Supplementary Table 1: Median values of biomarkers

Median (pg/mL) and (Q1, Q3)	Brain Injury Markers				Cytokines					
	NfL	GFAP	Tau	UCH-L1	IL-1RA	IL-6	IL-12p40	CCL2	M-CSF	HGF
ISARIC GCS=15 (n=76)	26.5 (12.9, 62.3)	125 (86.9, 230.0)	1.1 (0.9, 1.4)	21.9 (11.3, 36.3)	772.5 (534.8, 1722.3)	2.12 (1.4, 12.8)	166.5 (109.3, 253.8)	53.3 (36.6, 69.6)	46.6 (28.5, 67.1)	809.1 (530.5, 1505.0)
ISARIC GCS≤14 (n=35)	58.2 (30.7, 122.8)	151 (90.5, 263.0)	1.2 (0.9, 1.7)	33.7 (18.8, 48.5)	1501.3 (1093.0, 3128.8)	33.8 (12.6, 72.6)	286.1 (224.1, 395.2)	132.8 (55.5, 208.4)	75.9 (54.0, 107.1)	1965.0 (1570.0, 2956.6)
COVID-CNS COVID (n=36)	12.6 (8.3, 27.9)	92.9 (61.3, 197.0)	1.3 (1.1, 1.9)	7.4 (4.0, 19.6)	290.0 (197.2, 476.0)	1.4 (1.4, 5.8)	123.7 (68.4, 268.9)	32.10 (23.1, 49.2)	29.1 (17.6, 51.6)	668.0 (385.9, 1693.2)
COVID-CNS Neuro-COVID (n=56)	32.3 (17.9, 111.8)	106.5 (79.5, 191.0)	1.7 (1.3, 2.2)	9.3 (5.3, 20.9)	303.1 (218.1, 546.7)	1.36 (1.36, 1.36)	108.8 (91.1, 141.9)	32.5 (20.0, 50.0)	24.4 (16.0, 30.5)	529.9 (405.2, 727.6)

Supplementary Table 2: COVID-CNS Neuro-COVID cases

	Condition, n (%)	Diagnosis	n
Central Nervous System Condition 41 (73%)	Cerebrovascular 12 (21%)	Ischaemic stroke	6
		Haemorrhagic stroke	2
		Cerebral venous sinus thrombosis	1
		Vasculitic stroke	1
		CNS vasculitis	1
		PRES*	1
	CNS inflammation 9 (16%)	Encephalitis	4
		Demyelinating**	5
	Movement disorder 3 (5.4%)	Hyperkinetic movement disorder	3
	Seizures and others 17 (30%)	Seizures	8
		Encephalopathy	5
		Neuropsychiatric	2
		Others	2
Peripheral Nervous System Condition 15 (27%)	Various PNS 15 (27%)	Peripheral nerves dysfunction	11
		Myopathy	2
		Cranial nerve palsy	2

*PRES = posterior reversible encephalopathy syndrome
**Includes: multiple sclerosis, Acute disseminated encephalomyelitis (ADEM),
Chronic relapsing inflammatory optic neuritis (CRION)

Supplementary Table 3: ISARIC cohort cytokines correlations with brain injury markers (Pearson's coefficients)

	Variables	NFL		GFAP		Tau		UCHL	
		Correlation	Adj p-value (Estimate)	Correlation	Adj p-value (Estimate)	Correlation	Adj p-value (Estimate)	Correlation	Adj p-value (Estimate)
1	CCL5	-0.168	1.000	-0.190	1.000	-0.157	1.000	-0.023	1.000
2	SCGF-beta	-0.086	1.000	0.018	1.000	-0.020	1.000	-0.012	1.000
3	CXCL10	-0.056	1.000	-0.086	1.000	-0.031	1.000	-0.042	1.000
4	IL-6	-0.013	1.000	-0.054	1.000	-0.007	1.000	0.081	1.000
5	CCL2	0.118	1.000	0.106	1.000	0.098	1.000	0.070	1.000
6	CCL27	0.128	1.000	0.124	1.000	0.125	1.000	0.054	1.000
7	Eotaxin	0.091	1.000	0.056	1.000	0.161	1.000	-0.019	1.000
8	CXCL9	0.120	1.000	-0.067	1.000	0.075	1.000	-0.004	1.000
9	IL-2Ra	0.067	1.000	0.019	1.000	0.064	1.000	0.114	1.000
10	HGF	0.616	<0.001* (0.033)	0.250	0.773	0.682	<0.001* (0.0005)	0.156	1.000
11	IL-12(p40)	0.632	<0.001* (0.414)	0.401	0.002* (1.027)	0.651	<0.001* (0.005)	0.367	0.004* (0.096)
12	IL-10	0.180	1.000	0.399	0.004* (30.74)	0.119	1.000	0.610	<0.001* (4.932)
13	TNF	0.239	0.464	0.460	<0.001* (9.518)	0.167	1.000	0.561	<0.001* (1.246)
14	IL-2	0.222	1.000	0.534	<0.001* (42.03)	0.112	1.000	0.764	<0.001* (6.439)
15	IL-3	0.212	1.000	0.567	<0.001* (965.6)	0.140	1.000	0.758	<0.001* (137.331)
16	LTalpha	-0.077	1.000	0.204	1.000	-0.078	1.000	0.386	0.002* (0.184)
17	IL-9	0.003	1.000	0.266	0.288	0.030	1.000	0.487	<0.001* (0.307)
18	IL-12(p70)	0.093	1.000	0.330	0.091	0.095	1.000	0.379	0.004* (1.807)
19	IL-13	-0.040	1.000	0.047	1.000	0.013	1.000	0.052	1.000
20	GM-CSF	0.060	1.000	0.110	1.000	0.046	1.000	0.154	1.000
21	IL-5	0.065	1.000	0.154	1.000	0.045	1.000	0.299	0.116
22	b-NGF	0.041	1.000	0.180	1.000	0.007	1.000	0.407	0.001* (5.598)
23	CCL4	-0.009	1.000	-0.007	1.000	-0.051	1.000	0.347	0.015* (0.115)
24	IL-15	0.003	1.000	-0.035	1.000	-0.050	1.000	0.273	0.258
25	IL-8	0.010	1.000	-0.025	1.000	-0.028	1.000	0.297	0.109
26	CCL3	-0.003	1.000	-0.034	1.000	-0.043	1.000	0.282	0.193
27	G-CSF	-0.023	1.000	-0.019	1.000	-0.030	1.000	0.296	0.120
28	VEGF	0.013	1.000	-0.055	1.000	-0.077	1.000	0.187	1.000
29	CXCL1	-0.049	1.000	0.006	1.000	-0.091	1.000	0.205	1.000
30	TRAIL	0.028	1.000	0.264	0.498	0.046	1.000	0.441	<0.001* (4.545)
31	IL-1alpha	0.227	1.000	0.306	0.299	0.144	1.000	0.528	<0.001* (1.717)
32	FGF basic	0.305	0.118	0.278	0.468	0.279	0.241	0.408	0.001* (1.032)
33	IFN-alpha2	0.173	1.000	0.006	1.000	0.178	1.000	0.296	0.110
34	IL-4	0.191	1.000	0.119	1.000	0.195	1.000	0.248	0.673
35	IL-17A	0.244	1.000	0.150	1.000	0.242	1.000	0.303	0.109
36	LIF	0.119	1.000	0.044	1.000	0.073	1.000	0.273	0.316
37	MIF	0.037	1.000	-0.056	1.000	-0.008	1.000	0.191	1.000
38	IL-1Ra	0.188	1.000	0.017	1.000	0.079	1.000	0.247	0.572
39	CCL7	0.098	1.000	0.045	1.000	0.022	1.000	0.140	1.000
40	IFN-gamma	0.194	1.000	0.169	1.000	0.163	1.000	0.276	0.157
41	SCF	0.334	0.007* (0.419)	0.113	0.889	0.304	0.009* (0.005)	0.237	0.213
42	M-CSF	0.293	0.094	0.112	1.000	0.211	0.727	0.234	0.359
43	IL-16	0.206	1.000	0.117	1.000	0.156	1.000	0.148	1.000
44	IL-18	0.205	1.000	0.036	1.000	0.113	1.000	0.173	1.000
45	IL-1beta	0.195	1.000	0.112	1.000	0.160	1.000	0.328	0.037* (7.381)
46	PDGF-bb	-0.065	1.000	-0.125	1.000	-0.163	1.000	0.114	1.000
47	CXCL12	0.081	1.000	0.140	1.000	0.118	1.000	0.271	0.375
48	IL-7	-0.001	1.000	0.024	1.000	-0.030	1.000	0.121	1.000

