
Depression: higher temporal variability of the functional connectivity of the ventromedial prefrontal cortex and hippocampal system

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Supplementary Material

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S1. Modified ordering of the Human Connectome Project MultiModal Parcellation atlas (HCP-MMP)

The atlas used to define human cortical regions was the HCP-MMP surface-based atlas (Glasser et al., 2016), illustrated in Figs. 3, 4 and S1. In the HCP-MMP atlas, each region has its RegionID, which we show in Table S1. Detailed information about the regions is available in the Supplementary Material File NIHMS68870-supplement-Neuroanatomical_Supplementary_Results.pdf provided by Glasser et al (2016). In that Supplementary Material file, a grouping of the regions is suggested based on geographic proximity and functional similarities, and this grouping is shown in the column labelled CortexID in Table S1. That has led to a different ordering of the regions, which we show in Table S1, with the original regionIDs from the HCP atlas shown in the column headed 'regionID'. This reordered version of the HCP-MMP atlas is described by Dr Dianne Patterson of the University of Arizona at <https://neuroimaging-core-docs.readthedocs.io/en/latest/pages/atlasses.html>, where the following supporting files used to help generate Table S1 are available: HCP-MMP_UniqueRegionList.csv and Glasser_2016_Table.xlsx. We made file HCPMMP_CortexID_Ordering.xlsx from this, and this is available from the present authors. The connectivity matrices shown in the present paper used the ordering shown in Table S1, which is also used in the volumetric and extended form of this atlas (Huang et al., 2022).

Table S1. Regions defined in the modified Human Connectome Project atlas (Glasser et al., 2016). L=left hemisphere, R=right. The column ‘Reordered region ID’ is that used in this paper, and is a reordering of that based on suggestions in the Supplementary Information of Glasser et al (2016). In that Supplementary Information of that paper, the 360 regions are grouped based on geographic proximity and functional similarities, which was reorganized and provided by Dr Dianne Patterson of the University of Arizona at <https://neuroimaging-core-docs.readthedocs.io/en/latest/pages/atlas.html> with the HCP-MMP_UniqueRegionList.csv and is shown in the column labelled CortexID in Table S1. The volumes are in mm³. This modified and extended atlas with the reordering is described elsewhere (Huang et al., 2022).

Reordered ID (L, R)	Region	RegionLongName	Cortical Division	Cortex ID	Original ID	Voxel numbers (1mm ³) (L,R)
1, 181	V1	Primary_Visual_Cortex	Primary_Visual	1	1	13812, 13406
2, 182	V2	Second_Visual_Area	Early_Visual	2	4	9515, 9420
3, 183	V3	Third_Visual_Area	Early_Visual	2	5	7106, 7481
4, 184	V4	Fourth_Visual_Area	Early_Visual	2	6	4782, 4537
5, 185	IPS1	IntraParietal_Sulcus_Area_1	Dorsal_Stream_Visual	3	17	1751, 1750
6, 186	V3A	Area_V3A	Dorsal_Stream_Visual	3	13	2191, 2212
7, 187	V3B	Area_V3B	Dorsal_Stream_Visual	3	19	639, 731
8, 188	V6	Sixth_Visual_Area	Dorsal_Stream_Visual	3	3	1402, 1559
9, 189	V6A	Area_V6A	Dorsal_Stream_Visual	3	152	904, 734
10, 190	V7	Seventh_Visual_Area	Dorsal_Stream_Visual	3	16	1005, 1041
11, 191	FFC	Fusiform_Face_Complex	Ventral_Stream_Visual	4	18	3848, 4402
12, 192	PIT	Posterior_InferoTemporal_complex	Ventral_Stream_Visual	4	22	1392, 1386
13, 193	V8	Eighth_Visual_Area	Ventral_Stream_Visual	4	7	1361, 1175
14, 194	VMV1	VentroMedial_Visual_Area_1	Ventral_Stream_Visual	4	153	939, 1219
15, 195	VMV2	VentroMedial_Visual_Area_2	Ventral_Stream_Visual	4	160	639, 923
16, 196	VMV3	VentroMedial_Visual_Area_3	Ventral_Stream_Visual	4	154	941, 1242
17, 197	VVC	Ventral_Visual_Complex	Ventral_Stream_Visual	4	163	2487, 2753
18, 198	FST	Area_FST	MT+_Complex	5	157	1324, 1683
19, 199	LO1	Area_Lateral_Occipital_1	MT+_Complex	5	20	619, 909
20, 200	LO2	Area_Lateral_Occipital_2	MT+_Complex	5	21	1179, 1062
21, 201	LO3	Area_Lateral_Occipital_3	MT+_Complex	5	159	438, 915
22, 202	MST	Medial_Superior_Temporal_Area	MT+_Complex	5	2	794, 1036
23, 203	MT	Middle_Temporal_Area	MT+_Complex	5	23	620, 1005
24, 204	PH	Area_PH	MT+_Complex	5	138	3453, 3205
25, 205	V3CD	Area_V3CD	MT+_Complex	5	158	876, 1222
26, 206	V4t	Area_V4t	MT+_Complex	5	156	1037, 1249
27, 207	1	Area_1	SomaSens_Motor	6	51	6590, 5925
28, 208	2	Area_2	SomaSens_Motor	6	52	4278, 4727
29, 209	3a	Area_3a	SomaSens_Motor	6	53	2247, 2286
30, 210	3b	Primary_Sensory_Cortex	SomaSens_Motor	6	9	5451, 4350
31, 211	4	Primary_Motor_Cortex	SomaSens_Motor	6	8	10776, 10254
32, 212	23c	Area_23c	ParaCentral_MidCing	7	38	2259, 2498
33, 213	24dd	Dorsal_Area_24d	ParaCentral_MidCing	7	40	2665, 2820
34, 214	24dv	Ventral_Area_24d	ParaCentral_MidCing	7	41	1076, 1349
35, 215	5L	Area_5L	ParaCentral_MidCing	7	39	2249, 2327
36, 216	5m	Area_5m	ParaCentral_MidCing	7	36	1483, 2079

