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## SARS-CoV-2 invades cognitive centers of the brain and induces Alzheimer's-like neuropathology

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#### Abstract

The neurotropism of SARS-CoV-2 and the phenotypes of infected neurons are still in debate. Long COVID manifests with "brain diseases" and the cause of these brain dysfunction is mysterious. Here, we analyze 34 age- and underlying disease-matched COVID-19 or non-COVID-19 human brains. SARS-CoV-2 RNA, nucleocapsid, and spike proteins are present in neurons of the cognitive centers of all COVID-19 patients, with its non-structural protein NSF2 detected in adult cases but not in the infant case, indicating viral replications in mature neurons. In adult COVID-19 patients without underlying neurodegeneration, SARS-CoV-2 infection triggers A $\beta$  and p-tau deposition, degenerating neurons, microglia activation, and increased cytokine, in some cases with A $\beta$  plaques and p-tau pretangles. The number of SARS-CoV-2<sup>+</sup> cells is higher in patients with neurodegenerative diseases than in those without such conditions. SARS-CoV-2 further activates microglia and induces A $\beta$  and p-tau deposits in non-Alzheimer's neurodegenerative disease patients. SARS-CoV-2 infects mature neurons derived from inducible pluripotent stem cells from healthy and Alzheimer's disease (AD) individuals through its receptor ACE2 and facilitator neuropilin-1. SARS-CoV-2 triggers AD-like gene programs in healthy neurons and exacerbates AD neuropathology. An AD infectious etiology gene signature is identified through SARS-CoV-2 infection and silencing the top three downregulated genes in human primary neurons recapitulates the neurodegenerative phenotypes of SARS-CoV-2. Thus, our data suggest that SARS-CoV-2 invades the brain and activates an AD-like program.

#### Competing Interest Statement

The authors have declared no competing interest.

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