Supplementary Table 4: ISARIC Median-centred data
Differences between GCS=15 and GCS≤14
(two-tailed Mann-Whitney tests)

Count	Cytokines	Adj p-value[1] (test,p-value[2])	Effect size	Count	Cytokines	Adj p-value[1] (test,p-value[2])	Effect size
1	CCL5	1 (M, <0.001)	-0.018	25	IL-8	0.453 (M, <0.001)	-0.247
2	SCGF-beta	1 (M, <0.001)	-0.042	26	CCL3	1 (M, <0.001)	-0.103
3	CXCL10	0.717 (M, <0.001)	-0.232	27	G-CSF	1 (M, <0.001)	-0.011
4	IL-6	<0.001* (M, <0.001)	-0.429	28	VEGF	1 (M, <0.001)	0.033
5	CCL2	0.137 (M, <0.001)	-0.284	29	CXCL1	1 (M, <0.001)	-0.066
6	CCL27	0.16 (M, <0.001)	0.279	30	TRAIL	0.014* (M, <0.001)	0.345
7	Eotaxin	<0.001* (M, <0.001)	0.436	31	IL-1alpha	1 (M, <0.001)	0.012
8	CXCL9	1 (M, <0.001)	-0.103	32	FGF basic	0.018* (M, <0.001)	0.339
9	IL-2Ra	1 (M, <0.001)	-0.028	33	IFN-alpha2	1 (M, <0.001)	-0.093
10	HGF	<0.001* (M, <0.001)	-0.425	34	IL-4	<0.001* (M, <0.001)	0.46
11	IL-12(p40)	0.034* (M, <0.001)	-0.322	35	IL-17A	1 (M, <0.001)	-0.022
12	IL-10	1 (M, <0.001)	-0.156	36	LIF	1 (M, <0.001)	0.154
13	TNF	1 (M, <0.001)	0.04	37	MIF	1 (M, <0.001)	-0.066
14	IL-2	1 (M, <0.001)	0.116	38	IL-1Ra	0.071* (M, <0.001)	-0.302
15	IL-3	0.022* (M, <0.001)	0.333	39	CCL7	1 (M, <0.001)	-0.092
16	LTalpha	0.168 (M, <0.001)	0.277	40	IFN-gamma	1 (M, <0.001)	-0.135
17	IL-9	0.003* (M, <0.001)	0.383	41	SCF	1 (M, <0.001)	0.185
18	IL-12(p70)	0.127 (M, <0.001)	0.286	42	M-CSF	0.611 (M, <0.001)	-0.236
19	IL-13	1 (M, <0.001)	0.07	43	IL-16	1 (M, <0.001)	-0.145
20	GM-CSF	1 (M, <0.001)	-0.02	44	IL-18	1 (M, <0.001)	-0.204
21	IL-5	0.019* (M, <0.001)	0.336	45	IL-1beta	0.421 (M, <0.001)	0.249
22	b-NGF	1 (M, <0.001)	0.216	46	PDGF-bb	1 (M, <0.001)	-0.146
23	CCL4	0.002* (M, <0.001)	0.388	47	CXCL12	1 (M, <0.001)	0.102 (M, <0.001)
24	IL-15	0.125 (M, <0.001)	0.286	48	IL-7	1 (M, <0.001)	0.001 (M, <0.001)

Supplementary Table 5: Correlations of cytokines and brain injury markers in the COVID-CNS Neuro-COVID cohort with regression models (Pearson's coeffecients)