37, 217	5mv	Area_5m_ventral	ParaCentral_MidCing	7	37	1651, 1996
38, 218	6ma	Area_6m_anterior	ParaCentral_MidCing	7	44	3941, 4251
39, 219	6mp	Area_6mp	ParaCentral_MidCing	7	55	3701, 3105
40, 220	SCEF	Supplementary_and_Cingulate_Eye_Field	ParaCentral_MidCing	7	43	3500, 3371
41, 221	55b	Area_55b	Premotor	8	12	2422, 1537
42, 222	6a	Area_6_anterior	Premotor	8	96	4233, 3752
43, 223	6d	Dorsal_area_6	Premotor	8	54	2916, 2909
44, 224	6r	Rostral_Area_6	Premotor	8	78	3029, 3981
45, 225	6v	Ventral_Area_6	Premotor	8	56	2075, 2516
46, 226	FEF	Frontal_Eye_Fields	Premotor	8	10	1787, 1889
47, 227	PEF	Premotor_Eye_Field	Premotor	8	11	1006, 1258
48, 228	43	Area_43	Posterior_Opercular	9	99	1889, 1678
49, 229	FOP1	Frontal_Opercular_Area_1	Posterior_Opercular	9	113	879, 932
50, 230	OP1	Area_OP1-SII	Posterior_Opercular	9	101	1275, 1072
51, 231	OP2-3	Area_OP2-3-VS	Posterior_Opercular	9	102	943, 792
52, 232	OP4	Area_OP4-PV	Posterior_Opercular	9	100	2332, 2409
53, 233	52	Area_52	Early_Auditory	10	103	725, 580
54, 234	A1	Primary_Auditory_Cortex	Early_Auditory	10	24	1023, 796
55, 235	LBelt	Lateral_Belt_Complex	Early_Auditory	10	174	820, 901
56, 236	MBelt	Medial_Belt_Complex	Early_Auditory	10	173	1242, 1236
57, 237	PBelt	ParaBelt_Complex	Early_Auditory	10	124	1719, 1439
58, 238	PFcm	Area_PFcm	Early_Auditory	10	105	1486, 1485
59, 239	RI	RetroInsular_Cortex	Early_Auditory	10	104	1149, 1334
60, 240	A4	Auditory_4_Complex	Auditory_Association	11	175	3514, 3610
61, 241	A5	Auditory_5_Complex	Auditory_Association	11	125	3346, 3881
62, 242	STGa	Area_STGa	Auditory_Association	11	123	2509, 2187
63, 243	STSda	Area_STSd_anterior	Auditory_Association	11	128	1944, 2389
64, 244	STSdp	Area_STSd_posterior	Auditory_Association	11	129	1994, 2605
65, 245	STSva	Area_STSv_anterior	Auditory_Association	11	176	1694, 1900
66, 246	STSvp	Area_STSv_posterior	Auditory_Association	11	130	2898, 2515
67, 247	TA2	Area_TA2	Auditory_Association	11	107	1518, 1726
68, 248	AAIC	Anterior_Agranular_Insula_Complex	Insula_FrontalOperc	12	112	1859, 1691
69, 249	AVI	Anterior_Ventral_Insular_Area	Insula_FrontalOperc	12	111	1446, 1792
70, 250	FOP2	Frontal_Opercular_Area_2	Insula_FrontalOperc	12	115	750, 720
71, 251	FOP3	Frontal_Opercular_Area_3	Insula_FrontalOperc	12	114	754, 614
72, 252	FOP4	Frontal_Opercular_Area_4	Insula_FrontalOperc	12	108	2522, 1678
73, 253	FOP5	Area_Frontal_Opercular_5	Insula_FrontalOperc	12	169	1297, 1365
74, 254	Ig	Insular_Granular_Complex	Insula_FrontalOperc	12	168	841, 1077
75, 255	MI	Middle_Insular_Area	Insula_FrontalOperc	12	109	2102, 1960
76, 256	PI	Para-Insular_Area	Insula_FrontalOperc	12	178	1033, 1058
77, 257	Pir	Piriform_Cortex	Insula_FrontalOperc	12	110	2287, 1856
78, 258	Pol1	Area_Posterior_Insular_1	Insula_FrontalOperc	12	167	1811, 1835
79, 259	Pol2	Posterior_Insular_Area_2	Insula_FrontalOperc	12	106	2747, 2675
80, 260	H	Hippocampus	Medial_Temporal	13	120	4283, 3626
81, 261	PreS	PreSubiculum	Medial_Temporal	13	119	1817, 1558
82, 262	EC	Entorhinal_Cortex	Medial_Temporal	13	118	2127, 2110
83, 263	PeEc	Perirhinal_Ectorhinal_Cortex	Medial_Temporal	13	122	4826, 4755

