

1 **Neuroinflammation in post-acute sequelae of COVID-19 (PASC) as assessed by**
2 **[¹¹C]PBR28 PET correlates with vascular disease measures**

3

4 Authors

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24 ABSTRACT

25 The COVID-19 pandemic caused by SARS-CoV-2 has triggered a consequential public
26 health crisis of post-acute sequelae of COVID-19 (PASC), sometimes referred to as
27 long COVID. The mechanisms of the heterogeneous persistent symptoms and signs
28 that comprise PASC are under investigation, and several studies have pointed to the
29 central nervous and vascular systems as being potential sites of dysfunction. In the
30 current study, we recruited individuals with PASC with diverse symptoms, and examined
31 the relationship between neuroinflammation and circulating markers of vascular
32 dysfunction. We used [¹¹C]PBR28 PET neuroimaging, a marker of neuroinflammation,
33 to compare 12 PASC individuals versus 43 normative healthy controls. We found
34 significantly increased neuroinflammation in PASC versus controls across a wide swath
35 of brain regions including midcingulate and anterior cingulate cortex, corpus callosum,
36 thalamus, basal ganglia, and at the boundaries of ventricles. We also collected and
37 analyzed peripheral blood plasma from the PASC individuals and found significant
38 positive correlations between neuroinflammation and several circulating analytes related
39 to vascular dysfunction. These results suggest that an interaction between
40 neuroinflammation and vascular health may contribute to common symptoms of PASC.

41

42

43 KEYWORDS:

44 COVID-19, Long COVID pathogenesis, neuroimaging, positron emission tomography,
45 fibrinogen, cardiovascular, glia, microglia, brain inflammation

46

47 1. INTRODUCTION

48

49 The coronavirus disease 2019 (COVID-19) global pandemic caused by severe acute
50 respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a consequential public
51 health crisis of long COVID or post-acute sequelae of COVID-19 (PASC), defined by
52 symptoms that begin following acute SARS-CoV-2 infection or persist from that initial
53 acute illness (Centers for Disease Control and Prevention, 2022; World Health
54 Organization, 2021).

55

56 The US Census Bureau's Household Pulse Survey found that, as of June 2023, about
57 11% of adults who had ever had COVID-19 reported that they were currently
58 experiencing symptoms of PASC or long COVID, with nearly 16% of adults stating that
59 they had PASC or long COVID symptoms at some point in time (National Center for
60 Health Statistics, 2023). PASC is an umbrella term applied to a heterogeneous group of
61 patients. Symptoms can be diverse and commonly include nonspecific neurological and
62 neuropsychiatric symptoms including difficulty concentrating or subjective 'brain fog,'
63 unusually profound fatigue, headaches, depression, anxiety, body pain, and disrupted
64 sleep (Davis et al., 2021; Zeng et al., 2023). These symptoms can significantly impact
65 quality of life (Líška et al., 2022), and can be initiated even by mild acute COVID-19
66 illness (Boribong et al., 2022; Ma et al., 2023).

67

68 PASC mechanisms remain under study, however SARS-CoV-2 is now understood to
69 infect a wide range of tissue types and is capable of driving inflammation, coagulation,

70 and vascular problems (Klein et al., 2022; Pretorius et al., 2022; Proal & VanElzakker,
71 2021). Early evidence demonstrates that vascular related problems seen in acute
72 COVID-19 illness (Varga et al., 2020) may persist in some individuals (Xie et al., 2022),
73 and thus may contribute to PASC symptoms. The current study investigated whether
74 PASC patients with diverse symptom presentation showed increases in a measure of
75 neuroinflammation relative to healthy controls with no known history of COVID-19, and
76 whether PASC neuroinflammation was related to measures of vascular health.

77

78 As a densely vascularized organ that uses 15-20% of the body's total circulating blood
79 supply (Berkman et al., 2021), the brain is uniquely vulnerable to disruptions to vascular
80 health. COVID-19 appears to confer a potent vulnerability to neurovascular problems.
81 For example, in patients that survived acute COVID-19, in the following year the risk for
82 hemorrhagic stroke and for cerebral venous thrombosis more than doubled (Xie et al.,
83 2022; Xu et al., 2022). As evidence of general consequences for the brain, a
84 longitudinal study comparing pre-pandemic structural neuroimaging data to post-COVID
85 structural neuroimages from the same individual showed small but significant reduction
86 of grey matter thickness and whole-brain volume as well as increased markers of tissue
87 damage, relative to longitudinal scans from individuals not infected with SARS-CoV-2
88 (Douaud et al., 2022). In PASC, a neuroimaging study using arterial spin labeling fMRI
89 found evidence of decreased neurovascular perfusion in patients reporting persistent
90 cognitive problems (Ajčević et al., 2023), potentially relating central nervous system and
91 vascular dysfunctions. Despite these observations, no PASC study has yet directly
92 linked neuroinflammation and vascular dysfunction.

93

94 In addition to their role as the innate immune cells of the central nervous system, glial
95 cells are critical to normal central nervous system functioning, including playing a
96 central role in neurotransmission, neurovascular function, and blood-brain barrier
97 integrity. Thus, the activity of glial cells may be an important connection between brain
98 and vascular abnormalities in PASC (Cabezas et al., 2014; Mestre et al., 2017). Like
99 other innate immune cells, glia can enter a spectrum of 'activated' states when they
100 detect paracrine inflammatory mediators (e.g. proinflammatory cytokines), pathogen-
101 associated molecular patterns (PAMPs), or damage-associated molecular patterns
102 (DAMPs). Short-term glial activation is central to their role as cells of innate, or
103 nonspecific, immunity that clear multiple forms of pathogens or cell debris. The glial role
104 in the innate immune system also involves general 'sickness' symptoms that shift an
105 organism's behavior to preserve energy at a time of high energy demand (Dantzer &
106 Kelley, 2007; VanElzakker et al., 2019). However, long-term glial activation can disrupt
107 the delicate symbiosis of glia, blood vessels, neurons, and cerebrospinal fluid in normal
108 central nervous system function, and ongoing glial activation occurs in multiple
109 neurological and neuropsychiatric conditions (VanElzakker et al., 2019) and is
110 associated with symptoms that are commonly reported in PASC such as disrupted
111 cognition (Barrientos et al., 2006; Lindgren et al., 2020), increased pain (Loggia et al.,
112 2015), and other nonspecific symptoms of sickness.

