The Pandemic Brain: neuroinflammation in healthy, non-infected individuals during the COVID-19 pandemic

Ludovica Brusaferri[1], Zeynab Alshelh[1], Minhae Kim[1], Akila Weerasekera[1], Hope Housman[1], Erin J. Morrisey[1], Paulina C. Knight[1], Kelly A. Castro-Blanco[1], Daniel S. Albrecht[1], Chieh-En Tseng[1], Nicole R. Zürcher[1], Eva-Maria Ratai[1], Oluwaseun Johnson-Akeju[1,2], Nathaniel D. Mercaldo[1], Nouchine Hadjikhani[1], Bruce R. Rosen[1], Jacob M. Hooker[1], Marco L. Loggia[1,2]

[1]Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
[2] Department of Anesthesia, Critical Care & Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Background:

- The impact of the **COVID-19 pandemic** on human health extends **beyond** the **morbidity** and death toll directly caused by the virus.
- Anecdotal evidence indicates that "sickness behaviors", such as **fatigue** and **depression**, have increased in the world-wide population, perhaps as a result of **health concerns** and/or **socio-economic disruptions** induced by the pandemic[1].
- Previous literature suggests that these **symptoms** may be manifestations of **neuroimmune activation**[2]:

- Would individuals examined after the enforcement of **lockdown**/stay-at-home measures demonstrate **increased brain neuroinflammation**?

Methods:

- Brain **Positron Emission Tomography / Magnetic Resonance Imaging** in healthy volunteers either before (n=57) or after (n=13) the Massachusetts lockdown (March-May 2020), using **[^{11}C]PBR28**, a radioligand for the glial marker 18 kDa translocator protein [3]
- In a subset (n=13 pre-lockdown; n=10 post-lockdown), we also quantified brain (thalamic) levels of **myoinositol** (**mIns**), another glial marker, with **Magnetic Resonance Spectroscopy**
- Using General Linear Models, we tested [^{11}C]PBR28 signal and/or mIns levels for
  - **Stability** before the lockdown
  - **Group differences** between pre- and post-lockdown cohorts
  - **Temporal associations** with estimates from an open-source population dataset assessing **depression** in >2 million individuals in the **US**

Interpretation:

- Our results suggest that elevated **neuroimmune responses** might be a mechanism of the sickness behaviors experienced during the pandemic by healthy individuals that were never infected with SARS-CoV-2.

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The protocol was approved by the local Institutional Review Board and the Radioactive drug Research Committee. Written informed consent was obtained from all participants prior to participation.

We report no conflict of interest.

