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Neuroimmune Activation And Increased Brain Aging In Chronic Pain Patients After The COVID-19 Pandemic Onset

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Abstract

The COVID-19 pandemic has exerted a global impact on both physical and mental health, and clinical populations have been disproportionally affected. To date, however, the mechanisms underlying the deleterious effects of the pandemic on pre-existing clinical conditions remain unclear. Here we investigated whether the onset of the pandemic was associated with an increase in brain/blood levels of inflammatory markers and MRI-estimated brain age in patients with chronic low back pain (cLBP), irrespective of their infection history. A retrospective cohort study was conducted on 56 adult participants with cLBP (28 'Pre-Pandemic', 28 'Pandemic') using integrated Positron Emission Tomography/ Magnetic Resonance Imaging (PET/MRI) and the radioligand [^{11}C]PBR28, which binds to the neuroinflammatory marker 18 kDa Translocator Protein (TSPO). Image data were collected between November 2017 and January 2020 ('Pre-Pandemic' cLBP) or between August 2020 and May 2022 ('Pandemic' cLBP). Compared to the Pre-Pandemic group, the Pandemic patients demonstrated widespread and statistically significant elevations in brain TSPO levels (P=.05, cluster corrected). PET signal elevations in the Pandemic group were also observed when 1) excluding 3 Pandemic subjects with a known history of COVID infection, or 2) using secondary outcome measures (volume of distribution -V_T- and V_T ratio -DVR) in a smaller subset of participants. Pandemic subjects also exhibited elevated serum levels of inflammatory markers (IL-16; P<.05) and estimated BA (P<.0001), which were positively correlated with [^{11}C]PBR28 SUVR (r's≥.35; *P's*<.05). The pain interference scores, which were elevated in the Pandemic group (P<.05), were negatively correlated with [^{11}C]PBR28 SUVR in the amygdala (r=-.46; P<.05).

This work suggests that the pandemic outbreak may have been accompanied by neuroinflammation and increased brain age in cLBP patients, as measured by multimodal imaging and serum testing. This study underscores the broad impact of the pandemic on human health, which extends beyond the morbidity solely mediated by the virus itself.

Introduction

The COVID-19 pandemic has caused unprecedented world-wide disruptions to human wellbeing (Xiong et al., 2020), impacting lifestyle, reshaping social and work environments, and causing stress, worries and uncertainty about the future. In fact, it has altered the way people interact with one another, carry out their social roles, and manage their health.(Karos et al., 2020) Those living with health conditions may have been disproportionately affected by the pandemic (Karos et al., 2020; Shanthanna et al., 2022). However, the neurobiological mechanisms underlying these effects are largely unexplored.

In a recent brain imaging study, we observed that (otherwise healthy) individuals evaluated after the onset of the pandemic, including those without a history of COVID-19, demonstrated elevated levels of brain and blood inflammatory markers compared to pre-pandemic subjects. Additionally, those neuroinflammatory signals were linked to measures of pandemic-related symptom burden of mood alteration and fatigue (Brusaferri et al., 2022). Given these observations, and the fact neuroinflammation may have a key role in the pathophysiology of many conditions [including neurodegenerative (Alshikho et al., 2016; Kreisl et al., 2013; Lyoo et al., 2015); pain (Albrecht et al., 2019a; Albrecht et al., 2019b; Alshelh et al., 2020; Alshelh et al., 2022; Loggia et al., 2015; Weerasekera et al., 2021) and psychiatric (Holmes et al., 2018) disorders], we reasoned that an exacerbation of pre-existing neuroinflammatory levels may be a plausible mechanism underlying the deleterious effect of the pandemic on some clinical populations.

Chronic pain is a complex and poorly understood condition affecting about 20% of the world's population, and can result in physical, psychological, and social vulnerabilities (Treede et al., 2015). During the pandemic, many individuals with chronic pain reported an exacerbation of their symptoms. This could potentially be attributed to the restricted access to non-urgent but vital healthcare services, including pain management, which were temporarily halted to reduce the risk of viral spread (Puntillo et al., 2020). Additionally, it is also possible that the exposure to social (and other) stressors might have played an important role (Karos et al., 2018). While empirical data on the impacts of the pandemic on the health of chronic pain patients are currently limited (Ziadni et al., 2022), multimodal neuroimaging offers the possibility to quantitatively measure and mechanistically characterize such effects (Liu et al., 2015).

In this study, we compare data from participants with chronic low back pain (cLBP) who underwent brain [^{11}C]PBR28 Positron Emission Tomography/Magnetic Resonance (PET/MR) imaging and blood testing either before or after the pandemic onset [March 2020 (Cucinotta and Vanelli, 2020)]. Our group has previously demonstrated that individuals with cLBP exhibit elevated brain levels of the 18 kDa translocator protein (TSPO), a putative marker of neuroinflammation that can be quantified using the PET ligand [^{11}C]PBR28 (Owen et al., 2015). Here, we test the hypothesis that the pandemic may have been accompanied by a further increase in brain [^{11}C]PBR28 signal. We also assessed the plasma levels of interleukin-16 (IL-16) and monocyte chemoattractant protein-1 (MCP-1), two inflammatory markers regulating migration and tissue infiltration of monocyte/macrophages (Deshmane et al., 2009; Hridi et al., 2021), which were previously found elevated in healthy volunteers evaluated after the pandemic onset.