113

114 Activation of glia is a key component of neuroinflammation, which can include other
115 mechanisms such as activated peripheral immune cells penetrating into brain,

116 inflammatory activation of neurovascular endothelial cells, or density of motile microglia.
117 Rodent models have shown upregulation of the translocator protein (TSPO) during glial
118 activation states (Pannell et al., 2020), and PET neuroimaging with TSPO-specific
119 radioligands is a widely used method in the study of human neuroinflammation (Albrecht
120 et al., 2016; VanElzakker et al., 2019). [¹¹C]PBR28 is a second-generation TSPO-
121 binding radioligand that has good specificity for TSPO and a low background signal-to-
122 noise ratio (Albrecht et al., 2016). Thus, the measurement of central nervous system
123 TSPO concentration in concert with analysis of circulating measures related to vascular
124 damage may provide insight into PASC mechanisms.

125

126 2. MATERIALS AND METHODS

127

128 2.1 STUDY DESIGN

129

130 In this case-control, cross-sectional study, we compared 12 PASC versus an existing
131 dataset of 43 control individuals with no known prior COVID-19 exposure. We used PET
132 neuroimaging to study neuroinflammation (here operationalized as increased TSPO
133 radioligand binding) in PASC by comparing [¹¹C]PBR28 standardized uptake value
134 ratios (SUVR) in PASC versus controls. All participants answered questionnaires related
135 to pain and depression; PASC participants answered additional questionnaires related
136 to their PASC symptoms and history.

137

138 We also analyzed peripheral blood collected from PASC participants immediately before
139 their PET scan to study the relationship between central nervous system glial activation
140 in PASC and measures related to vascular health, inflammation, and angiogenesis. For
141 the blood measurements, platelet-poor plasma (PPP) was collected from 11 PASC
142 cases immediately before [¹¹C]PBR28 injection.

143

144 2.2 PARTICIPANTS

145

146 As PASC is an umbrella term with a heterogeneous presentation, cohort phenotyping is
147 key to study design. To prioritize recruitment of individuals with diverse nonspecific
148 symptoms, we used a modified myalgic encephalomyelitis/chronic fatigue syndrome
149 (ME/CFS) International Consensus Criteria (ICC, Carruthers et al., 2011) as PASC
150 group inclusion criteria, requiring at least one symptom from each of the 4 ICC symptom
151 clusters: post-exertion exhaustion, neurological impairments, immune/gastro-
152 intestinal/genito-urinary, and energy/autonomic. All PASC participants had onsetting
153 COVID-19 illness that occurred before August 2021 and at least 10 months prior to the
154 scan date (mean=20.50 months, SD=7.75), reflecting pre-Omicron strains and
155 qualifying them for both CDC and WHO definitions of PASC (4 weeks and 3 months of
156 symptoms, respectively). Two of the 12 PASC participants were hospitalized during their
157 acute COVID-19 (without being put on a ventilator), and 1 of 12 reported being
158 vaccinated prior to the acute COVID-19 infection that initiated their PASC.

159

160 A total of 12 PASC study participants were compared to an existing normative dataset of
161 43 healthy controls with no known history of COVID-19, that were scanned with the
162 same protocol in the same scanner, between 2013-2021. Control scans were selected
163 from multiple completed or ongoing studies (e.g., Albrecht et al., 2019; Alshelh et al.,
164 2020; Loggia et al., 2015); 34 of the 43 controls were scanned pre-pandemic and all
165 post-pandemic-onset controls had a negative plasma antibody test but were scanned in
166 Massachusetts' state-of-emergency period of the pandemic (Brusaferrri et al., 2022).
167 Participants of any sex were recruited to participate in a ~90 minute scanning session at
168 the HST/MGH (Harvard-Massachusetts Institute of Technology Program in Health
169 Sciences and Technology/Massachusetts General Hospital) A.A. Martinos Center for
170 Biomedical Imaging, in Boston MA.

171
172 Exclusionary criteria included PET or MRI contraindications (e.g., metallic implants,
173 surpassed FDA research-related PET scan limit in past 12 months, major kidney or liver
174 problems, pregnancy), history of other neurological disorders (epilepsy, history of stroke,
175 tumor, brain tissue-damaging pathologies), history of major head trauma (loss of
176 consciousness for more than 5 minutes), type 1 diabetes, major cardiac event in the
177 past decade, current acute illness or infection (e.g., COVID-19, cold, flu), or history of
178 psychotic disorder or other major psychiatric illness except posttraumatic stress disorder
179 (PTSD), depression, and anxiety which were exclusionary only if the conditions were so
180 severe as to require hospitalization in the past 5 years. Before the scan day, patients
181 were genotyped via saliva or blood for the Ala147Thr polymorphism in the *TSPO* gene
182 (rs6971 polymorphism), which is known to affect binding affinity for several TSPO

183 radioligands, including [¹¹C]PBR28 (Owen et al., 2012, 2015). Individuals with the
184 Ala/Ala or Ala/Thr genotypes (predicted high- and mixed-affinity binders, respectively)
185 were included, and the genotype was modeled as a covariate in the statistical design.
186 Individuals with the Thr/Thr genotype (predicted low-affinity binders) were excluded at
187 the time of the screening and therefore not represented in our dataset. Medication
188 exclusions included use of immunosuppressive medications such as prednisone or TNF
189 blocking medications within the 2 weeks preceding the visit, routine use of
190 benzodiazepines or any use in the past 2 weeks except clonazepam (Klonopin),
191 lorazepam (Ativan), and alprazolam (Xanax), which have documented or predicted low
192 affinity for TSPO (e.g., Kalk et al., 2013).

193

194 Before the scan, all participants underwent a history and physical examination by an
195 experienced nurse practitioner to confirm PET-MRI safety. Participants answered
196 several questionnaires and their height and weight were recorded. Immediately before
197 neuroimaging, IV blood was drawn. Blood-based pregnancy testing (hCG) was
198 performed on all individuals capable of becoming pregnant.

199

200 2.3 PET IMAGING PARAMETERS

201

202 Our dual PET-MRI scanner consists of a 3-Tesla (3T) Siemens TIM Trio MRI (60 cm
203 bore diameter) with 8-channel head coil and a photodiode-based high-resolution
204 BrainPET head camera insert. The BrainPET prototype is a dedicated brain scanner
205 that has 32 detector cassettes, each consisting of 6 detector blocks, each made up of a

206 1212 array of lutetium oxyorthosilicate crystals (2.52 mm³) read out by magnetic field-
207 insensitive avalanche photodiodes. The transaxial and axial fields of view are 32 cm
208 and 19.125 cm, respectively. The 3T MR system is equipped with the standard “TIM”
209 (total imaging matrix) 32 RF channel receivers, accommodating up to 32 element array
210 coils. [¹¹C]PBR28 radioligand was produced by an in-house Siemens Eclipse HP self-
211 shielded 11 MeV cyclotron with single-beam extraction and a four position target-
212 changer. During the PET scan, [¹¹C]PBR28 (up to 15 mCi, which is equivalent to ~3.7
213 mSv) was injected intravenously with a slow bolus over a ~30 second period (Debruyne
214 et al., 2003). The catheter was then flushed post-injection with 0.9% sterile saline
215 solution. Dynamic data was collected by the head PET camera over 90 minutes list
216 mode and framed post-collection; concurrent high-resolution T1-weighted
217 (MEMPRAGE) structural MRI images were collected for spatial registration of the PET
218 data, as well as generation of attenuation correction maps (Izquierdo-Garcia et al.,
219 2014) and scatter correction.

