

Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment

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Supplementary Table 1. Demographics of acute COVID cohort. Data was analysed by two-sided Kruskal-Wallis test with Bonferroni correction for multiple comparisons or two-sided z-test for comparisons of column proportions.

	Unaffected	Mild	Moderate	Severe	p-value
Gender (M/F)	11/14	8/35	2/8	12/11	
Age (years)	44	40	42	54	0.012
Hospitalisation					
Hospitalisation		0 (0%)	8 (80%)	21 (91%)	
No hospitalisation		43 (100%)	2 (20%)	2 (9%)	
ICU					
Required		0 (0%)	0 (0%)	2 (9%)	
Not required		43 (100%)	10 (100%)	21 (91%)	
Oxygen					
Required		0 (0%)	0 (0%)	17 (74%)	
Not required		43 (100%)	10 (100%)	6 (26%)	
COVID medication					
Required		0 (0%)	4 (40%)	21 (91%)	
Not required		43 (100%)	6 (60%)	2 (9%)	
	Brain Fog (-)		Brain Fog (+)		p-value
Gender (M/F)	18/44		4/10		
Age (years)	43		54		0.011
Hospitalisation					0.026
Hospitalisation	42 (68%)		5 (36%)		
No hospitalisation	20 (32%)		9 (64%)		
ICU					
Required	2 (3%)		0 (0%)		
Not required	60 (97%)		14 (100%)		
Oxygen					0.006
Required	10 (16%)		7 (50%)		
Not required	52 (84%)		7 (50%)		
COVID medication					0.033
Required	17 (27%)		8 (57%)		
Not required	45 (73%)		6 (43%)		

Supplementary Table 2. Demographics of Long COVID cohort. Data was analysed by two-sided Kruskal-Wallis test with Bonferroni correction for multiple comparisons.

	Unaffected	Recovered	Brain Fog (-)	Brain Fog (+)	p-value
Gender (M/F)	18/42	4/6	2/9	0/11	
Age	40	40	38	46	
Comorbidity score		0.3	0.36	0.33	
Time from PCR+ to scan		46.6	170.6	211	0.0004
Anosmia, n (%)		0 (0%)	8 (73%)	8 (73%)	
Anosmia duration (days)		0	110	121	0.002
Q-SIT		2.6	1.5	1.4	0.009
MOCA				24.9	

Supplementary Table 3. Volumetric measurements and statistical analysis. Data was analysed by ANCOVA adjusting for age and sex with Bonferroni correction for multiple comparisons.

	No adjustment	Age adjusted	FDR corrected
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Omnibus statistics

Region	F	P-value	eta	F	P-value	eta	q-value	Discovery?
Global brain volume	5.749	0.001	0.167	5.092	0.003	0.152	0.001683	Yes
CSF volume	6.769	0.0004	0.191	6.251	0.0007	0.181	0.000583	Yes
White matter volume	11.794	<0.0001	0.291	11.883	<0.0001	0.295	0.000005	Yes
Grey matter volume	2.34	0.079	0.075	2.974	0.036	0.095	0.01818	No
Cerebrum volume	6.281	0.0007	0.18	5.79	0.001	0.17	0.000721	Yes
Cerebrum right volume	6.276	0.0007	0.18	5.812	0.001	0.17	0.000721	Yes
Cerebrum left volume	6.083	0.0008	0.175	5.543	0.002	0.164	0.001188	Yes
Cerebrum white matter volume	11.016	<0.0001	0.278	11.126	<0.0001	0.282	0.000008	Yes
Cerebrum white matter right volume	11.328	<0.0001	0.283	11.45	<0.0001	0.288	0.000007	Yes
Cerebrum white matter left volume	10.54	<0.0001	0.269	10.636	<0.0001	0.273	0.000008	Yes
Cerebrum grey matter volume	1.981	0.123	0.065	2.367	0.076	0.077	0.030704	No
Cerebrum grey matter right volume	1.787	0.156	0.059	2.123	0.103	0.07	0.037154	No
Cerebrum grey matter left volume	2.168	0.098	0.07	2.587	0.058	0.084	0.024408	No
Frontal cortex mm	2.842	0.043	0.09	2.848	0.042	0.091	0.019741	No
Frontal cortex right mm	2.502	0.065	0.08	2.313	0.082	0.075	0.031854	No
Frontal cortex left mm	3.139	0.029	0.099	3.322	0.024	0.105	0.012758	No
Frontal pole mm	9.975	<0.0001	0.258	10.87	<0.0001	0.277	0.000008	Yes
Frontal pole right mm	5.225	0.002	0.154	5.342	0.002	0.159	0.001188	Yes
Frontal pole left mm	14.173	<0.0001	0.331	15.203	<0.0001	0.349	5.33E-07	Yes
Superior frontal gyrus mm	5.918	0.001	0.171	8.126	<0.0001	0.223	0.000091	Yes
Superior frontal gyrus right thickness	5.004	0.003	0.149	6.604	0.0005	0.189	0.000421	Yes
Superior frontal gyrus left thickness	6.542	0.0005	0.186	8.879	<0.0001	0.239	0.000051	Yes
Medial temporal gyrus mm	3.585	0.017	0.111	2.84	0.043	0.091	0.019741	No
Medial temporal gyrus right mm	2.981	0.036	0.094	2.269	0.086	0.074	0.03217	No
Medial temporal gyrus left mm	3.349	0.023	0.105	2.673	0.052	0.086	0.022835	No
Superior temporal gyrus mm	8.243	<0.0001	0.223	8.194	<0.0001	0.224	0.000091	Yes
Superior temporal gyrus right mm	7.579	0.0001	0.209	7.34	0.0002	0.206	0.000198	Yes
Superior temporal gyrus left mm	5.775	0.001	0.168	5.169	0.002	0.154	0.001188	Yes

Supplementary Table 4. Correlations between BBB disruption, structural brain data and clinical measurements. Data was analysed by ANCOVA adjusting for age and sex with Bonferroni correction for multiple comparisons.

Correlations between % BBB disruption, brain region and clinical data

Region	Age-uncorrected rho	Age-uncorrected p-value	Age-corrected rho	Age-corrected p-value
Global brain volume	-0.555	0.001	-0.614	0.00039
Cerebrum volume	-0.526	0.002	-0.57	0.001
Cerebrum right volume	-0.521	0.003	-0.544	0.002
Cerebrum left volume	-0.509	0.003	-0.557	0.002
Cerebrum white matter volume	-0.468	0.008	-0.505	0.005
Cerebrum white matter right volume	-0.449	0.011	-0.487	0.007
Cerebrum white matter left volume	-0.491	0.005	-0.516	0.004
Cerebrum grey matter volume	-0.293	0.11	-0.342	0.069

Cerebrum grey matter right volume	-0.29	0.113	-0.329	0.081
Cerebrum grey matter left volume	-0.307	0.093	-0.35	0.062
Cerebellum volume	-0.143	0.442	-0.195	0.312
Cerebellum white matter volume	-0.259	0.16	-0.316	0.095
Cerebellum grey matter volume	-0.002	0.99	-0.041	0.831
CSF volume	0.552	0.001	0.595	0.000664
Brainstem volume	-0.06	0.749	-0.103	0.596
Amygdala volume	0.433	0.015	0.389	0.037
Hippocampus volume	0.15	0.419	0.143	0.459
QSIT score	-0.428	0.218	-0.243	0.561
Anosmia duration	0.656	0.039	0.603	0.114
MOCA	-0.049	0.893	-0.08	0.851