Additionally, because neuroinflammation has previously been linked to accelerated brain aging (Salminen, 2022) and, in turn, the aged brain has shown a predisposition towards exaggerated responses to neuroimmune challenges (Sparkman and Johnson, 2008), we explored the possibility of a parametric association between pandemic-related elevations in neuroinflammatory signals and markers of brain age.

Methods

Study design and participants

This study was conducted on 56 cLBP participants, 19-73 years old (y.o.), originally enrolled in a clinical trial assessing the potential anti-neuroinflammatory effect of minocycline in this population (Morrissey et al., 2023). However, to avoid the potential confound of medication, only baseline (i.e., pre-treatment) clinical measures, blood samples, and PET/MR imaging data were analyzed for inclusion in the present report. In that trial, subjects were considered eligible if they reported ongoing pain that was at least 3/10 in its intensity and present for 50% of their typical week.

Anxiety, depression, and other mood disorders were assessed as part of a behavioral visit, utilizing self-report measures, examination of medical records, and the administration of the Beck Depression Inventory (BDI). Participants with a history of major psychiatric or neurological illness were excluded. Such conditions as PTSD, depression, and anxiety were considered exclusion criteria only if they were accompanied by hospitalization within the past 5 years. Detailed inclusion/exclusion criteria are listed in our recent work (Morrissey et al., 2023)(Alshelh et al., 2022). All participants provided written informed consent.

Overall, 28 ‘Pre-Pandemic’ (acquired between 11/2017 and 01/2020) and 28 ‘Pandemic’ imaging datasets (acquired between 08/2020 and 05/2022) were analyzed retrospectively. All subjects in the Pandemic cohort underwent COVID-19 antibody testing (Elecsys® Anti-SARS-CoV-2, Roche Diagnostics; 99.81% specificity; 100% sensitivity 14+ days post infection) on the day of the scan (Methods in Supplementary). All Pandemic were vaccinated against COVID-19,

with each of them receiving at least two vaccine doses where applicable, except in cases where a single-dose vaccine was administered. Participants' demographics are reported in Table 1.

Variables	Level	Pre-Pandemic	Pandemic
N		28	28
Sex	Male	12 (42.86)	9 (32.14)
	Female	16 (57.14)	19 (67.86)
Age [y]		48.03 (15.35)	44.17 (16.56)
Pain Duration [y]		9.86 (10.22)	9.53 (9.64)
Race	American Indian/Alaskan Native	0	1 (3.57)
	Asian/Pacific Islander	4 (14.28)	3 (10.71)
	Black	1 (3.57)	3 10.71)
	White	23 (82.15)	20 (71.44)
	Other	0	1 (3.57)
Ethnicity	Non-Hispanic	1 (3.57)	2 (7.14)
	Hispanic	27 (96.43)	26 (92.86)
Education	No degree	2 (7.14)	0
	High School	5 (17.86)	10 (35.71)
	Associates	2 (7.14)	9 (32.14)
	Bachelors	11 (39.29)	5 (17.86)
	Masters	8 (28.57)	4 (14.29)
	PhD	0	0
Employment status	Employed	26 (92.86)	23 (82.15)

	Retired	1 (3.57)	0
	Student	0	5 (17.85)
	Unemployed	1 (3.57)	0
TSPO genotype **	HAB	21(75)	11 (39.3)
	MAB	7(25)	17 (60.7)
Injected dose [mCi]		14.14 (1.01)	14.04 (1.61)
BMI		26.13 (4.61)	26.40 (5.28)
Molar activity [Gbq/µmol]		43.53 (14.17)	43.13 (16.40)
COVID-19 antibody	Positive	0	3 (10.71)
	Negative	0	25 (89.29)
	Unknown	28 (100)	0

Table 1. Patient Characteristics. Categorical variables are summarized as frequencies (proportions) and continuous variables are summarized as mean and standard deviation. Abbreviations: HAB = High Affinity Binders. MAB = Mixed Affinity Binders. BMI = Body Mass Index. ***P*<.01

Screening visit

All participants completed a behavioral visit, during which a trained clinician assessed their eligibility to participate in the study and collect initial behavioral variables. This visit included an informed consent process, behavioral assessments and biological specimen collection. Patients were genotyped for the Ala147Thr polymorphism in the TSPO gene, known to affect binding affinity for several TSPO radioligands, including [^{11}C]PBR28 (Owen et al., 2015). Only individuals with the Ala/Ala and Ala/Thr genotypes (predicted high-affinity binders, HABs, and mixed-affinity binders, MABs, respectively) were included.