220

221 2.4 BLOOD COLLECTION

222

223 Immediately before [¹¹C]PBR28 injection and scanning, venous blood was collected
224 from 11 PASC participants into a citrated vacutainer tube (BD 369714 light blue cap)
225 (one participant was scanned when a study team member had COVID-19 and therefore
226 blood was not collected). The citrate tube was gently upended 3x then left to sit at room
227 temperature for 30 minutes, before centrifugation at 15min x 3000 RCF x 20°C. Platelet-
228 poor plasma (PPP) supernatant was pipetted into sterile 1.5mL microtubes (Sarstedt

229 Biosphere 72.703.217) and stored at -80°C. For analysis, these samples from the 11
230 PASC participants were thawed on wet ice and 275µL aliquots were pipetted into sterile
231 SureSeal™ 0.65mL microfuge tubes (VWR Ward's Science 470228-444), marked with
232 de-identified alphanumeric sequences, and sent overnight on dry ice to Eve
233 Technologies (Calgary Canada) for analysis.

234

235 Three multiplex panels were conducted based upon previous PASC literature: vascular
236 health, cytokine, and angiogenesis (e.g., Proal & VanElzakker, 2021); Klein et al., 2022;
237 Patel et al., 2022). Analytes per multiplex were as follows: Vascular health (α 2-
238 macroglobulin, orosomucoid, CRP [C-reactive protein], fetuin A, fibrinogen, haptoglobin,
239 sL-selectin, PF4 [platelet factor 4], pentraxin-2) (Millipore HCVD3MAG-67K Luminex
240 magnetic bead panel); Cytokines (GM-CSF, IFN γ , IL-1 β , IL-1RA, IL-2, IL-4, IL-5, IL-6,
241 IL-8, IL-10, IL-12(p40), IL-12(p70), IL-13, MCP-1, TNF α) (Millipore HCYTA-60K Luminex
242 magnetic bead panel); Angiogenesis (angiopoietin-2, BMP-9, EGF, endoglin, endothelin-
243 1, FGF-1, FGF-2, follistatin, G-CSF, HB-EGF, HGF, IL-8, leptin, PLGF, VEGF-A, VEGF-
244 C, VEGF-D) (Millipore HAGP1MAG-12K Luminex magnetic bead panel).

245 Concentrations of these analytes were entered into a correlation matrix to test their
246 relationship to extracted SUVR values and symptom measures in the PASC
247 participants. Items from the vascular health panel are described in Box 1.

248

249 2.5 BEHAVIORAL MEASURES

250

251 All 12 PASC and 43 eligible control participants were administered items from the Brief
252 Pain Inventory (BPI) (Cleeland & Ryan, 1994) and the Beck Depression Inventory (BDI)
253 (Beck et al., 1996).

254

255 PASC participants were screened to fulfill a modified myalgic encephalomyelitis/chronic
256 fatigue syndrome (ME/CFS) International Consensus Criteria (ICC) criteria, and then on
257 the day of the scan were asked to rate each ICC symptom's severity from 0-10. PASC
258 individuals were also given a revised medical history questionnaire that asked about the
259 history of several neurological or neuropsychiatric symptoms by naming a symptom
260 then giving the option to either leave blank or select one of three options: 1) This was a
261 problem for me before COVID-19, 2) This is a problem for me since I had COVID-19, or
262 3) This is a serious problem for me since I had COVID-19.

263

264 2.6 PET DATA PROCESSING

265

266 For the PASC versus control PET comparison, PET data processing was performed on
267 a custom Linux-based pipeline used in several previous studies (e.g., Albrecht et al.,
268 2019; Alshelh et al., 2021; Brusaferrri et al., 2022; Loggia et al., 2015), including
269 standard preprocessing and PET-MRI spatial registration to MNI (Montreal Neurological
270 Institute) space.

271

272 Following data acquisition, several quality control steps were performed including by-
273 participant visual inspection of detector blocks (Tayal et al., 2021), spatial registration,

274 skull stripping, artifacts, and attenuation image map alignment. After normalizing
275 radioactivity by injected dose by body weight, PET data were scatter- and attenuation-
276 corrected using a custom MR-based method developed at the Martinos Center for
277 Biomedical Imaging (Izquierdo-Garcia et al., 2014). For all subjects, 30-minute static
278 standardized uptake value (SUV) PET images were reconstructed from data acquired
279 ~60-90 min after the injection of the tracer. SUV maps were spatially normalized by
280 nonlinear transformation into common MNI space and smoothed with an 8mm FWHM
281 (full-width half-maximum) Gaussian kernel. Standard uptake value ratio (SUVR) images
282 were then created by intensity-normalizing individual MNI-space SUV maps to
283 cerebellum uptake, anatomically-defined by AAL (automatic anatomical labeling) atlas
284 (Tzourio-Mazoyer et al., 2002). There were no group differences in cerebellum SUV in
285 the 12 vs. 43 primary or the 11 vs. 11 validation analyses ($t(53)=0.82, p=.42$;
286 $t(10)=0.85, p=.41$ respectively).

287

288 2.7 STATISTICAL ANALYSIS

289

290 We conducted a primary unpaired (between groups) comparison including all available
291 PET data (12 PASC vs. 43 control). Cerebellum-normalized, MNI-registered SUVR
292 maps for each participant were entered into a general linear model, using the FEAT
293 software tool (version 6.00, Woolrich et al., 2004) within FSL (FMRIB Software Library,
294 Wellcome Centre). Nonparametric permutation inference of [^{11}C]PBR28 SUVR images
295 was performed using FSL Randomise, with 5000 permutations (Winkler et al., 2014)
296 and statistically controlling for sex and TSPO polymorphism. Cluster-correction was

297 used to account for multiple comparisons, using a cluster-forming threshold of $Z=2.3$
298 and cluster size of $p=.05$. Demographic and PET-relevant data comparisons for the
299 primary analysis are shown in Table 1. Reflecting the sex distribution of PASC (Bai et
300 al., 2022), there was a relatively high proportion of females (10) in the PASC group.
301 While we did statistically control for sex in the primary analysis, we performed a second
302 validation analysis using a paired approach in which each PASC participant was
303 matched to a control participant for genotype, sex, and age ± 5 years (Supplemental
304 data).