84, 264	TF	Area_TF	Medial_Temporal	13	135	3986, 4752
85, 265	PHA1	ParaHippocampal_Area_1	Medial_Temporal	13	126	1281, 1168
86, 266	PHA2	ParaHippocampal_Area_2	Medial_Temporal	13	155	783, 771
87, 267	PHA3	ParaHippocampal_Area_3	Medial_Temporal	13	127	2023, 1122
88, 268	PHT	Area_PHT	Lateral_Temporal	14	137	4182, 3410
89, 269	TE1a	Area_TE1_anterior	Lateral_Temporal	14	132	5227, 4180
90, 270	TE1m	Area_TE1_Middle	Lateral_Temporal	14	177	3339, 3429
91, 271	TE1p	Area_TE1_posterior	Lateral_Temporal	14	133	7116, 6010
92, 272	TE2a	Area_TE2_anterior	Lateral_Temporal	14	134	5691, 5753
93, 273	TE2p	Area_TE2_posterior	Lateral_Temporal	14	136	4115, 3040
94, 274	TGd	Area_TG_dorsal	Lateral_Temporal	14	131	10192, 10269
95, 275	TGv	Area_TG_Ventral	Lateral_Temporal	14	172	3694, 4515
96, 276	PSL	PeriSylvian_Language_Area	TPO	15	25	2154, 2759
97, 277	STV	Superior_Temporal_Visual_Area	TPO	15	28	2322, 2294
98, 278	TPOJ1	Area_TemporoParietoOccipital_Juncti on_1	TPO	15	139	2102, 3938
99, 279	TPOJ2	Area_TemporoParietoOccipital_Juncti on_2	TPO	15	140	1930, 2068
100, 280	TPOJ3	Area_TemporoParietoOccipital_Juncti on_3	TPO	15	141	1290, 1277
101, 281	7AL	Lateral_Area_7A	Superior_Parietal	16	42	2134, 2030
102, 282	7Am	Medial_Area_7A	Superior_Parietal	16	45	2995, 2379
103, 283	7PC	Area_7PC	Superior_Parietal	16	47	3151, 3415
104, 284	7PL	Lateral_Area_7P	Superior_Parietal	16	46	1695, 1363
105, 285	7Pm	Medial_Area_7P	Superior_Parietal	16	29	1601, 1308
106, 286	AIP	Anterior_IntraParietal_Area	Superior_Parietal	16	117	1999, 2542
107, 287	LIPd	Area_Lateral_IntraParietal_dorsal	Superior_Parietal	16	95	1008, 869
108, 288	LIPv	Area_Lateral_IntraParietal_ventral	Superior_Parietal	16	48	1681, 1783
109, 289	MIP	Medial_IntraParietal_Area	Superior_Parietal	16	50	1872, 2403
110, 290	VIP	Ventral_IntraParietal_Complex	Superior_Parietal	16	49	1890, 1577
111, 291	IP0	Area_IntraParietal_0	Inferior_Parietal	17	146	1203, 1239
112, 292	IP1	Area_IntraParietal_1	Inferior_Parietal	17	145	1692, 1632
113, 293	IP2	Area_IntraParietal_2	Inferior_Parietal	17	144	2102, 1861
114, 294	PF	Area_PF_Complex	Inferior_Parietal	17	148	5457, 5251
115, 295	PFm	Area_PFm_Complex	Inferior_Parietal	17	149	8220, 8141
116, 296	PFop	Area_PF_Opercular	Inferior_Parietal	17	147	1797, 1783
117, 297	PFt	Area_PFt	Inferior_Parietal	17	116	1983, 2039
118, 298	PGi	Area_PGi	Inferior_Parietal	17	150	4791, 4970
119, 299	PGp	Area_PGp	Inferior_Parietal	17	143	2501, 3740
120, 300	PGs	Area_PGs	Inferior_Parietal	17	151	4552, 3366
121, 301	23d	Area_23d	Posterior_Cingulate	18	32	1261, 1513
122, 302	31a	Area_31a	Posterior_Cingulate	18	162	1260, 1116
123, 303	31pd	Area_31pd	Posterior_Cingulate	18	161	1428, 864
124, 304	31pv	Area_31p_ventral	Posterior_Cingulate	18	35	950, 1022
125, 305	7m	Area_7m	Posterior_Cingulate	18	30	2128, 2067
126, 306	d23ab	Area_dorsal_23_a+b	Posterior_Cingulate	18	34	1607, 1106
127, 307	DVT	Dorsal_Transitional_Visual_Area	Posterior_Cingulate	18	142	1806, 2176
128, 308	PCV	PreCuneus_Visual_Area	Posterior_Cingulate	18	27	2245, 2416
129, 309	POS1	Parieto-Occipital_Sulcus_Area_1	Posterior_Cingulate	18	31	2531, 2727