Data acquisition and processing

At the beginning of the imaging visit, a subset of subjects (N=48; 20 Pre-Pandemic; 28 Pandemic) had venous blood collected to measure the serum level of two circulating inflammatory

mediators (IL-16, MCP-1; see Methods in Supplementary), which we have previously reported to be elevated in healthy subjects evaluated after the pandemic onset (Brusaferri et al., 2022). Additionally, all patients filled out the PROMIS-29 questionnaire (Morrissey et al., 2023), which assesses eight domains including pain severity and interference, and BDI.

For all subjects, dynamic [^{11}C]PBR28 PET/MR scans were performed with a Siemens Biograph mMR, a 3T whole-body PET/MRI scanner (Delso et al., 2011). Participants were injected with up to 15 mCi of [^{11}C]PBR28, a second-generation radioligand widely used to image the glial marker TSPO (Owen et al., 2015) in various neuroinflammatory conditions (Albrecht et al., 2019b; Alshelh et al., 2020; Alshelh et al., 2022; Loggia et al., 2015; Richards et al., 2018).

Simultaneous to the PET, a multi-echo MPRAGE (T1-weighted structural MRI) volume was acquired for anatomical localization, spatial normalization of PET data, generation of attenuation correction maps(Izquierdo-Garcia et al., 2014), as well as to estimate brain age (Methods in Supplementary). SUV ratio (SUVR) images (primary PET outcome) were obtained via intensity-normalization using the cerebellar gray matter as pseudo-reference region(Lyoo et al., 2015) and, for sensitivity purposes, the occipital cortex (Albrecht et al., 2018). SUV from neither putative a-priori region differed significantly across groups, *P*'s>.18; Methods in Supplementary).

In a subset of participants (N=21; 12 Pre-Pandemic; 9 Pandemic), a radial artery catheter was inserted to collect arterial blood for radioligand binding quantification, of which 17 yielded usable data (11 Pre-Pandemic; 6 Pandemic). Using Logan graphical analysis(Logan, 2000), we calculated distribution volume (V_T) and V_T ratio (DVR) values (secondary PET outcomes), which were used to complement the SUVR metric used for all study participants.

In this study, we utilized brainageR (Cole et al., 2017), a machine learning software, to predict an individual's apparent brain age (BA) based on structural brain characteristics derived from T1-weighted MRI data. Using this technique, it is possible to calculate 'Delta Brain Age' (DBA) and therefore estimate whether an individual or group displays brain morphological features that would be compatible with either an older (BA > chronological cage) or younger (chronological age > BA) individual.

Because BA estimates show a frequently observed bias (with BA being typically under-estimated in older individuals (de Lange and Cole, 2020; Gotlib et al., 2022)), we used a recently suggested calibration procedure (de Lange and Cole, 2020) (Methods in Supplementary).

Statistical analysis

Group differences in demographics were assessed with t-tests for continuous variables (e.g., age, injected dose) and chi-square (χ^2) tests for categorical variables (i.e., sex, TSPO genotype). When conducting group analyses on outcome measures, the effect of potential confounds was assessed by adjusting for the respective confounding variables and via matching (Methods in Supplementary). Given the higher prevalence of MABs in the Pandemic group (Table 1), we performed sensitivity analyses in a subset of patients (N=46; 23 Pre-Pandemic, 23

Pandemic) with balanced demographics and negative result in SARS-CoV-2 antibody testing (Table 1 in Supplementary). For brevity, we will refer to this subset of participants as "the matching subset".

Overall, we conducted two main tests to compare the Pre-Pandemic and Pandemic [^{11}C]PBR28 signal. First, we performed an *a-priori* region-of-interest (ROI) analysis in those areas where the PET signal was also found to be elevated in our previous study on healthy subjects (Brusaferri et al., 2022) (intraparietal sulcus, precuneus, insular cortex, subcallosal cortex, anterior cingulate cortex, nucleus accumbens, supplementary motor area, middle frontal gyrus and hippocampus). Second, we conducted a non-parametric voxel-wise permutation test, using a cluster-forming threshold of P=.01 and a cluster size threshold of P=.05 (Methods in Supplementary). Both tests accounted for TSPO binding affinity. The resulting significant cluster was parcellated by intersecting it with anatomical labels in MNI space, and from these parcels, the mean PET signal was extracted for visualization, correlational and support/sensitivity analyses. The association between [^{11}C]PBR28 signals from the cluster parcellates and clinical outcomes, as well as with peripheral inflammatory markers, was assessed using partial correlation analyses (controlling for TSPO binding).

Regarding the brain age analyses, a one-sample t-test was used to compare DBA from each group to the reference value of 0. Group differences in DBA were assessed with a GLM, including chronological age as covariate in the model, as suggested by the literature (Gotlib et al., 2022) (Cole and Franke, 2017). An ANOVA tested for the interaction between DBA and chronological age across three age ranges (18-40 [n=22], 40-60 [n=22] and 60+ y.o. [n=12]) then decomposed with a Tukey's HSD test. Furthermore, the DBA for each subject was also correlated with the mean [^{11}C]PBR28 signal extracted from the cluster parcellates (correcting for age and genotype). T1 image quality, estimated using FreeSurfer (Dale et al., 1999), was compared across groups for sensitivity purposes (Methods in Supplementary).