305

306 Table 1

307

	PASC	Control	Statistics
Age mean (SD)	47.25 yr (14.19)	50.86 yr (14.19)	$t(53)=0.84, p=.20$
Sex	F=10, M=2	F=17, M=26	$\chi^2(1.55)=7.20, p=.007$
Genotype count	GG=5, GA=7	GG=27, GA=16	$\chi^2(1.55)=1.72, p=.19$
BMI mean (SD)	27.25 (5.01)	26.19 (4.96)	$t(53)=0.66, p=.51$
Injected Dose	13.64 mCi (1.90)	13.26 mCi (1.58)	$t(53)= 0.70, p=.49$

308

309 Table 1 legend:

310 In the primary PET comparison (i.e. $n=12$ PASC vs. $n=43$ control), an unpaired t-test or
311 Chi-square revealed no significant difference between PASC and control groups in age,
312 genotype frequency, BMI, or injected dose. Reflecting the sex distribution of PASC (Bai
313 et al., 2022), there was a higher proportion of female participants in the PASC group
314 relative to the larger historical control group. In this primary analysis, we statistically
315 controlled for genotype and sex.

316

317

318 To test the relationship between SUVR and blood analytes or questionnaire data, simple
319 Pearson's correlations were calculated. For these correlation analyses, we used the
320 significant cluster that arose from the primary 12 PASC vs 43 control comparison (see
321 Results) and extracted each participant's average SUVR value from that cluster. For
322 behavioral/demographic data, group statistical comparisons were performed using
323 unpaired or paired Student's t-tests, Chi-square tests, or Pearson's correlation as
324 appropriate, while BDI subscales were analyzed with a mixed-model ANOVA. Two-tailed
325 p-values are reported in all cases. Cohen's D effect size for the primary analysis was
326 calculated using each participant's mean SUVR from the whole-brain significant cluster.

327

328

329 3. RESULTS

330

331 3.1 IMAGING RESULTS: VOXEL-WISE GROUP DIFFERENCES

332

333 The voxelwise whole-brain comparison of PASC cases versus healthy controls revealed
334 a significant increase in [¹¹C]PBR28 PET signal at the Z=2.3 threshold (large Cohen's D
335 effect size of 1.28). This increased PET signal spanned a wide swath of brain regions
336 including midcingulate cortex, corpus callosum, thalamus, basal ganglia/striatum,
337 subfornical organ, anterior cingulate cortex, medial frontal gyrus, and precentral gyrus
338 (see Figure 1 and Table 2), and is suggestive of glial activation or neuroinflammation.

339 There were no voxels with significantly greater SUVR values in the controls > PASC
340 contrast.

341

342 In order to visualize data distribution, individual participants' data were extracted from
343 the primary voxelwise analysis' significant cluster, and from a selection of atlas-defined
344 anatomical regions that showed significant signal. The distribution pattern of extracted
345 SUVR values showed that this effect was not driven by outliers or by hospitalized cases
346 (Figure 1B).

347 We conducted a paired validation analysis with individually matched PASC-control pairs
348 and found a very similar PET signal pattern (Supplemental Figure 1). In this analysis the
349 average injected radioligand dose also did not differ between PASC (mean 13.85 mCi,
350 SD 1.83) and controls (mean 12.63 mCi, SD 1.47), $t(10)=1.69$, $p=.12$.

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362 Figure 1

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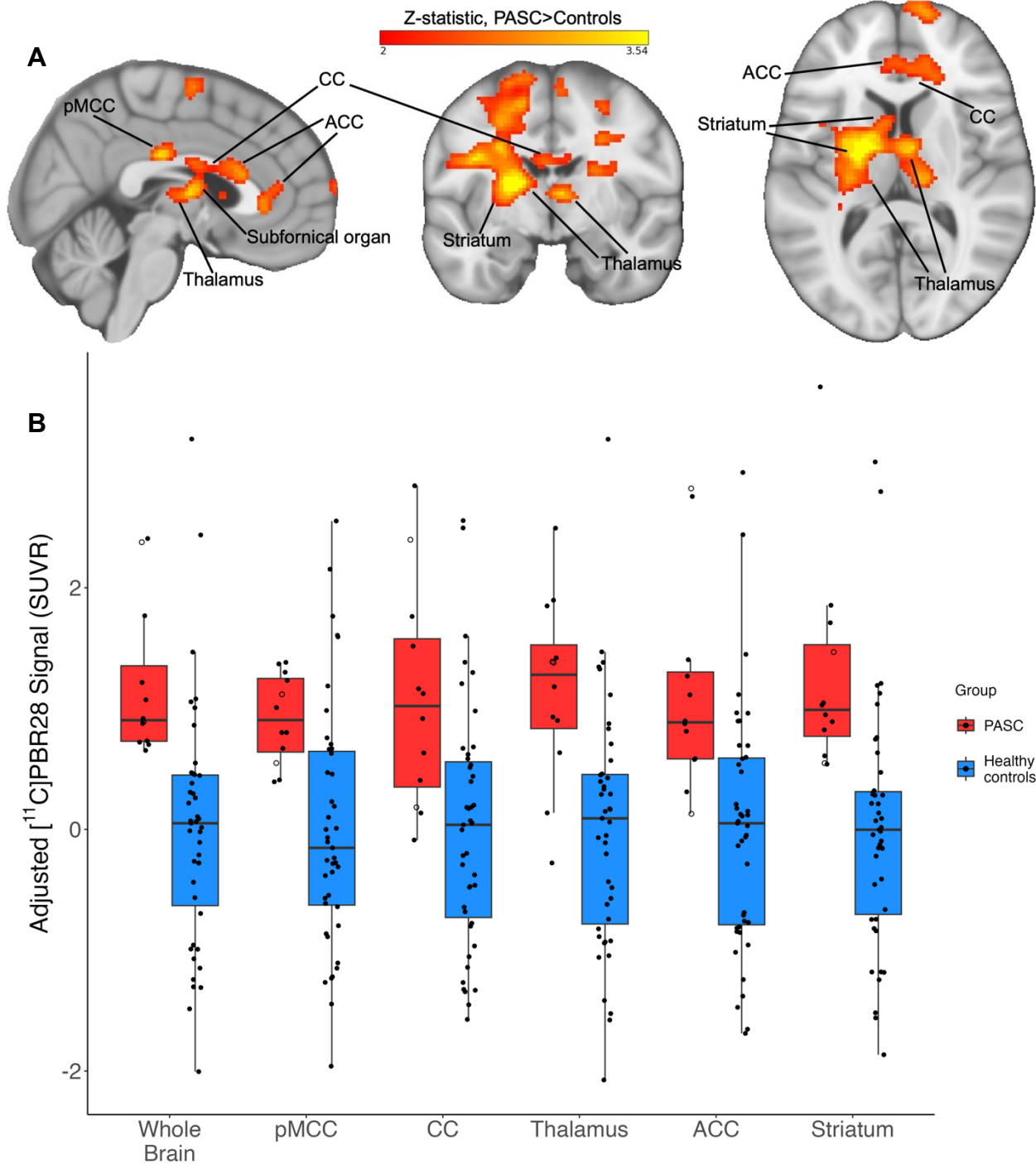
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385 Figure 1 legend:

386 Figure 1A: Example slices through sagittal ($x=3$), coronal ($y=-7$), and axial ($z=10$)

387 sections of the 12 PASC > 43 control group-level unpaired (between-groups)

388 comparison, showing the pattern of increased [^{11}C]PBR28 signal (shown in neurological

389 convention). Color bar: threshold min. Z score of 2 and max. 3.54.

390 Figure 1B: PET signal data extracted from individual study participants, depicted from

391 the primary whole-brain analysis and across five example bilateral brain regions. Y-axis

392 data points represent the mean SUVR values of significant voxels within each

393 significant cluster region, with each structure's data normalized to the control average.

394 PASC participants hospitalized during their acute COVID-19 illness are indicated with

395 an open circle. Brain regions are anatomically defined by the Harvard-Oxford Atlas

396 (thalamus, ACC, striatum) or CC by the Jülich Atlas at >70% probability threshold. In

397 the case of the pMCC, we used the Harvard-Oxford posterior cingulate anatomical

398 mask, but the activation cluster was only within pMCC. In the PASC group, the two

399 hospitalized cases are depicted by open circles.

400 pMCC = posterior midcingulate cortex; CC = corpus callosum; ACC = anterior cingulate

401 cortex

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408 Table 2

409

Region with local peak	Z value	MNI coordinates (x,y,z)
Posterior midcingulate	3.54	4, -22, 28
Corpus callosum	2.94	3, 20, 18
Thalamus (L)	3.54	-20, -2, 8
Basal ganglia (L)	3.54	-14, -6, 15
Superior frontal gyrus (R)	3.54	14, 38, 40
Subfornical organ (estimated)	3.09	4, -7, 8
Anterior midcingulate	2.95	4, 19, 19
Precentral gyrus (R)	3.54	36, 1, 36
Postcentral gyrus (R)	3.54	40, -18, 40
Retrolenticular internal capsule (L)	3.54	-28, -38, 18
Superior corona radiata (L)	3.54	-26, -6, 32

410

411 Table 2 legend:

412 Peak voxel coordinates from brain regions significantly increased in PASC versus
413 controls in whole-brain [¹¹C]PBR28 voxelwise comparison.

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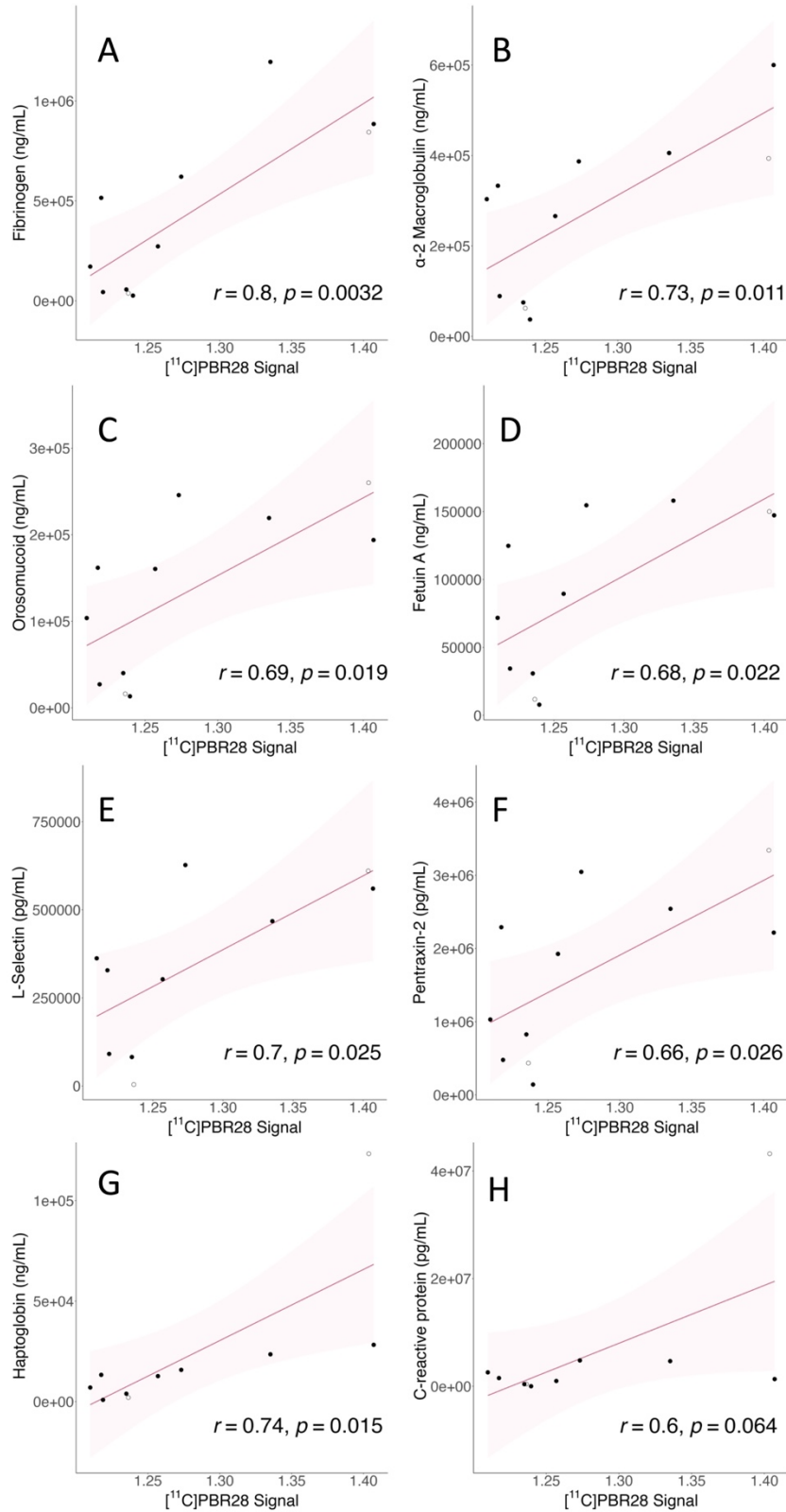
419 3.2 BLOOD ANALYTE MEASURES and CORRELATIONS