130, 310	POS2	Parieto-Occipital_Sulcus_Area_2	Posterior_Cingulate	18	15	3261, 3093
131, 311	ProS	ProStriate_Area	Posterior_Cingulate	18	121	1222, 1055
132, 312	RSC	RetroSplenial_Complex	Posterior_Cingulate	18	14	2830, 3067
133, 313	v23ab	Area_ventral_23_a+b	Posterior_Cingulate	18	33	916, 1089
134, 314	10r	Area_10r	AntCing_MedPFC	19	65	1589, 1053
135, 315	10v	Area_10v	AntCing_MedPFC	19	88	3906, 2667
136, 316	25	Area_25	AntCing_MedPFC	19	164	1911, 2135
137, 317	33pr	Area_33_prime	AntCing_MedPFC	19	58	1354, 1316
138, 318	8BM	Area_8BM	AntCing_MedPFC	19	63	3122, 3436
139, 319	9m	Area_9_Middle	AntCing_MedPFC	19	69	6338, 5881
140, 320	a24	Area_a24	AntCing_MedPFC	19	61	2085, 2152
141, 321	a24pr	Anterior_24_prime	AntCing_MedPFC	19	59	1095, 1474
142, 322	a32pr	Area_anterior_32_prime	AntCing_MedPFC	19	179	1759, 1118
143, 323	d32	Area_dorsal_32	AntCing_MedPFC	19	62	2228, 2374
144, 324	p24	Area_posterior_24	AntCing_MedPFC	19	180	2394, 2442
145, 325	p24pr	Area_Posterior_24_prime	AntCing_MedPFC	19	57	1422, 1724
146, 326	p32	Area_p32	AntCing_MedPFC	19	64	1180, 1765
147, 327	p32pr	Area_p32_prime	AntCing_MedPFC	19	60	1569, 1305
148, 328	pOFC	Posterior_OFC_Complex	AntCing_MedPFC	19	166	2486, 2836
149, 329	s32	Area_s32	AntCing_MedPFC	19	165	604, 1015
150, 330	10d	Area_10d	OrbPolaFrontal	20	72	3644, 3096
151, 331	10pp	Polar_10p	OrbPolaFrontal	20	90	1997, 2487
152, 332	11l	Area_11l	OrbPolaFrontal	20	91	3531, 3793
153, 333	13l	Area_13l	OrbPolaFrontal	20	92	2429, 1757
154, 334	47m	Area_47m	OrbPolaFrontal	20	66	799, 781
155, 335	47s	Area_47s	OrbPolaFrontal	20	94	2795, 3080
156, 336	a10p	Area_anterior_10p	OrbPolaFrontal	20	89	1964, 1748
157, 337	OFC	Orbital_Frontal_Complex	OrbPolaFrontal	20	93	4560, 5232
158, 338	p10p	Area_posterior_10p	OrbPolaFrontal	20	170	2116, 2365
159, 339	44	Area_44	Inferior_Frontal	21	74	2435, 2589
160, 340	45	Area_45	Inferior_Frontal	21	75	3762, 2962
161, 341	47l	Area_47l_(47_lateral)	Inferior_Frontal	21	76	2527, 2592
162, 342	a47r	Area_anterior_47r	Inferior_Frontal	21	77	4167, 3763
163, 343	IFJa	Area_IFJa	Inferior_Frontal	21	79	1513, 1405
164, 344	IFJp	Area_IFJp	Inferior_Frontal	21	80	960, 740
165, 345	IFSa	Area_IFSa	Inferior_Frontal	21	82	2057, 2641
166, 346	IFSp	Area_IFSp	Inferior_Frontal	21	81	1589, 1730
167, 347	p47r	Area_posterior_47r	Inferior_Frontal	21	171	2133, 1761
168, 348	46	Area_46	Dorsolateral_Prefrontal	22	84	4863, 4394
169, 349	8Ad	Area_8Ad	Dorsolateral_Prefrontal	22	68	3386, 3492
170, 350	8Av	Area_8Av	Dorsolateral_Prefrontal	22	67	4807, 5902
171, 351	8BL	Area_8B_Lateral	Dorsolateral_Prefrontal	22	70	3377, 4078
172, 352	8C	Area_8C	Dorsolateral_Prefrontal	22	73	4085, 3134
173, 353	9-46d	Area_9-46d	Dorsolateral_Prefrontal	22	86	4534, 4666
174, 354	9a	Area_9_anterior	Dorsolateral_Prefrontal	22	87	3706, 3048
175, 355	9p	Area_9_Posterior	Dorsolateral_Prefrontal	22	71	3426, 2488
176, 356	a9-46v	Area_anterior_9-46v	Dorsolateral_Prefrontal	22	85	3314, 2628