Where applicable (e.g., when tests were performed on multiple non *a-priori* outcomes), results from the group analyses were presented Bonferroni-corrected. Uncorrected p-values were reported for analysis on *a-priori* outcomes, or for exploratory purposes. A 2-sided value of P<.05 was considered statistically significant in all group analyses.

Analyses were performed with FSL's FEAT GLM tool (version 5.0.10) and Statistica (TIBCO Software Inc., v.13).

Results

In both *a-priori* ROI and voxel-wise analyses (including in all support/sensitivity analyses; Supplementary Material), the Pandemic group demonstrated higher [^{11}C]PBR28 PET signal (SUVR) compared to the Pre-Pandemic group. In ROI analyses, a group effect was observed in all tested regions .002<P's<.04), except for the intraparietal sulcus, precuneus, nucleus accumbens and anterior cingulate cortex (.06<P's<.16; Figure 1 in Supplementary). In whole-brain voxel-wise analyses, the Pandemic group exhibited higher [^{11}C]PBR28 PET signal in a widespread cluster encompassing, bilaterally, the orbital frontal cortex, occipital pole, cerebellar white matter and

brain stem and, on the left side, the precentral, postcentral, supramarginal, superior and middle frontal gyri, posterior middle cingulate cortex, anterior cingulate cortex, insula, amygdala, and hippocampus (Figure 1A-C, Table 2 in Supplementary). Sensitivity analyses confirmed that [^{11}C]PBR28 PET signal elevation in the Pandemic group could still be observed when 1) a different pseudo-reference region was used (occipital, instead of cerebellar, cortex), 2) the two groups included only subjects with a negative COVID-19 antibody test, and were balanced in terms of TSPO genotype (Figure 2 in Supplementary), or 3) different PET metrics were used (for subjects with available arterial blood data).

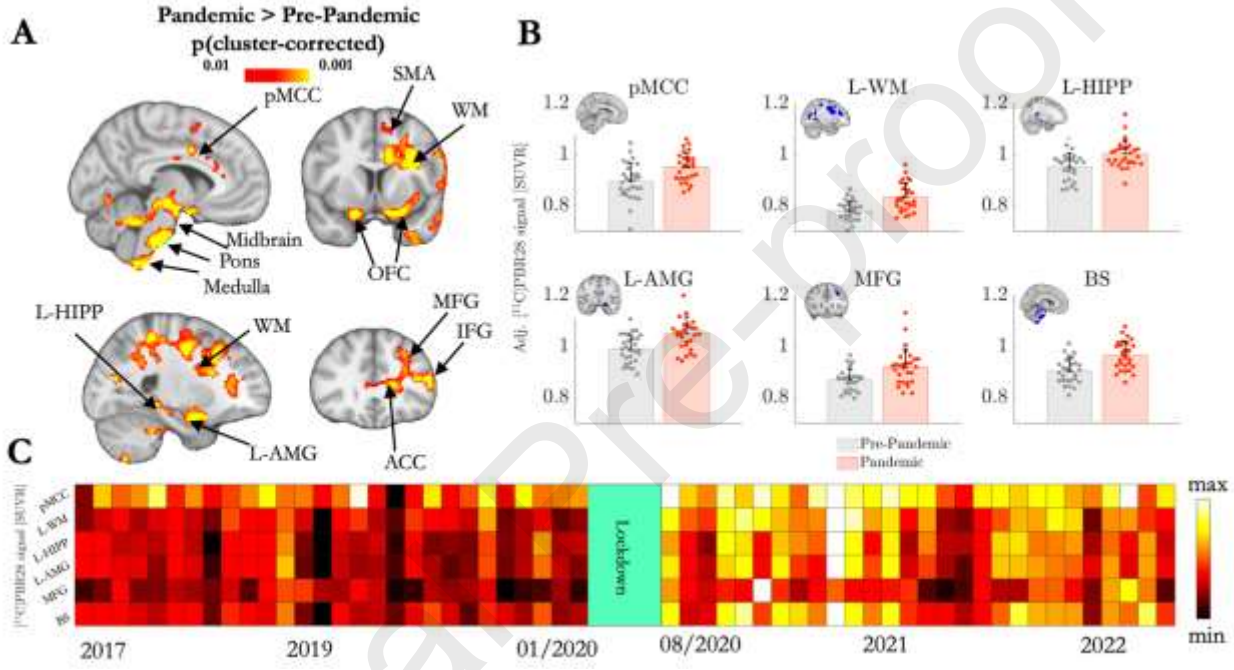

Figure 1. [^{11}C]PBR28 PET Signal. (A) Significant cluster from the Pandemic (N=28) > Pre-Pandemic (N=28) voxel-wise contrast is shown in a red–yellow color scale. There were no significant regions for the Pre-Pandemic > Pandemic contrast. (B) Visualization of mean [^{11}C]PBR28 SUVR extracted from sub-portions of the cluster statistically significant in A. Abbreviations: pMCC = posterior Mid-Cingulate Cortex. L-WM = Left White Matter. L-HIPP = Left Hippocampus. L-AMG = Left Amygdala. MFG = Middle Frontal Gyrus. BS = Brain Stem. (C) Mean [^{11}C]PBR28 SUVR extracted from sub-clusters in (B) and sorted by scan date.