Variables	NFL		GFAP		Tau		UCHL	
	Correlation	Adj p-value	Correlation	Adj p-value	Correlation	Adj p-value	Correlation	Adj p-value
CCL5	-0.245	1.000	-0.222	1.000	0.158	1.000	0.128	1.000
SCGF-beta	0.169	1.000	0.283	1.000	0.256	1.000	0.100	1.000
CXCL10	0.096	1.000	0.078	1.000	0.416	0.140	0.069	1.000
IL-6	-0.059	1.000	-0.010	1.000	0.003	1.000	-0.043	1.000
CCL2	0.083	1.000	0.128	1.000	0.492	0.016*	0.022	1.000
CCL27	0.183	1.000	0.032	1.000	0.255	1.000	0.006	1.000
Eotaxin	-0.042	1.000	0.010	1.000	-0.077	1.000	-0.100	1.000
CXCL9	0.017	1.000	-0.059	1.000	0.132	1.000	0.159	1.000
IL-2Ra	0.104	1.000	0.049	1.000	0.547	0.002*	0.517	0.007*
HGF	0.251	1.000	0.162	1.000	0.238	1.000	0.084	1.000
IL-12(p40)	0.298	1.000	0.116	1.000	0.200	1.000	0.124	1.000
IL-10	-0.068	1.000	-0.004	1.000	0.151	1.000	-0.032	1.000
TNF	0.064	1.000	0.167	1.000	0.409	0.165	0.042	1.000
IL-2	0.064	1.000	0.111	1.000	0.123	1.000	-0.129	1.000
IL-3	NA	NA	NA	NA	NA	NA	NA	NA
LTalpha	0.091	1.000	0.161	1.000	-0.069	1.000	-0.071	1.000
IL-9	-0.009	1.000	0.075	1.000	-0.051	1.000	-0.082	1.000
IL-12(p70)	0.043	1.000	-0.123	1.000	-0.139	1.000	-0.028	1.000
IL-13	-0.008	1.000	-0.079	1.000	-0.159	1.000	-0.049	1.000
GM-CSF	-0.079	1.000	-0.091	1.000	-0.161	1.000	-0.038	1.000
IL-5	-0.068	1.000	-0.063	1.000	-0.053	1.000	-0.054	1.000
b-NGF	-0.078	1.000	-0.070	1.000	-0.044	1.000	-0.042	1.000
CCL4	0.143	1.000	0.176	1.000	-0.044	1.000	-0.036	1.000
IL-15	-0.031	1.000	-0.016	1.000	-0.080	1.000	-0.009	1.000
IL-8	-0.172	1.000	-0.118	1.000	0.246	1.000	0.152	1.000
CCL3	0.094	1.000	0.052	1.000	0.006	1.000	0.008	1.000
G-CSF	0.086	1.000	0.044	1.000	0.031	1.000	0.001	1.000
VEGF	-0.078	1.000	-0.071	1.000	-0.009	1.000	-0.039	1.000
CXCL1	-0.060	1.000	-0.067	1.000	-0.171	1.000	-0.050	1.000
TRAIL	0.009	1.000	-0.022	1.000	0.167	1.000	-0.080	1.000
IL-1alpha	-0.006	1.000	-0.012	1.000	0.069	1.000	0.043	1.000
FGF basic	0.259	1.000	0.189	1.000	0.251	1.000	0.141	1.000
IFN-alpha2	0.034	1.000	0.052	1.000	0.368	0.432	-0.003	1.000
IL-4	-0.006	1.000	0.034	1.000	-0.009	1.000	-0.015	1.000
IL-17A	-0.074	1.000	0.004	1.000	0.002	1.000	-0.108	1.000
LIF	-0.100	1.000	-0.087	1.000	0.103	1.000	0.135	1.000
MIF	0.061	1.000	0.102	1.000	0.303	1.000	0.074	1.000
IL-1Ra	0.069	1.000	0.185	1.000	0.582	0.001*	0.039	1.000
CCL7	0.033	1.000	0.158	1.000	0.608	<0.001*	0.050	1.000
IFN-gamma	-0.035	1.000	0.019	1.000	0.177	1.000	0.003	1.000
SCF	0.039	1.000	0.119	1.000	0.621	<0.001*	0.084	1.000
M-CSF	0.077	1.000	0.139	1.000	0.680	<0.001*	0.231	1.000
IL-16	0.048	1.000	0.157	1.000	0.578	0.001*	0.098	1.000
IL-18	0.132	1.000	0.190	1.000	0.724	<0.001*	0.317	1.000
IL-1beta	0.100	1.000	-0.007	1.000	0.337	0.844	0.072	1.000
PDGF-bb	0.181	1.000	0.186	1.000	-0.005	1.000	-0.058	1.000
CXCL12	0.107	1.000	0.201	1.000	0.091	1.000	-0.091	1.000
IL-7	-0.030	1.000	-0.007	1.000	-0.029	1.000	-0.040	1.000