420

421 We found positive Pearson's r correlations between PET signal and the majority of
422 analytes from the vascular disease multiplex panel (see Figure 2, Table 3). Specifically,
423 we found positive moderate to strong correlations between the PET signal extracted for
424 each individual from the cluster derived from the voxelwise group comparison, and the
425 concentrations of seven plasma vascular health-associated factors: fibrinogen ($r(9)=.80$,
426 $p=.0032$), α 2-macroglobulin ($r(9)=.73$, $p=.011$), orosomucoid (alpha-1-acid glycoprotein
427 or AGP) ($r(9)=.69$, $p=.019$), fetuin A ($r(9)=.68$, $p=.022$), sL-selectin (soluble leukocyte
428 selectin, or sCD62L) ($r(8)=.70$, $p=.025$), pentraxin-2 (serum amyloid P component, or
429 SAP) ($r(9)=.66$, $p=.026$), and haptoglobin ($r(8)=.74$, $p=.015$). The haptoglobin scatterplot
430 appeared to include a potential outlier. However, removing this participant from the
431 analyses did not substantially affect significance, ($r(7)=.88$, $p=.0018$). The correlation
432 with the C-reactive protein (CRP) was trending but not statistically significant
433 ($r(8)=0.61$, $p=.064$). In this case, the relevant scatterplot appeared to include one outlier,
434 as well as another participant's levels that were not detected by the assay. The CRP
435 correlation remained non-significant after removing the potential outlier from the CRP
436 analysis ($p>.4$). The high-end outlier in both haptoglobin and CRP analyses was the
437 same participant, who was hospitalized during their acute COVID-19 illness. For both
438 the sL-selectin and haptoglobin assays the same participant's levels were not detected
439 by the respective assay, and platelet-factor 4 (PF4) was not detected by the assay in
440 the majority of samples.

441

442 Figure 2



443

444 Figure 2 legend:

445 Correlations between vascular health analytes and PET signal. Y-axis shows analyte
446 concentration; units vary. X-axis shows mean PET SUVR values extracted from the
447 whole-brain significant cluster of each individual. Shadow represents the 95%
448 confidence interval, all p-values are reported two-tailed. See Box 1 for analyte
449 descriptions and Table 2 for Pearson's r values.

450 a. Fibrinogen; b. α -2 macroglobulin; c. Orosomuroid; d. Fetuin A; e. sL-selectin; f.
451 Pentraxin-2; g. Haptoglobin; h. C-reactive protein

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467 Table 3

468

Peripheral blood vascular related analyte	Whole brain PET signal correlation
Fibrinogen	r(9)=.80, p=.0032
α 2-macroglobulin	r(9)=.73, p=.011
Orosomuroid (alpha-1-acid glycoprotein or AGP)	r(9)=.69, p=.019
Fetuin A	r(9)=.68, p=.022
sL-selectin (soluble leukocyte selectin)	r(8)=.70, p=.025
Pentraxin-2	r(9)=.66, p=.026
Haptoglobin	r(8)=.74, p=.015

469

470 Table 3 legend:

471 Vascular disease-related blood analytes that significantly correlated with whole-brain

472 [11 C]PBR28 uptake values extracted from the significant cluster in the PASC group.

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483 Cytokine concentrations from the 15-plex panel frequently correlated with one another
484 but did not correlate with PET signal (Supplemental Figure 2), which was our a-priori
485 hypothesis (VanElzakker et al., 2019). Analytes from the angiogenesis 17-plex panel
486 analytes also did not correlate with PET signal. We did not have strong a-priori
487 hypotheses regarding correlations between blood analytes and self-reported symptoms.

488

489 3.3 SYMPTOM SEVERITY AND HISTORY

490

491 Response scores to the BPI severity item "Pain at its worst in the past 24 hrs" were
492 higher in PASC (M=7.08, SD=3.72) versus controls (M=0.44, SD=0.81), $t(52)=10.91$,
493 $p<.001$, two-tailed, unequal variance. Mean scores from BPI-Interference subscale
494 items were higher in PASC (M=21.75, SD=15.42) versus controls (M=0.90, SD=0.31),
495 $t(51)=9.21$, $p<.001$, two-tailed, unequal variance.

496

497 Mean total BDI scores were higher in cases (M=11.58, SD=1.74) versus controls
498 (M=1.14, SD=5.58), $t(52)=9.96$, $p<.001$, two-tailed, unequal variance. Mean depression
499 severity according to the BDI was on average categorized as mild (10-18) in PASC and
500 none-to-minimal (0-9) in controls. Two PASC cases met the threshold of moderate
501 depression (i.e., 19-29), with scores of 19 and 25. Of the 12 PASC cases, six reported
502 that depression was not a problem, five reported "This is a problem for me since I had
503 COVID-19" and one reported "This is a serious problem for me since I had COVID-19"
504 about depression.

505

506 BDI responses can be divided into affective (mood-centered) versus somatic (body-
507 centered) subscales. To better understand which questionnaire items were driving the
508 higher BDI scores in PASC vs. controls, we conducted a 2x2 mixed model ANOVA with
509 diagnosis (PASC, control) as the between-groups factor and BDI subscale (affective,
510 somatic) as the within-subjects factor. This ANOVA revealed a significant interaction
511 between diagnosis and BDI subscale $F(1,52)=51.734$, $p<.001$, (partial $\eta^2=.499$, large
512 effect size) driven by higher average item somatic subscale scores within the PASC
513 group (Supplemental Table 1). There were also main effects of diagnosis
514 $F(1,52)=155.184$, $p<.001$ (consistent with the t-test) as well as a main effect of BDI
515 subscale $F(1,52)=54.236$, $p<.001$ in which average item score was higher in somatic
516 versus affective subscales independent of diagnosis.

517

518 On the day of the scan, PASC participants self-reported the severity of each of the 21
519 ICC symptoms on a 0-10 scale (see Supplemental Figure 3); all reported 5 out of 10
520 severity or greater on at least two of the eight ICC Neurological symptoms cluster items:
521 headache, unrefreshing sleep, significant pain, short-term memory loss, difficulty
522 processing information, sensory sensitivity, disturbed sleep pattern, and motor
523 symptoms (e.g., twitching, poor coordination). Supplemental Figure 3 depicts the six
524 symptoms that overlapped between both the ICC scale (rating day-of-scan severity 0-
525 10) and the medical history questionnaire (marking onset relative to acute COVID-19).