Specifically, within all the cluster parcellates from the voxelwise analyses, despite the much smaller sample size (~30% of the total sample), we observed significant group differences with DVR (*P*'s<.05). Group differences in V_T displayed the same general pattern but did not reach statistical significance (*P*=.07 for L hippocampus and .07<*P's*<.1 for other regions; Figure 3A, 4A and Table 3, all in Supplementary). SUVR and DVR signals showed a strong positive correlation (r's > .87; Figure 3B in the Supplementary) while, as expected, no significant correlation was observed between SUVR and V_T (r's > -.43; Figure 4B in the Supplementary).

The Pandemic group also demonstrated higher serum levels of the inflammatory marker IL-16 (*P*<.05) compared to the Pre-Pandemic Group, as hypothesized. IL-16 serum levels were positively correlated with [^{11}C]PBR28 signal within the left-hippocampus across both groups (r=.35; *P*<.05 Figure 2), although not in the other 5 regions examined (Table 4 in Supplementary). Notably, when testing the two groups separately, the correlations did not reach statistical significance; however, a nonsignificant positive trend was observed within both Pre-Pandemic and Pandemic cohorts separately (r's>.23; *P's*>.05).

Both group difference in IL-16 serum levels and correlation between IL-16 and [^{11}C]PBR28 signal were observed in the matching subset (Figure 5 in Supplementary). Contrary to our prior study in healthy subjects (Brusaferri et al., 2022), MCP-1 serum levels were not higher in the Pandemic group, but were in fact lower compared to the Pre-Pandemic Group (*P*<.05). The matching subset, however, did not show a significant difference in MCP-1 levels.

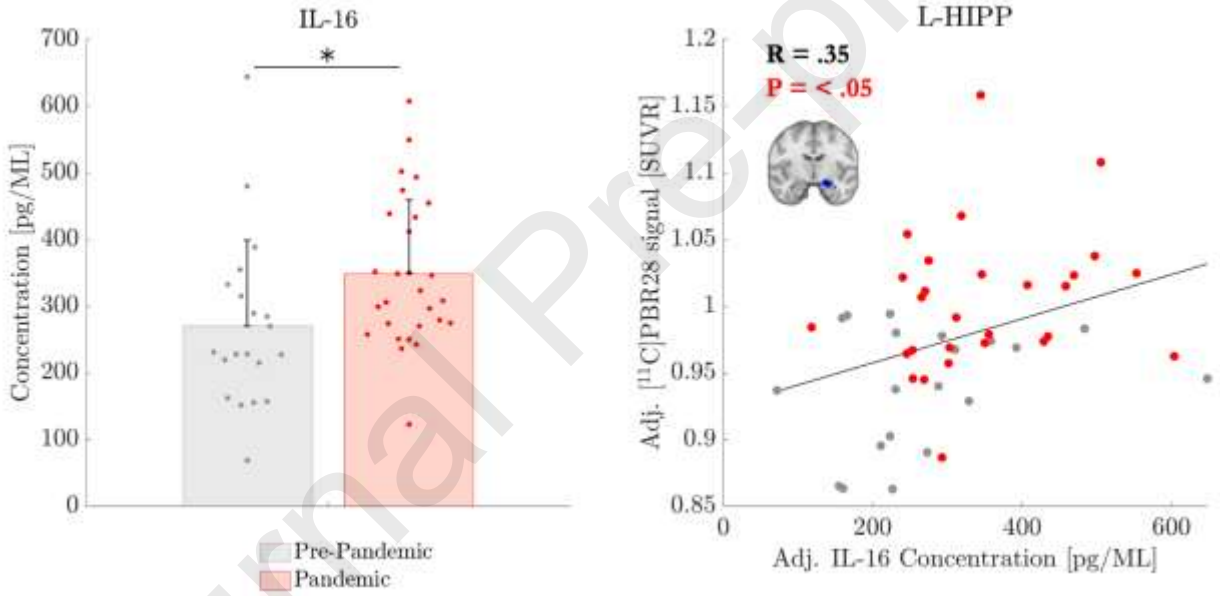

Figure 2. IL-16 Levels and correlation with PET signal. Plasma inflammatory marker (IL-16) elevations in the Pandemic group (N=20) compared to Pre-Pandemic group (N=28) and their correlation with [^{11}C]PBR28 signal in the Left Hippocampus (L-HIPP). **P*<.05

Overall, BDI scores did not differ across the two groups (Pre-Pandemic: 6.64+/-5.42; Pandemic: 6.17+/-5.4; P=0.74). Pandemic subjects however reported higher levels of Pain Interference (*P*<.05), while the other domains from PROMIS-29 were not significantly different across groups (*P's* >.16). This effect did not reach statistical significance within the matching subset and did not survive correction for multiple comparisons (Figure 6 in Supplementary). Overall, Pain Interference scores were negatively correlated with [^{11}C]PBR28 signal in the left-amygdala within the Pandemic cohort (r=-.46; *P*<.05; Figure 3), but neither across both groups nor

in other regions. No statistically significant correlations were observed in the other 5 regions examined (Table 4 in Supplementary).