# Supplementary Table 6: List of antigens on protein microarray

Number	Antigen	Type	Number	Antigen	Type	Number	Antigen	Type
1	ACE	Ubiquitous	52	GNRHR	Endocrine	103	MYL4	Cardiac
2	ACTA1	Muscle	53	GRIA2	Central Nervous System	104	MYL7	Cardiac
3	ADAMTS13	Coagulation	54	GRIA3	Central Nervous System	105	NEFL	Central Nervous System
4	AGER	Lung	55	GRIA4	Central Nervous System	106	NOVA1	Central Nervous System
5	AGTR1	Kidney	56	GRIN1	Central Nervous System	107	NPHS2	Kidney
6	ANKRD23	Muscle	57	GRIN2A	Central Nervous System	108	NPPA	Cardiac
7	ANXA4	Central Nervous System	58	GRIN3A	Central Nervous System	109	NPPB	Cardiac
8	ANXA5	Coagulation	59	GRIN3B	Central Nervous System	110	Nucleocapsid protein	SARS-CoV-2
9	APOH	Coagulation	60	GRINA	Central Nervous System	111	NUP210	Ubiquitous
10	APP	Central Nervous System	61	GRM1	Central Nervous System	112	OMG	Central Nervous System
11	BSG	Central Nervous System	62	GRM2	Central Nervous System	113	PLA2R1	Kidney
12	CD74	HLA	63	GRM3	Central Nervous System	114	PNMA1	Central Nervous System
13	CDH1	Ubiquitous	64	GRM4	Central Nervous System	115	PNMA2	Central Nervous System
14	CDH13	Central Nervous System	65	GRM7	Central Nervous System	116	POMC	Endocrine
15	CDR2	Central Nervous System	66	GRM8	Central Nervous System	117	PPP1R27	Muscle
16	CEACAM1	Ubiquitous	67	GSTT1	Kidney	118	PRL	Endocrine
17	CEACAM5	Ubiquitous	68	HARS	Muscle	119	PROC	Coagulation
18	CENPB	Ubiquitous	69	HLA-A	HLA	120	PROS1	Coagulation
19	CENPH	Ubiquitous	70	HLA-B	HLA	121	PRTN3	Kidney
20	CHRM2	Cardiac	71	HLA-C	HLA	122	S100B	Central Nervous System
21	CHRNA10	Muscle	72	HLA-DMA	HLA	123	SCGB1A1	Lung
22	CHRNA9	Central Nervous System	73	HLA-DMB	HLA	124	SCGB3A2	Lung
23	CLDN5	BBB	74	HLA-DOA	HLA	125	SELE	BBB
24	COL1A1	Lung	75	HLA-DOB	HLA	126	SFTPA1	Lung
25	COL1A2	Lung	76	HLA-DPA1	HLA	127	SFTPA2	Lung
26	COL4a3	Kidney	77	HLA-DPB1	HLA	128	SFTPC	Lung
27	COL4A3BP	Central Nervous System	78	HLA-DQA1	HLA	129	SLC22A12	Kidney
28	COL5A2	Lung	79	HLA-DQB1	HLA	130	SLC2A1	BBB
29	DBT	Ubiquitous	80	HLA-DQB2	HLA	131	SNCA	Central Nervous System
30	DCN	Central Nervous System	81	HLA-DRA	HLA	132	Spike protein	SARS-CoV-2
31	DDC	Ubiquitous	82	HLA-DRB1	HLA	133	SSB	Central Nervous System
32	DLAT	Ubiquitous	83	HLA-DRB3	HLA	134	TGM2	Ubiquitous
33	DPYSL5	Central Nervous System	84	HLA-DRB4	HLA	135	TJP1	BBB
34	DRD2	Central Nervous System	85	HLA-DRB5	HLA	136	TMEM174	Kidney
35	DUPD1	Muscle	86	HLA-E	HLA	137	TNNI3	Cardiac
36	EDNRA	Cardiac	87	HLA-F	HLA	138	TNNT2	Cardiac
37	ELAVL4	Central Nervous System	88	HLA-G	HLA	139	TPH1	Central Nervous System
38	F2	Coagulation	89	IDI2	Muscle	140	TPM1	Muscle
39	F7	Coagulation	90	IFNA1	Ubiquitous	141	TPO	Endocrine
40	F8	Coagulation	91	IGHG1	Immune system	142	TROVE2	Central Nervous System
41	F9	Coagulation	92	KCNJ10	Central Nervous System	143	TSHB	Endocrine
42	FGB	Coagulation	93	KRT18	Ubiquitous	144	TSHR	Endocrine
43	FSHB	Endocrine	94	LAMC2	BBB	145	TTN	Muscle
44	GABBR1	Central Nervous System	95	LGI1	Central Nervous System	146	TUBA1B	Lung
45	GABRA1	Central Nervous System	96	LRRC10	Cardiac	147	TUBB3	Central Nervous System
46	GABRB3	Central Nervous System	97	MAG	Central Nervous System	148	UCHL1	Central Nervous System
47	GAD1	Central Nervous System	98	MAPT	Central Nervous System	149	UCP3	Muscle
48	GAD2	Central Nervous System	99	MBP	Central Nervous System	150	UMOD	Kidney
49	GFAP	Central Nervous System	100	MOG	Central Nervous System	151	VIM	Kidney
50	GHRHR	Endocrine	101	MPO	Kidney	152	ZIC4	Central Nervous System
51	GLRA1	Central Nervous System	102	MYBPHL	Cardiac	153	ZNF397	Ubiquitous

Supplementary Table 7: COVID-CNS cohort co-morbidities

Condition	COVID	Neuro-COVID
Frailty Scale Score (Median, Q1, Q3)	2.5 (2,4)	2.0 (2,3)
Hypertension	36%	29%
Tobacco smoking	8%	2%
eCigarette smoking	0%	0%
Hypercholesterolaemia	6%	9%
Muscular disease	0%	0%
Multiple sclerosis	0%	2%
Movement disorder	0%	0%
Dementia	0%	0%
Epilepsy	6%	4%
Ischemic stroke	0%	0%
Hemorrhagic stroke	3%	0%
Diabetes	19%	21%
Motor neuron disease	0%	0%
Neurological disease	3%	0%
Atrial fibrillation	3%	2%
HIV	3%	0%
Psychiatric/psychological disorder	11%	25%
Brain cancer	0%	0%
Cardiac disease	3%	4%
Chronic kidney disease	14%	4%
TB	0%	0%
Malignant neoplasm	8%	4%
Myasthenia gravis	0%	0%
Developmental delay	0%	0%
Chronic pulmonary disease	17%	11%
Chronic liver disease	3%	2%
Autoimmune disease	3%	7%
Known treatment with anti-epileptic or sedative	3%	4%
Known treatment with immunomodulation	56%*	61%**

*COVID– corticosteroid administration
One additional participant with with tacrolimus

**Neuro-COVID– corticosteroid administration
One with tocilizumab, one additional participant with baricitinib and dimethyl fumarate

a

NfI

b
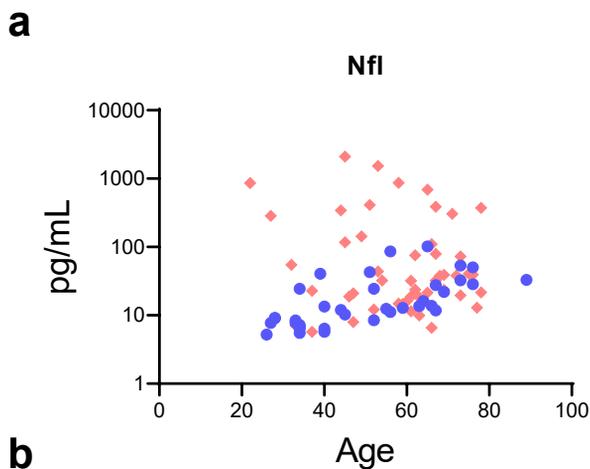
Multiple regression model with age as a co-variate		
Biomarker	Neuro-COVID/COVID estimate	p-value
NfL	186.3	0.007
GFAP	56.0	0.512
Tau	0.6	0.070
UCHL1	12.7	0.250