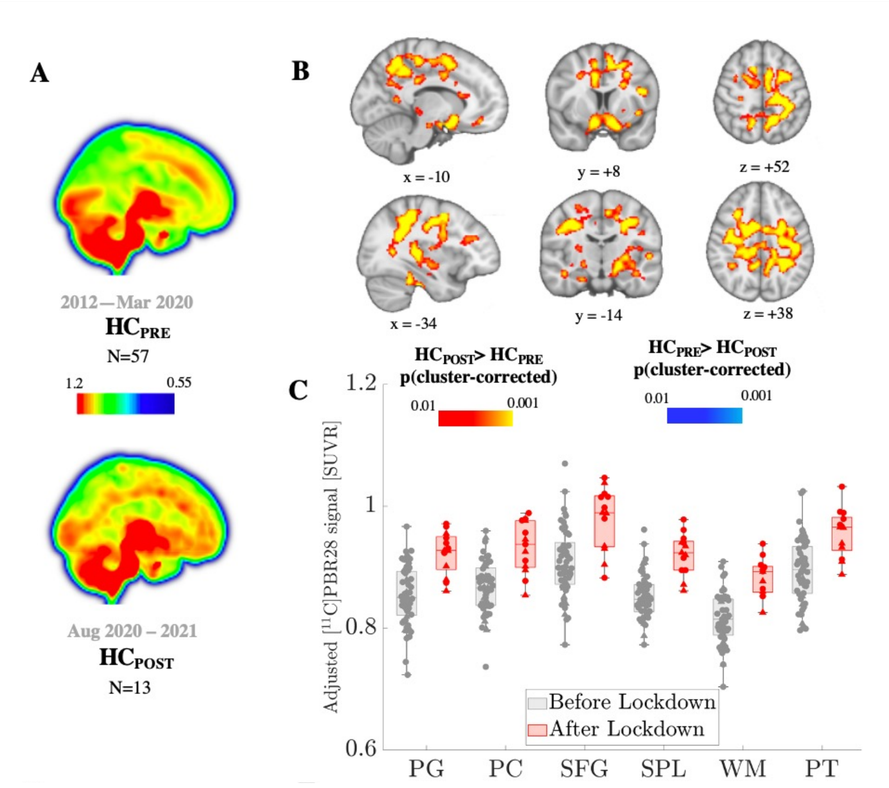

Figure 1. Areas of elevated PET [^{11}C]PBR28 SUVR signal in HC$_{POST}$ subjects. (A) Mean image computed from 57 HC$_{PRE}$ and 13 HC$_{POST}$ subjects are displayed as maximum intensity projection (MIP). (B) Significant cluster from a voxel-wise analyses (FSL randomise; 5000 permutations; cluster-forming threshold of p=0.01; cluster size threshold of p = 0.05) is shown in a red–yellow color scale. There were no significant regions for the HC$_{PRE}$ > HC$_{POST}$ contrast. (C) Visualization of mean SUVR in atomically separate sub-clusters using labels from the Harvard-Oxford Cortical Structural Atlas, including, pre-central gyrus (PG), precuneus cortex (PC), superior frontal gyrus (SFG), superior parietal lobe (SPL), white matter (WM), planum temporale (PT). Boxes represent the 25th to 75th inter-quartile range, and the horizontal line represents the median. Triangles denote data from Scanner 1 and circles denote data from Scanner 2.

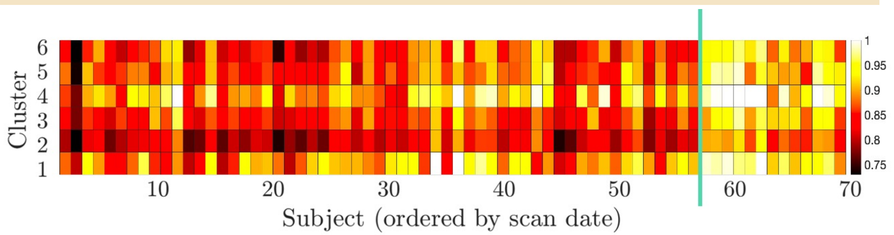

Figure 2. SUVR heat-map for the six significant sub-clusters (1=pre-cental gyrus, 2=precuneus, 3=superior frontal gyrus, 4=superior parietal lobe, 5white matter, 6=planum temporale).

Ludovica Brusaferri, PhD | Pain and neuroinflammation Imaging Laboratory | Harvard Medical School | lbrusaferri@mgh.harvard.edu

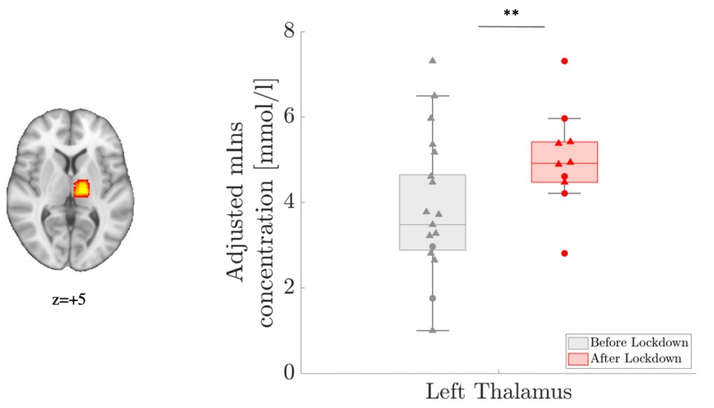

Figure 3. Group comparison for the glial marker myoinositol (mIns) acquired in the left thalamus

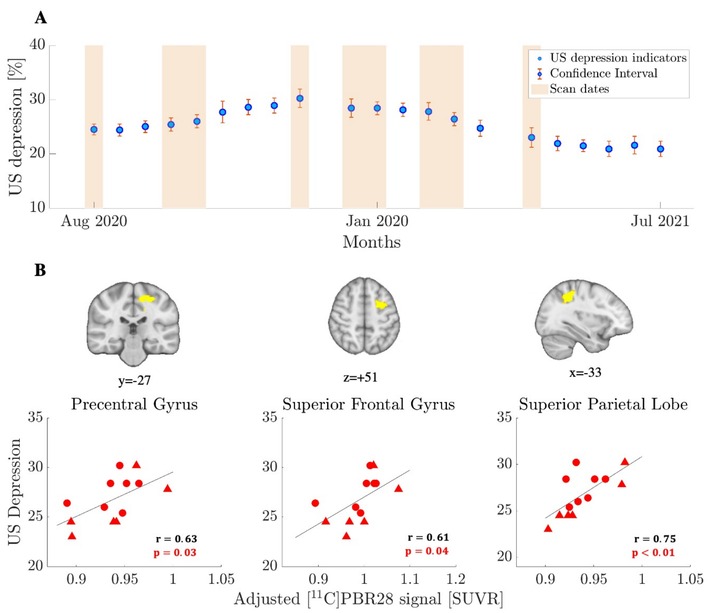

Figure 4. (A) Time-plot of US depression indicators (expressed as % of the population showing depressive symptoms); vertical bars highlight scan-dates for HC$_{POST}$. (B) Regions showing a significant positive correlation between [^{11}C]PBR28 signal and US estimates of depressive symptoms (controlling for scanner and TSPO genotype) within the post-lockdown cohort.

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