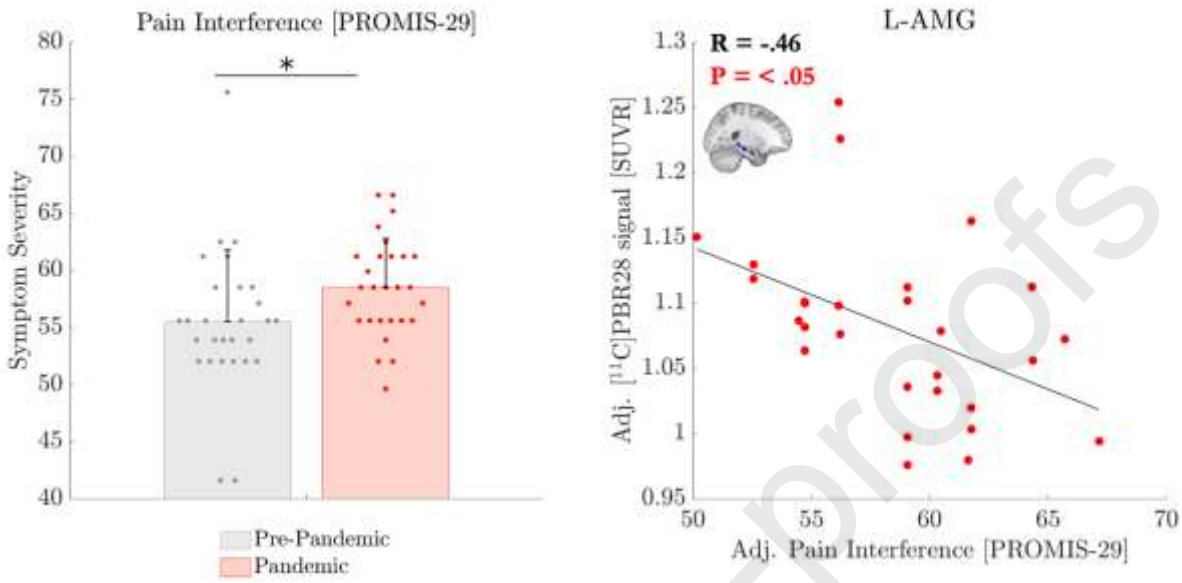

Figure 3. Pain interference and correlation with PET signal. Pain Interference score (PROMIS-29) elevations in the Pandemic group (N=28) compared to Pre-Pandemic group (N=28) and their correlation with [^{11}C]PBR28 signal in the Left Amygdala (L-AMG; Pandemic group only). *P<.05

Regarding the brain age analyses, the Pre-Pandemic group DBA values were not statistically significant from 0 (P=.14), meaning that, on average, the estimated BA was not statistically different from their chronological age. The DBA for the Pandemic group, on the other hand, was significantly higher than 0 (i.e., estimated > chronological age; P<.0001), with a mean value of ~10, suggesting that Pandemic participants exhibited brain features that, on average, resembled those of individuals ~10 years older. Overall, the DBA values of the Pre-Pandemic cLBPs were significantly higher than Pre-Pandemic cLBPs (P<.0001 Figure 4A-B). Significant elevations in DBA values remained consistent even after accounting for additional potential confounding variables, such as sex and education (P<.0001). No statistically significant differences were found in the MRI quality control metrics when comparing the two groups (P's>.24), ruling out data quality as a potential confounding factor (Results and Figure 7 in Supplementary).

When group analyses were repeated by subdividing the patients into age classes, we observed a statistically significant interaction between age class and group (P<.01), which revealed that DBA was significantly higher only for older Pandemic subjects (40 < age ≤ 60 and age > 60; P's<.0001) but not for younger Pandemic subjects (18 < age ≤ 40; P=.94) (Figure 4C, Table 5 in Supplementary). These results were confirmed in the matching subset (Figure 8 in Supplementary).

