while neuropathological postmortem workup revealed acute infarcts in 6 patients (Supplementary Table 2). Coexisting conditions included diabetes mellitus (N=4), hypertension (N=21), cardiovascular disease (N=9), hyperlipidemia (N=2), chronic kidney disease (N=2), prior stroke (N=6), and dementia (N=5) (Supplementary Table 1). Although all 33 patients required mechanical ventilation and at time of autopsy suffered from COVID-19-associated lung disease, nine did not receive mechanical ventilation due to the respective patients' will. a
Recruitment	not applicable/see above
Ethics oversight	This study was approved by the local Ethics Committee (Berlin: EA 1/144/13, EA2/066/20 and EA1/075/19 and Göttingen: 42/8/20)

Note that full information on the approval of the study protocol must also be provided in the manuscript.