177, 357	i6-8	Inferior_6-8_Transitional_Area	Dorsolateral_Prefrontal	22	97	1764, 2418
178, 358	p9-46v	Area_posterior_9-46v	Dorsolateral_Prefrontal	22	83	2871, 4635
179, 359	s6-8	Superior_6-8_Transitional_Area	Dorsolateral_Prefrontal	22	98	1336, 2132
180, 360	SFL	Superior_Frontal_Language_Area	Dorsolateral_Prefrontal	22	26	3873, 3055

Column 1 (Reordered ID) shows the order in HCPex based on the HCP-MMP1_UniqueRegionList.csv, as described in the Methods, of the 360 cortical regions originally defined by Glasser et al (2016). The names of the cortical divisions shown in column 4 come from the same .csv file. The sixth column shows the original order used by Glasser et al (2016). Abbreviations: L=left hemisphere, R=right. MT+_Complex, MT+_Complex_and_Neighboring_Visual_Areas; SomaSens_Motor, Somatosensory_and_Motor; ParaCentral_MidCing, Paracentral_Lobular_and_Mid_Cingulate; Insula_FrontalOperc, Insular_and_Frontal_Opercular; TPO, Temporo-Parieto-Occipital_Junction; AntCing_MedPFC, Anterior_Cingulate_and_Medial_Prefrontal; OrbPolaFrontal, Orbital_and_Polar_Frontal.