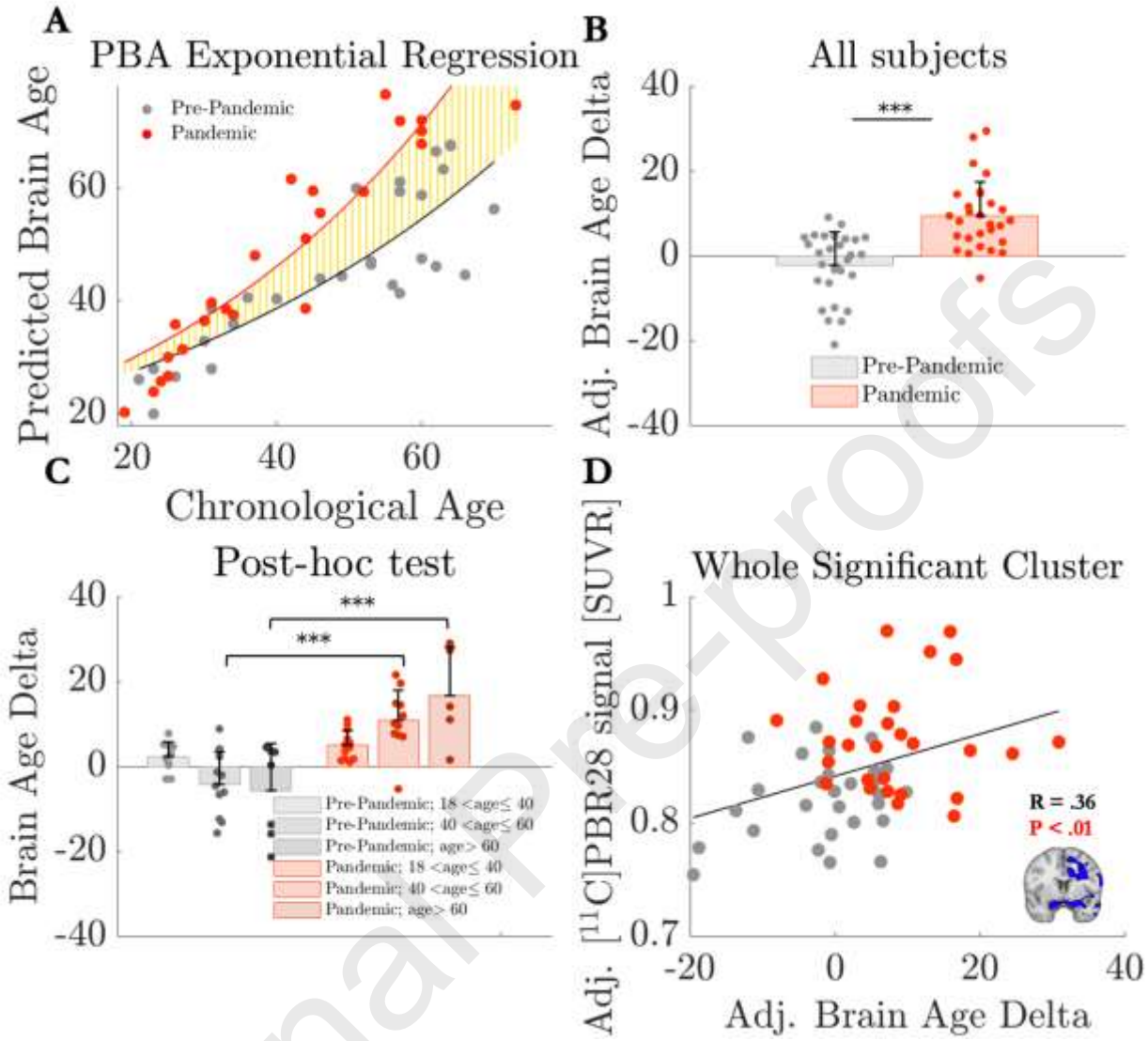

Figure 4. Predicted Brain Age and correlation with PET signal. (A) Visualization of Predicted Brain Age and Brain Age Delta plotted against chronological Age; the absolute distance between each exponential regression line is also displayed. (B) Group difference (28 Pre-Pandemic vs 28 Pandemic) in Brain Age Delta for all subjects (adjusting for age) and (C) for each age subgroup. (D) Partial correlations between [^{11}C]PBR28 signal and Brain Age Delta (adjusting for TSPO genotype and age) within the whole cluster from Figure 1A. ***P<.001

Finally, we observed an association between DBA and mean [^{11}C]PBR28 signal within the whole cluster (r=.36; P<.01; Figure 4D) and all its parcellates (R>.27, P's<.05), except pMCC (r=.16; P=.24). In other words, the higher the neuroinflammatory signal, the larger the difference between estimated and chronological age.

Discussion

The results from this study suggest the presence of elevated levels of brain/systemic inflammatory markers and accelerated aging in individuals with chronic pain evaluated after the onset of the COVID-19 pandemic, compared to pre-pandemic individuals. As in our prior study on healthy volunteers (Brusaferri et al., 2022), here we found [^{11}C]PBR28 signal to be sharply elevated (including within a set of grey and white matter brain regions partially overlapping those observed in that study), starting with the very first patients evaluated following the onset of the pandemic. Interestingly, those elevations could still be observed in subjects imaged up to two years into the pandemic.

Our results remained robust when including only individuals with a negative COVID-19 antibody tests, suggesting that exposure to the virus has unlikely confounded our findings.

Because we have previously shown that cLBP patients demonstrate elevated TSPO signal independent of a pandemic-related effect (Loggia et al., 2015), our results are compatible with a possible additive or synergistic effect of pandemic- and pain-related neuroinflammation.

Intriguingly, in the Pandemic cLBPs, the [^{11}C]PBR28 signal within the amygdala was negatively associated with pain interference levels (which were higher in the Pandemic group). This observation may reflect a pain-protective effect (Hao et al., 2022) (Discussion in Supplementary).