c
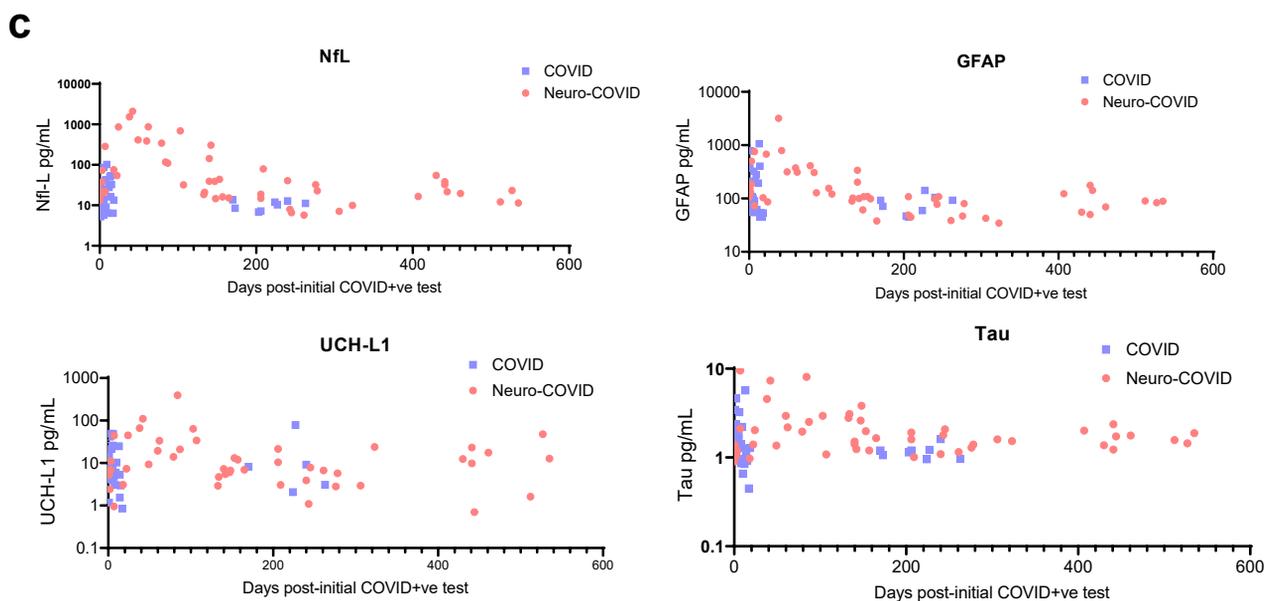
Supplementary Fig. 1: COVID-CNS Brain injury markers stratified by age and over time

(a) Serum NfL was measured by Simoa across ages of the participants in COVID control vs Neuro-COVID cases groups. The results show that age is not a major determinant of the overall difference. *Pearson's correlation p<0.05 in the COVID control group only

(b) Multiple regression model with age as a co-variate p-values for the four brain injury markers (NfL, GFAP, UCH-L1 and tTau)

(c) NfL, GFAP, UCH-L1 and Tau were measured by Simoa and plotted over time since initial COVID+ve test in the COVID-CNS (early and late convalescent participants)
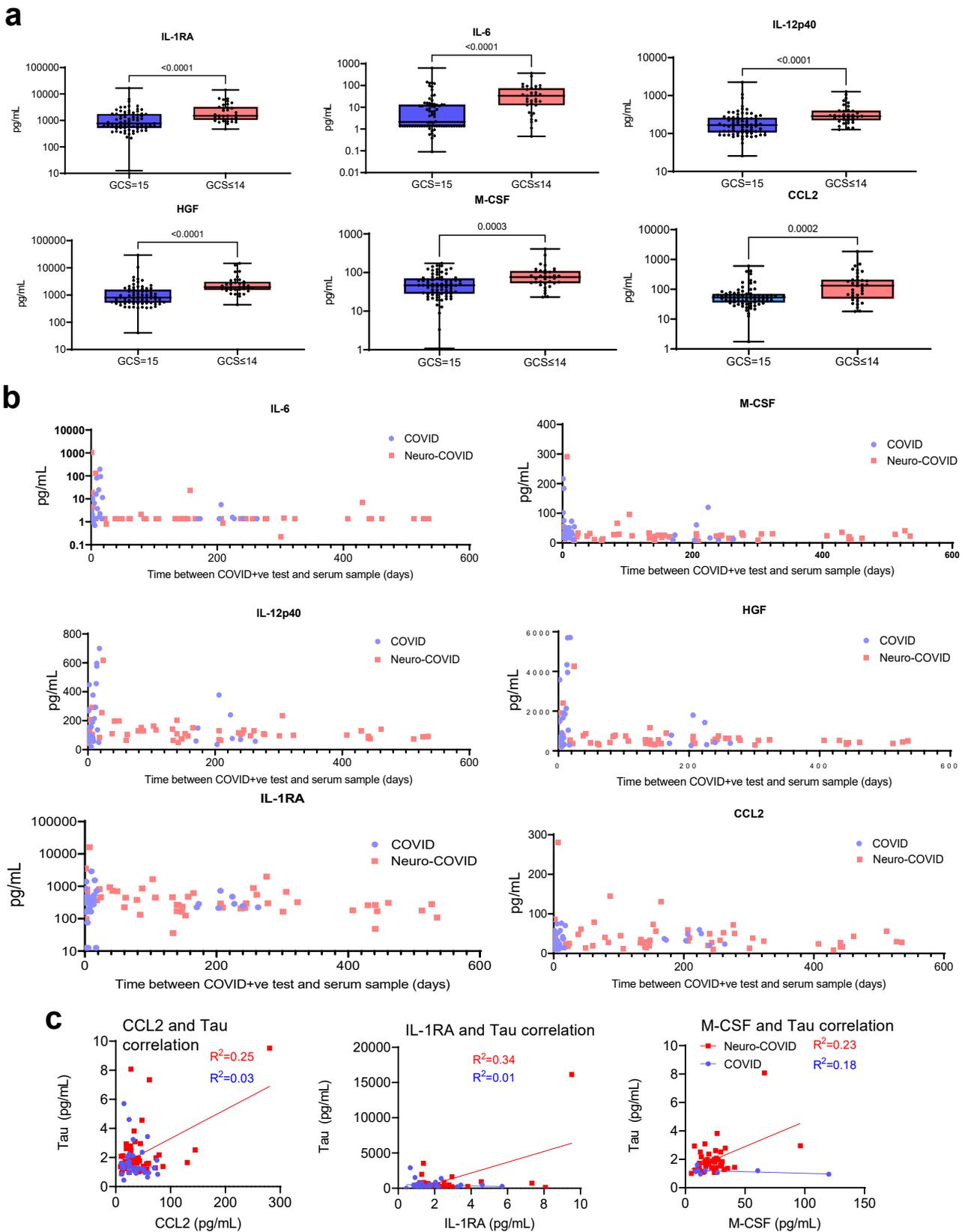
Supplementary Fig. 2: Cytokine comparisons

(a) Six cytokines measured by luminex were significantly higher in the sera of ISARIC participants (acute timepoints) with GCS≤14 compared to GCS=15 group. Two-tailed Mann-Whitney tests.