526

527 4. DISCUSSION

528

529 We conducted PET neuroimaging and blood analyses in individuals with ongoing
530 diverse symptoms that began with acute COVID-19 infection. The majority of PASC
531 participants' acute COVID-19 illness did not require hospitalization. We found a
532 significant increase in [¹¹C]PBR28 signal, an indicator of neuroinflammation, across a
533 wide area of brain regions such as the midcingulate cortex, corpus callosum, thalamus,
534 basal ganglia/striatum, subfornical organ, anterior cingulate cortex, medial frontal gyrus,
535 and precentral gyrus.

536

537 Of note, one study reported increased TSPO signal in moderately depressed PASC
538 participants, 45% (9 of 20) of which had pre-COVID depression (Braga et al., 2023). In
539 contrast, in the current study's PASC cohort, the average depression score was mild,
540 and no PASC participant reported a pre-COVID history of depression. Instead, they
541 either denied depression being a problem for them (50%, 6 of 12) or reported that it was
542 a new (~42%, 5 of 12) or serious new (~8%, 1 of 12) problem since COVID-19, and only
543 2 of 12 PASC participants were in the moderate depression severity range. Future
544 studies should also include COVID-19-recovered individuals as a comparison group.

545

546 Importantly, in our study, we found that intensity of whole-brain PET signal showed
547 significant positive correlations with blood measures related to vascular health (see
548 Figure 2 and Table 3). This is indirect evidence that differences in PET signal across
549 brain structures (Figure 1B) may partially reflect variance in vascular anatomy and
550 perivascular immune penetration. To our knowledge, ours is the first study to provide

551 direct evidence that processes related to neuroinflammation and vascular dysfunction
552 are directly related in PASC.

553

554 As examples, fibrinogen and sL-selectin were two analytes from the vascular health
555 multiplex panel that were significantly correlated with neuroinflammation-related PET
556 signal. Elevated fibrinogen is associated with worse outcome in acute COVID-19 (Sui et
557 al., 2021) and is not only associated with coagulation abnormalities in acute COVID-19
558 but also PASC (Pretorius et al., 2022; Sui et al., 2021). Related to neuroinflammation,
559 fibrinogen persistently activates glia at the glymphatic (Mestre et al., 2017) perivascular
560 spaces that surround neurovasculature (Davalos et al., 2012). Activated perivascular
561 glia attract both glia from within the brain parenchyma and attract circulating immune
562 factors to cross from neurovascular blood into brain. L-selectin (CD62L) is an adhesion
563 molecule involved in attaching leukocytes (white blood cells) to vascular endothelium at
564 sites of inflammation. Attraction of activated immune cells, inflammation of vascular
565 endothelium, mobilization of glia, and activation of glia would each increase TSPO
566 concentrations and therefore PET signal (as well as the symptoms associated with glial
567 activation). The fact that these and other measures related to vascular dysfunction
568 correlated with neuroinflammation provides evidence that the spatial pattern of PET
569 signal in PASC vs. controls may reflect a vascular-related anatomical pattern that is
570 likely to differ among patients. See Box 1 for further explanation of vascular analytes.

571

572

573

574 Box 1

Peripheral blood vascular health analytes

Fibrinogen is a protein commonly associated with coagulation (Pretorius et al., 2022), but is also a classic acute phase reactant in that inflammatory insults drive significantly increased liver expression and concentration in general blood circulation (Luyendyk et al., 2019). Furthermore, fibrinogen specifically induces a sustained glial response at the perivascular spaces surrounding neurovasculature, a process worsened by blood–brain barrier disruption during neuroinflammation (Davalos et al., 2012).

α 2-macroglobulin is an extracellular macromolecule mainly known for its role as a broad-spectrum protease inhibitor, but also has a role facilitating immune cell migration to vasculature. For example, α 2-macroglobulin aids neutrophils through stimulation of their capacity to migrate and bind to vascular endothelial cells, and to phagocytose and kill pathogens (Vandooren & Itoh, 2021).

Orosomucoid (also called alpha-1-acid glycoprotein or AGP) is known as an acute phase protein synthesized by liver, but can also be synthesized by several other tissues including brain under different physiological conditions as well as pathological conditions such as stroke and metabolic syndrome (Li et al., 2019). In a well-characterized in vitro blood-brain barrier model, human orosomucoid showed a dose-dependent effect on the permeability of microvessel endothelial cells (Zhang & Mark, 2012).

Fetuin A was previously called pp63 or countertrypsin and is a multifunctional protein made by the liver and some secretory tissues. Its role in cardiovascular health is multifactorial including protective effects such as mitigation of calcification but it is also associated with worse prognosis in cardiovascular disease and diabetes. Fetuin A may act as an endogenous ligand for TLR4 receptors (Abebe et al. 2022).

sL-selectin (soluble leukocyte selectin) is also called CD62L and is a cell adhesion molecule that is expressed on most circulating leukocytes and facilitates endothelial adhesion and transendothelial migration of activated immune cells (Ivetic et al., 2019; Seekamp et al., 2001), which in turn would activate local glia. A study of acute COVID patients found that patients with severe COVID-19 had greater frequencies of CD4+ T cells expressing CD62L, in particular severe patients with hypertension (Lesteborg et al., 2023).

Pentraxin-2 (also called serum amyloid P component or SAP) is a short pentraxin protein like C-reactive protein and is a component of the humoral arm of the innate immune system, involved in infection resistance and tissue remodeling. Pentraxin-2 binds to organisms such as viruses, bacteria, and fungi (Doni et al. 2021). In mice it was also found to regulate the interaction between macrophage activation and coagulation cascades and is thought to be involved in the pathogenic buildup of amyloid fibrils by reducing normal proteolytic cleavage (Muczynsk et al. 2017 28213380).

Haptoglobin protein circulating in plasma scavenges extracellular hemoglobin and is thought to have a protective effect against hemoglobin-induced vasoconstriction, however in murine models vascular endothelial dysfunction prevents this function (Graw et al., 2017). The gut permeability marker zonulin, which is reduced in the post-acute-COVID condition multisystem inflammatory syndrome in children (MIS-C) (Yonker et al. 2021) is the precursor for haptoglobin-2.