Similarly to our prior study, individuals examined after the pandemic onset exhibited higher serum concentration of the peripheral pro-inflammatory cytokine IL-16, which was also positively correlated with the [^{11}C]PBR28 signal within the hippocampus. Contrary to our expectations, however, patients in the Pandemic groups did not show an increase, and in fact exhibited a decrease, in MCP-1 serum levels, compared to the Pre-Pandemic cohort. Whether this inconsistency reflects population-specific differences in the effect of the pandemic on levels of this chemokine remains to be understood.

In addition to replicating TSPO PET signal and IL-16 elevations in a different (clinical) population, our study also provides novel evidence for a pandemic-related increased expression of imaging markers of BA, which was proportional to brain inflammation.

The observed association between [^{11}C]PBR28 PET signal and DBA suggests a connection between neuroinflammation and accelerated aging, although the exact causality underlying this relationship requires further investigation. Speculatively, at least two alternative mechanisms might explain this relationship. Firstly, chronic stressors may have contributed to accelerate aging and subsequently triggered inflammation. Recent literature suggests that chronic stress can contribute to the development of oxidative stress, creating conditions for accelerated aging. Senescent cells can acquire a senescence-associated secretory phenotype (SASP) and secrete pro-inflammatory components, thus contributing to a vicious circle of oxidative stress and inflammation(Yegorov et al., 2020). Alternatively, stressors may have accelerated aging by inducing inflammation. Extensive evidence indicates that stress can activate inflammatory responses (Calcia et al., 2016; Liu et al., 2017; Rohleder, 2014), and it has been recently discussed that chronic inflammatory states can promote premature aging (Kooman et al., 2017; Salminen, 2022). Nevertheless, the exact mechanisms underlying the inflammation-driven brain aging process remain unclear. While further research is needed to establish the precise causality between

stressors, inflammation, and aging, these pathways offer valuable perspectives on the complex interplay between these factors. Overall, the link between DBA and TSPO suggests that neuroinflammation could underlie the accelerated brain aging reported in conditions with known inflammatory substrate (Cruz-Almeida et al., 2019; Eickhoff et al., 2021; Hung et al., 2022; Lee et al., 2022; Yu et al., 2021).

Interestingly, the purported pandemic-related effect on BA appeared to be more pronounced in older individuals. Because of the observed link between brain aging and neuroinflammation, it is possible that older individuals may have been more susceptible to accelerating brain aging. This could be attributed to a higher likelihood of having pre-existing neuroinflammatory levels, potentially due to a longer pain duration, the emergence of comorbidities, or simply the process of ageing itself.

When interpreting the outcomes of our study, due consideration should be given to some limitations. First, the study design was unpaired and cross-sectional, which limits our ability to establish causal relationships between neuroinflammation and pandemic stressors. It is, therefore, crucial to approach the interpretation of these findings with caution. It is worth mentioning that in our prior study (Brusaferri et al., 2022) however, we observed within-subject patterns in a single individual that broadly replicated those seen in cross-sectional comparisons (in healthy volunteers). While it is possible that this observation could also be generalized for the cLBP patients, this will need to be evaluated in the future.

Second, it is important to stress that our data do not allow us to determine which specific pandemic-related factors would be responsible for the observed increase in brain and blood inflammatory markers. Speculatively, changes in sleep patterns or lifestyle, social connectedness, financial strain, fear of losing loved ones, isolation from social networks, uncertainty about the future, disruptions in work and education, health concerns, access to healthcare, public health restrictions, the impact on mental health services, and various other factors could have had a could have played a key role (Brusaferri et al., 2022).

Finally, arterial line data, necessary for the calculation of V_T or DVR in the PET analyses, was available only in a subset of participants. However, DVR and, more weakly, V_T identified similar patterns of TSPO signal elevation in the Pandemic individuals, even despite the much smaller sample size (Discussion in Supplementary). Additionally, DVR and SUVR showed a strong positive correlation, as shown in previous studies (Albrecht et al., 2018; Alshelh et al., 2020; Alshelh et al., 2022; Kreisl et al., 2013). Altogether, these results support the use of SUVR as a valid metric.

Conclusion

This work provides insights into the potential synergistic/additive effect between pandemic-disruptions and pain-related neuroinflammation in cLBP participants. Our findings suggest that the pandemic could have contributed to the neuroimmune activation and accelerated brain aging of cLBP patients. Future studies will need to evaluate whether these effects will have long-lasting consequences on their physical and mental health.

Ethics approval and consent to participate

The Mass General Brigham (MGB) institutional review board (IRB) gave ethical approval to the study. Written informed consent was obtained from all participants before enrollment, according to the ethical standards of the 1964 Helsinki declaration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Sharing Statement

Following publication of the study results, data will be made available upon reasonable request.

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Highlights

- Human study documenting elevated markers of neuroinflammation and brain aging in individuals with chronic pain during the COVID-19 pandemic, irrespective of their infection history
- Higher levels of inflammatory markers, brain (TSPO) and serum (IL-16), as well as pain interference scores, were observed in chronic low back pain patients evaluated after the pandemic onset
- Accelerated brain aging in pandemic subjects was revealed by MRI-based indicators of brain age
- Brain inflammation and brain age markers were positively correlated