Fig. S1-1. Example coronal slices showing regions defined in the HCPex atlas and added subcortical regions (Huang et al., 2022). The abbreviations are as in Table S1. The y values for the coronal slices are in MNI coordinates.

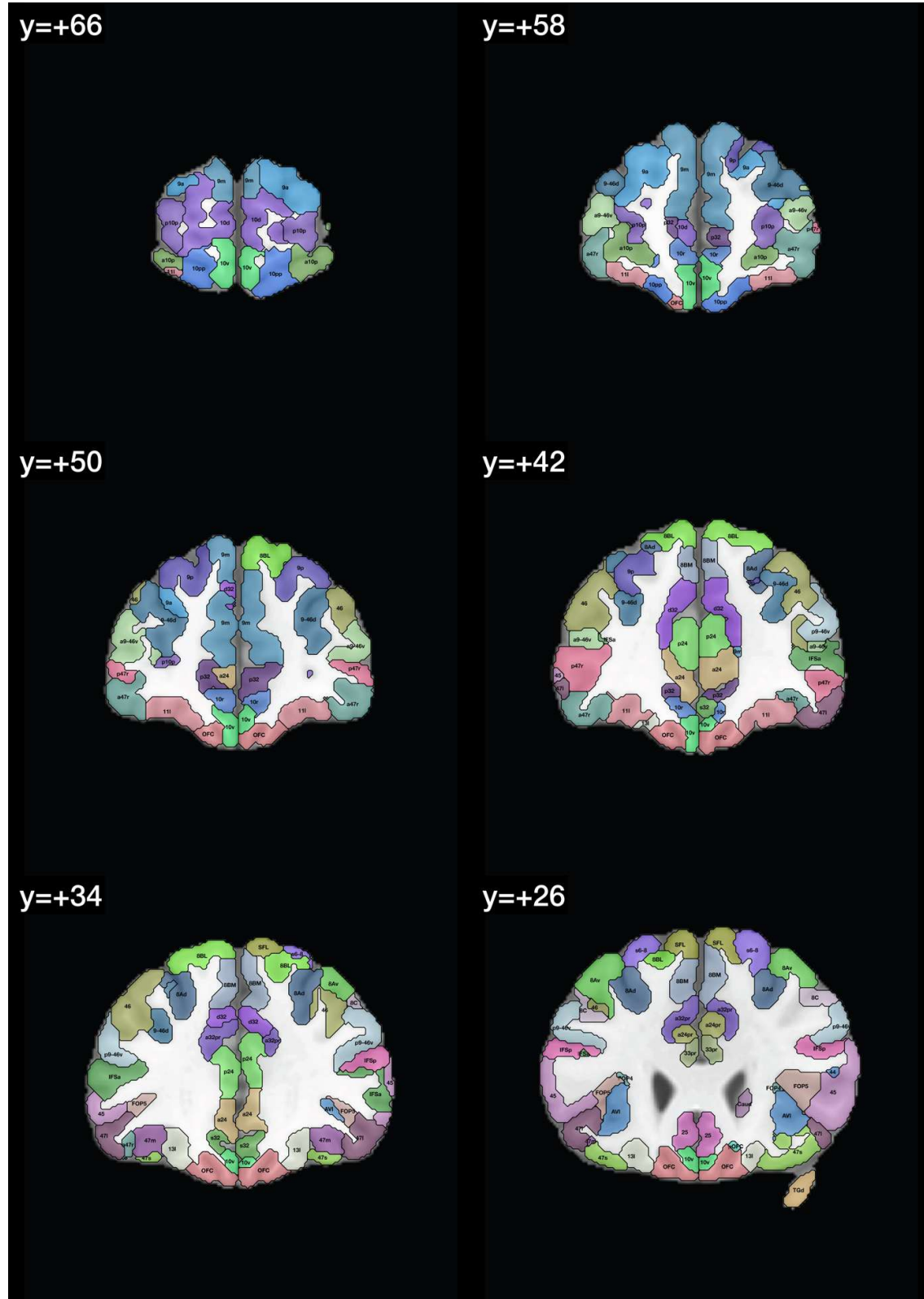


Fig. S1-2. Example coronal slices showing regions defined in the HCPex atlas and added subcortical regions (Huang et al., 2022). The abbreviations are as in Table S1. The y values for the coronal slices are in MNI coordinates.