(b) The six serum cytokines plotted over time since initial COVID+ve test in the COVID-CNS (sub-acute/convalescent) cohort

(c) Significant correlations of three cytokines of interest with Tau in the COVID-CNS Neuro-COVID cohort (sub-acute/convalescent) with Pearson's correlations shown

a

ISARIC: GCS≤14/GCS=15

Protein	p_value	log2FC
IL-8	0.0016	-2.097
CCL3	0.0066	-1.424
IL-16	0.0072	0.610
IL-2Ralpha	0.0221	0.647
IL-12p40	0.0000	0.673
IFNgamma	0.0042	0.683
M-CSF	0.0003	0.736
IL-10	0.0033	0.749
IL-18	0.0017	0.754
IL-1RA	0.0001	0.882
HGF	0.0000	0.907
CXCL9	0.0270	0.920
IL-6	0.0000	1.129
CXCL10	0.0024	1.179
CCL7	0.0161	1.287
CCL2	0.0003	1.510

COVID-CNS: NeuroCOVID/COVID

Protein	p_value	log2FC
IL-3	0.0123	-0.9919
IL-18	0.0007	-0.8797
PDGFbb	0.0021	-0.7306
IL-6	0.0043	0.7541

b

ID	Description	Ratio	pvalue	Count
hsa04060	Cytokine-cytokine receptor interaction	15/17	1.36E-20	15
hsa04061	Viral protein interaction with cytokine and cytokine receptor	11/17	4.15E-18	11
hsa05144	Malaria	7/17	3.01E-12	7
hsa05323	Rheumatoid arthritis	7/17	2.73E-10	7
hsa05142	Chagas disease	7/17	5.28E-10	7
hsa05143	African trypanosomiasis	5/17	7.18E-09	5
hsa04657	IL-17 signaling pathway	6/17	1.79E-08	6
hsa05164	Influenza A	7/17	1.99E-08	7
hsa04620	Toll-like receptor signaling pathway	6/17	3.3E-08	6
hsa05321	Inflammatory bowel disease	5/17	1.32E-07	5
hsa04062	Chemokine signaling pathway	6/17	1.27E-06	6
hsa05146	Amoebiasis	5/17	1.27E-06	5
hsa05417	Lipid and atherosclerosis	6/17	2.45E-06	6
hsa05134	Legionellosis	4/17	4.12E-06	4
hsa05135	Yersinia infection	5/17	5.46E-06	5
hsa05133	Pertussis	4/17	1.31E-05	4
hsa04630	JAK-STAT signaling pathway	5/17	1.4E-05	5
hsa05152	Tuberculosis	5/17	2.07E-05	5
hsa05330	Allograft rejection	3/17	5.43E-05	3
hsa04668	TNF signaling pathway	4/17	6.49E-05	4
hsa05171	Coronavirus disease - COVID-19	5/17	7.00E-05	5

Supplementary Fig. 3: Pathways enriched during neurological complications of COVID-19
(a) Cytokine differences in ISARIC Abnormal GCS and COVID-CNS neuro-COVID groups (positive or negative fold change denoted in far right column, significant by two-tailed Mann-Whitney tests
(b) KEGG enrichment pathway analysis of the ISARIC cohort (GCS≤14/GCS=15; pathways significant in both ISARIC and COVID-CNS cohorts shaded in grey)

a

ISARIC IgG

GCS ≤14 (n=34); GCS = 15 (n=72)

Spike

Nucleocapsid

Raw Fluorescence

Antigens (n=153)