575

576 These vascular factors may penetrate into brain parenchyma via the perivascular
577 spaces that line the neurovasculature and form the blood-brain barrier (Ineichen et al.,
578 2022). During neuroinflammation, the blood-brain barrier becomes more permissive by
579 opening up at the perivascular spaces, allowing circulating factors to affect the brain's
580 glia (Galea, 2021). We found increased PET uptake in some regions that tend to have
581 dilated perivascular spaces. For example, we found significantly increased PET signal
582 especially within left lentiform nucleus of the basal ganglia. The basal ganglia are a
583 group of subcortical nuclei with many small, thin blood vessels that are common sites of
584 unique perivascular anatomy and enlarged/dilated perivascular spaces (Mestre et al.,
585 2017; Rudie et al., 2018), and apparently-subclinical neurovascular abnormalities such
586 as cerebral microhemorrhages (Viswanathan & Chabriat, 2006), both of which have
587 been reported in acute COVID-19 autopsy (Kantonen et al., 2020). In neuroradiology,
588 dilated perivascular spaces on the lenticulostriate arteries projecting into the basal
589 ganglia are relatively common and referred to as "Type 1." Enlarged Type 1 perivascular
590 spaces are sometimes seen in normal healthy aging but are associated with disease
591 severity in some neurological conditions (Chan et al., 2021) and in one study were
592 associated with sleep dysfunction in PASC (Del Brutto et al., 2022).

593

594 Within subcortical areas, some of the TSPO signal elevation pattern we measured also
595 appears to be compatible with the location of the subfornical organ and the choroid
596 plexus and ependymal glial cells at the roof of the third and floor of lateral ventricles,
597 which are circumventricular organs (CVOs). CVOs are dense with ACE2 receptors (Ong
598 et al., 2022), highly vascularized, and (except for the subcommissural organ) feature

599 fenestrated blood vessels that lack a complete blood-brain barrier. This renders the glia
600 near CVOs particularly vulnerable to being activated by blood-borne factors. We also
601 detected elevated [¹¹C]PBR28 PET signal across cingulate and corpus callosum, a
602 pattern that follows the anterior cerebral artery pericallosal branch. More posterior
603 regions of cingulate are particularly highly vascularized (Vogt, 2019). Unlike the CVOs
604 but like the rest of the brain, these regions feature an intact blood brain barrier.
605 However, neurovascular endothelial cells are the blood-facing component of the blood-
606 brain barrier and can be activated by circulating factors, in turn driving activation of glia
607 (Kanda et al., 1995; Lécuyer et al., 2016; Pan et al., 2011). Furthermore, a reduced
608 integrity of the blood-brain barrier, as observed during neuroinflammation (Galea, 2021),
609 would likely contribute to this effect.

610

611 While our observational case-control study design cannot determine a causal
612 relationship between neuroinflammation and vascular health, multiple potential non-
613 mutually exclusive drivers (Proal & VanElzakker, 2021) of these effects are possible.
614 Ongoing vascular-related problems and neuroinflammation may reflect lingering
615 consequences from tissue injury during acute COVID-19. However most of our PASC
616 participants did not report severe acute illness, and the acute COVID-19 illness that
617 initiated their PASC was an average of 20.5 months prior to the scan visit. Under these
618 circumstances, the ongoing objective neurological and vascular abnormalities may be
619 more likely to reflect pre-COVID vulnerability factors and/or persistent stimulation by
620 ongoing biological factors.

621

622 Previous studies have examined the contribution of other circulating factors in PASC.
623 Vascular dysfunction may be consistent with the ongoing presence of fibrin-amyloid
624 'microclots' (Pretorius et al., 2022) or with neutrophil hyperactivation (Boribong et al.,
625 2022) that have been reported in individuals with PASC. These factors may represent
626 continuous provocation by uncleared viral reservoirs at least in some PASC patients
627 (Proal et al., 2023; Proal & VanElzakker, 2021). SARS-CoV-2 RNA or protein have been
628 identified in PASC tissue after acute COVID-19, and multiple research groups have
629 identified SARS-CoV-2 proteins including spike in blood in a subset of PASC individuals
630 up to 16 months after initial infection (M. Peluso, 2023; Swank et al., 2023). These
631 proteins may have leaked into general circulation from a tissue reservoir site via
632 extracellular vesicle transport (Craddock et al., 2023; M. J. Peluso et al., 2022). Given
633 that the spike protein drives coagulation cascades (Zheng et al., 2021) and a profound
634 inflammatory response (e.g., Boribong et al., 2022), future PASC studies should
635 measure these variables together in PASC cases versus COVID-recovered controls to
636 better understand how they may be related to neuroinflammation and ongoing
637 symptoms. Better understanding of these potential sources of neuroinflammation would
638 be important for guiding related treatments and clinical trials.

639

640 4.2 LIMITATIONS

641

642 The current study compared 12 PASC patients to 43 controls, the majority of whom (34)
643 were scanned pre-pandemic, the rest of whom tested negative for SARS-CoV-2
644 antibodies. Future studies should also recruit a specific well-defined PASC phenotype

645 but increase the number of PASC participants, and should also compare PASC to
646 COVID-19-recovered controls. While there was a higher proportion of female
647 participants in the PASC group, we statistically controlled for sex in the primary analysis,
648 and conducted a paired validation analysis in which PASC participants were directly
649 matched for sex, genotype, and age (± 5 yrs). Furthermore, we conducted a confirmatory
650 unpaired analysis comparing only female PASC cases to only female controls and found
651 a very similar pattern (data not shown).

652

653 While the TSPO-targeting radioligand [^{11}C]PBR28 is a widely used measure in studies
654 of neuroinflammation, the specific function of TSPO is an area of ongoing study. In a
655 non-mutually exclusive fashion, increased TSPO may reflect various activation states of
656 glial cell types such as microglia and astrocytes (Paolicelli et al., 2022), density of glial
657 cells (some of which are motile (Smolders et al., 2019)), peripheral immune cells
658 penetrating into brain, or inflammatory activation of neurovascular endothelial cells
659 (Guilarte et al., 2022). Therefore the exact biological driver of the observed increased
660 PET signal in PASC remains to be fully elucidated.

661

662 Kinetic modeling using radiometabolite-corrected arterial input function, which is
663 considered by many to be the gold-standard for TSPO signal quantification, was not
664 included in the current study because the PASC participants did not undergo arterial line
665 blood analysis during scanning and arterial line data were available only in a small
666 subset of controls. While several previous studies have used arterial line blood-derived
667 distribution volume (VT) ratio (DVR) to demonstrate the validity of SUVR as a

668 semiquantitative ratio metric (e.g., (Alshelh et al., 2020)), future studies should include
669 arterial line analyses in all participants or in a validation subset to further quantify the
670 relationship between TSPO and measures of vascular health.

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