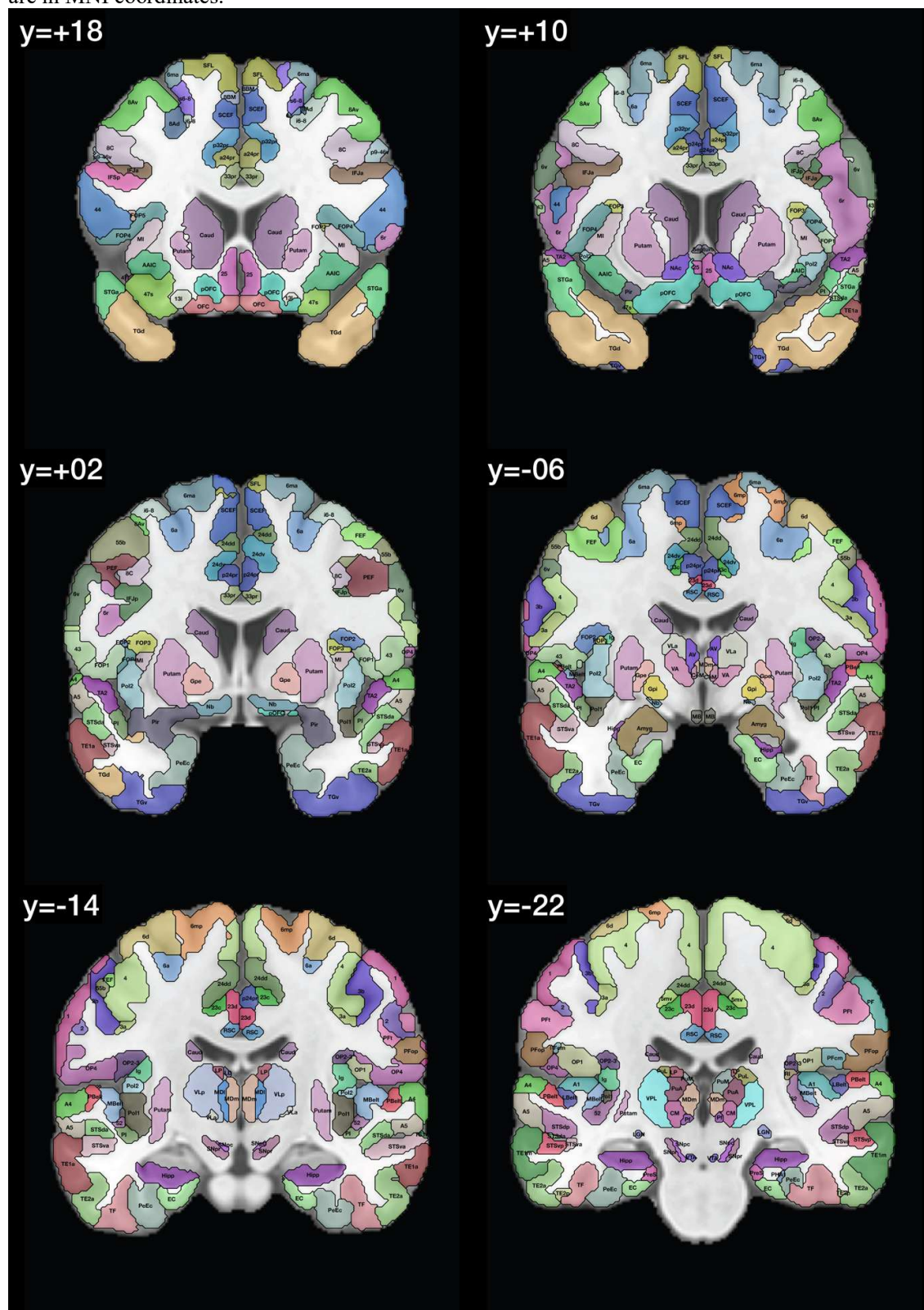


Fig. S1-3. Example coronal slices showing regions defined in the HCPex atlas and added subcortical regions (Huang et al., 2022). The abbreviations are as in Table S1. The y values for the coronal slices are in MNI coordinates.