b

ISARIC IgM

	NfL	GFAP	Tau	UCH-L1
ACE				
DLAT				
DPYSL5				
GLRA1				
HLA-B				
SFTPC				
Spike				

c

ISARIC IgG

	NfL	GFAP	Tau	UCH-L1
FGB				
GRIN3B				
DRD2				
MYL7				
F2				
UCH-L1				
Spike				
GLRA1				

Pearson Correlation
1.0
0.5
0.0
-0.5
-1.0
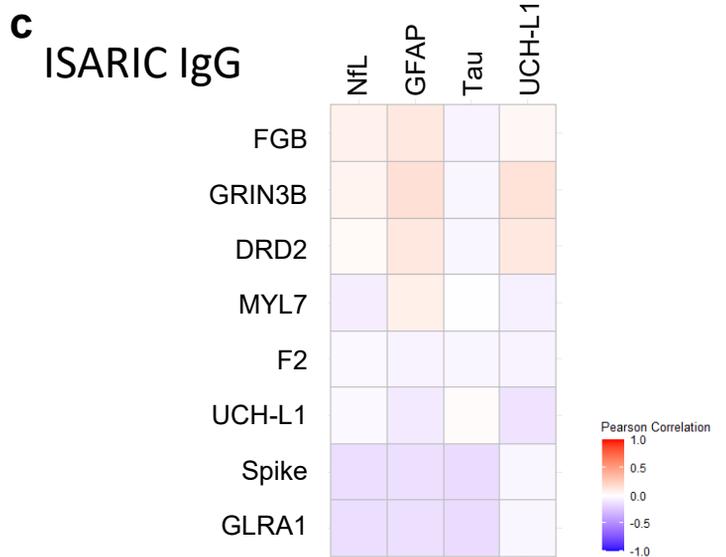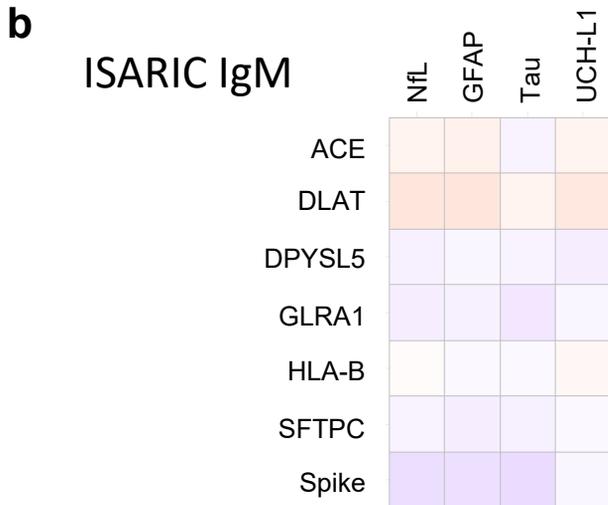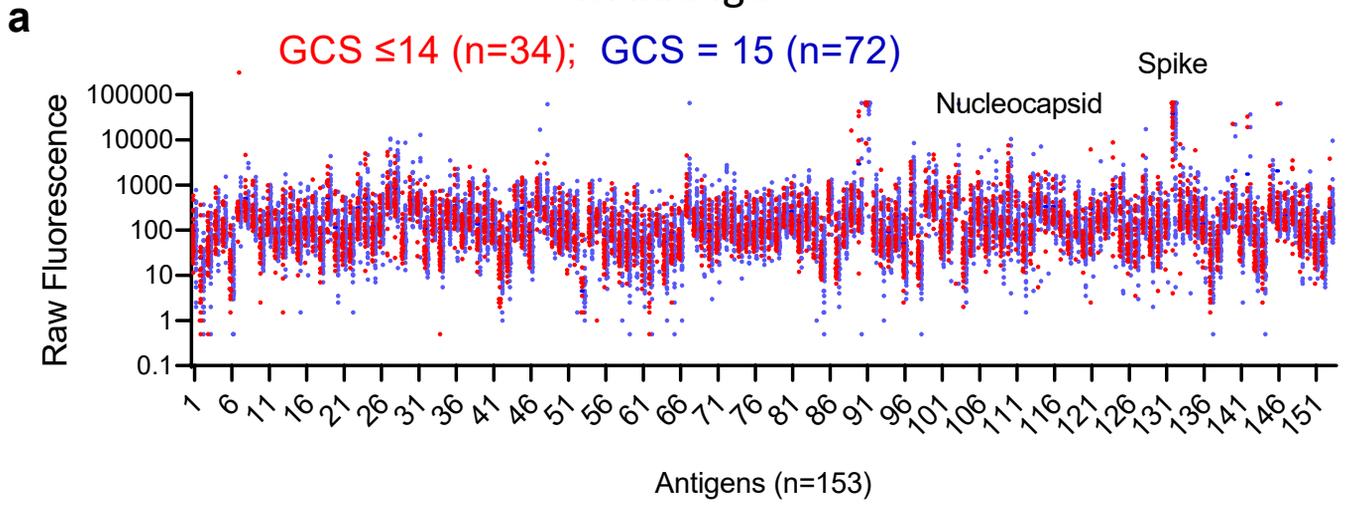
Supplementary Fig. 4: ISARIC (acute) autoantibody screen
(a) Raw fluorescence data from the protein chip used to screen antibodies against 153 antigens.
(b) Frequency of IgM autoantibodies in the ISARIC (acute) cohort (*Fisher's exact tests p<0.05)
(c) Heatmaps showing the insignificant Pearson's correlations between IgM or IgG autoantibodies and brain injury markers, UCH-L1, Tau, GFAP, and NfL
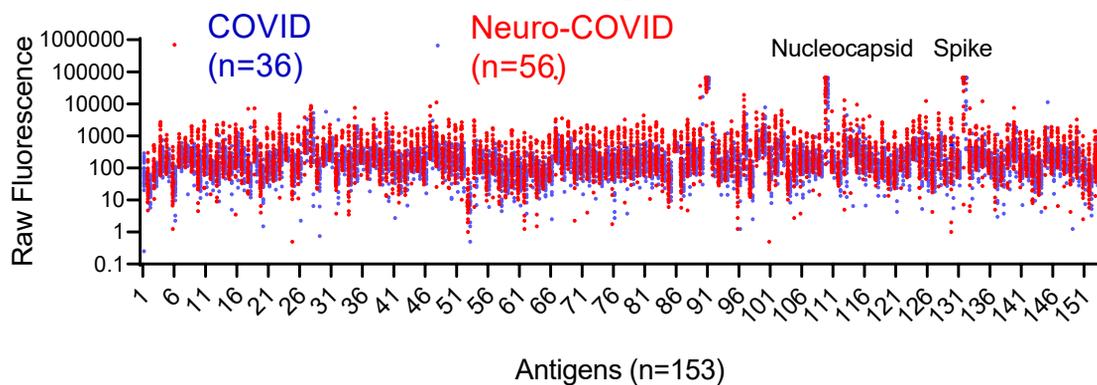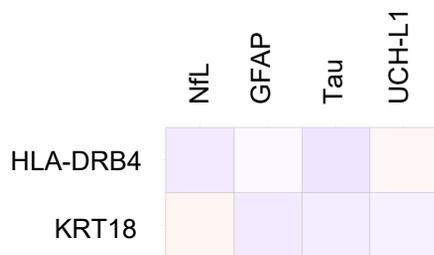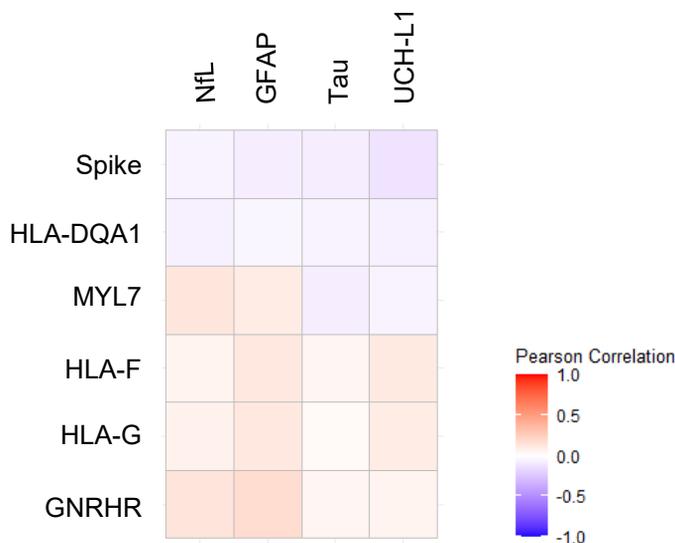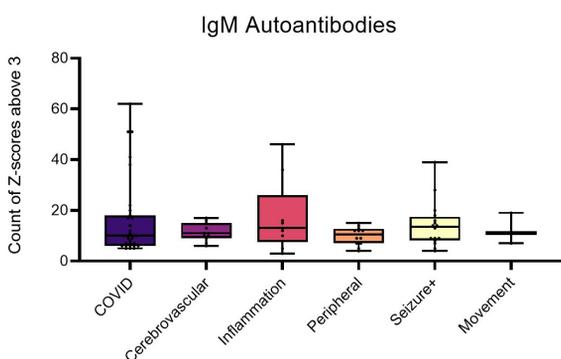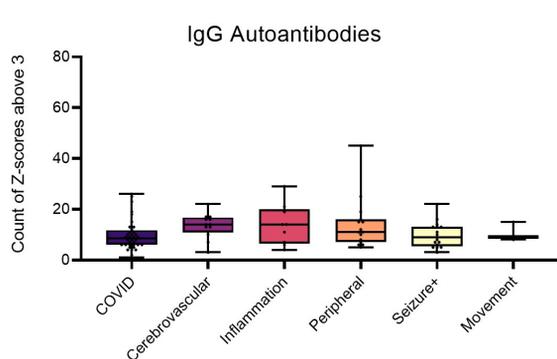
Supplementary Fig 5: COVID-CNS (early and late convalescent) autoantibody screen

(a) Raw fluorescence data from the protein chip used to screen antibodies against 153 antigens . The raw fluorescence shows higher binding in the Neuro-COVID compared with COVID, but this difference is not found after normalization (see Figure 3,4).

(b) Heatmaps showing the insignificant Pearson's correlations between IgM or (c) IgG autoantibodies and brain injury markers, UCH-L1, Tau, GFAP, and NfL

(d) Count of IgM and (e) IgG autoantibody positive hits split by condition (Z-scores above 3)
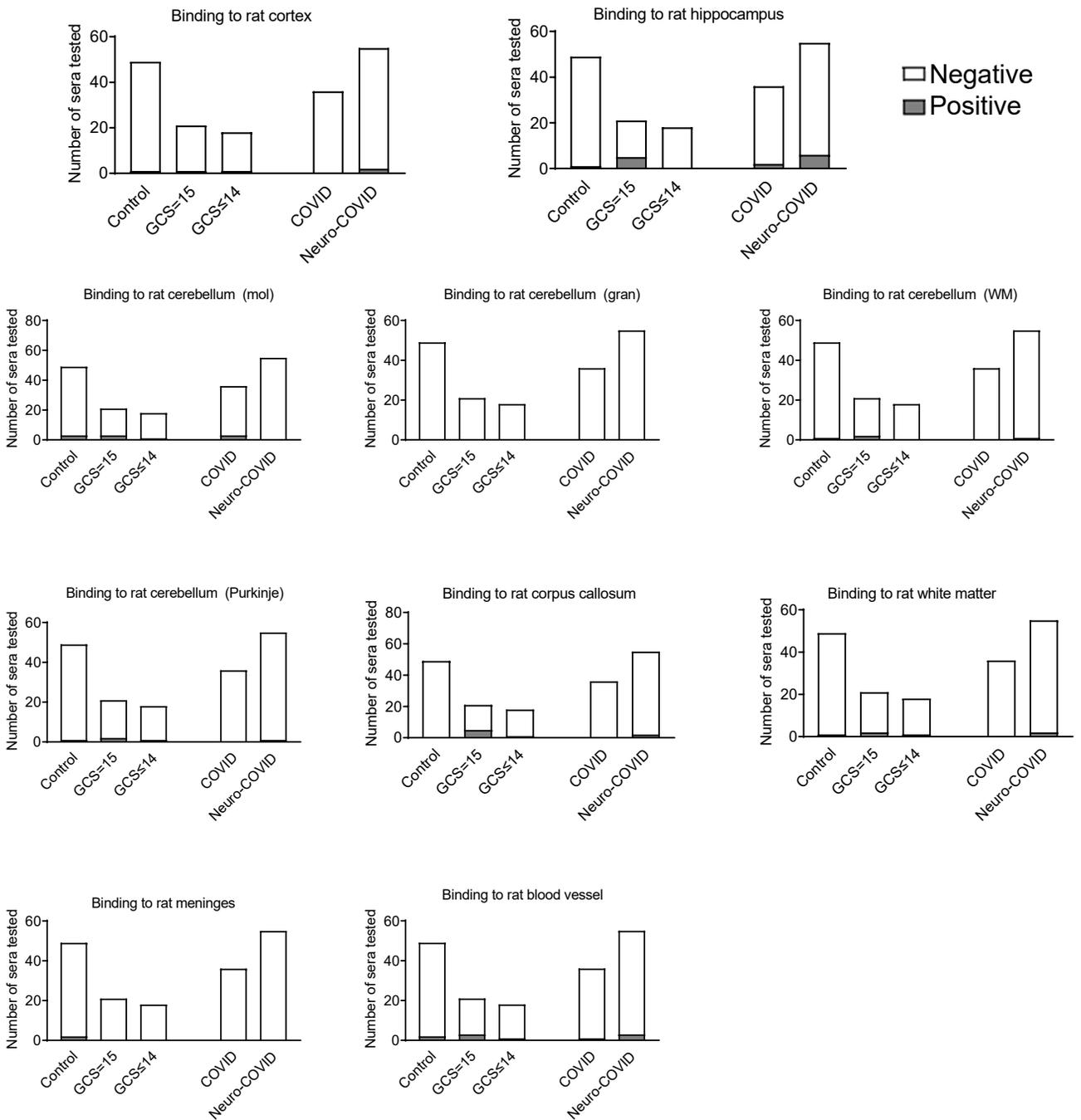
Supplementary Fig. 6: CNS antibody screen

Rat brain reactivity as detected by IHC in sera from ISARIC and COVID-CNS cohorts. The numbers positive were analysed by Fisher's exact test with Benjamini and Hochberg correction. Only binding to brainstem showed significant differences between groups, as shown in main text Fig. 3.

a

Negative control

b

ISARIC positive serum
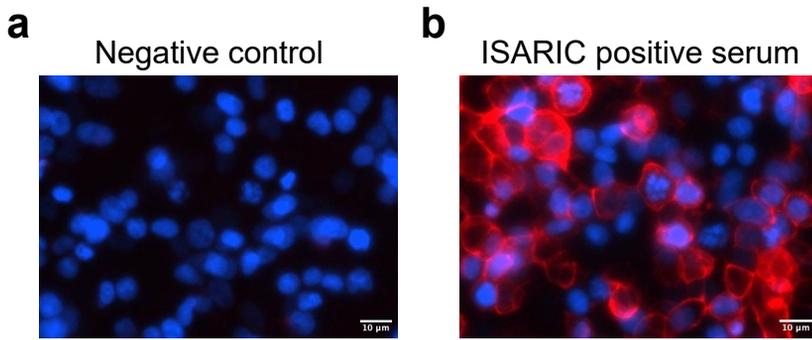
Supplementary Fig. 7: CNS autoantibody screen by cell-based assay
Serum samples selected from the rat brain reactive screen were checked for specific autoantibodies (LGI1, CASPR2, NMDAR, and GABA$_B$ receptor). Shown here is the (a) negative control and the (b) ISARIC cohort participant sample that was positive for GABA$_B$ receptor antibodies