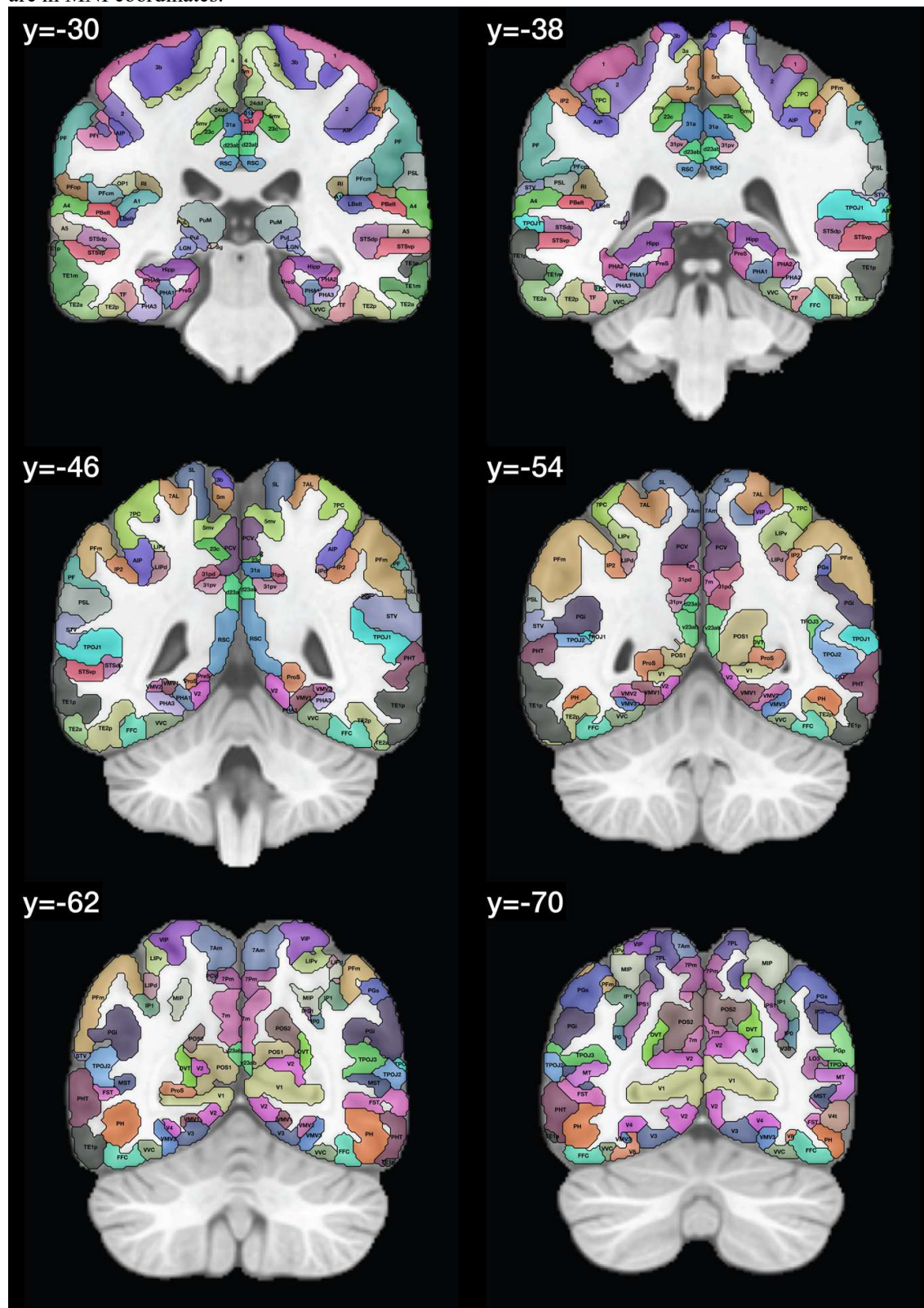
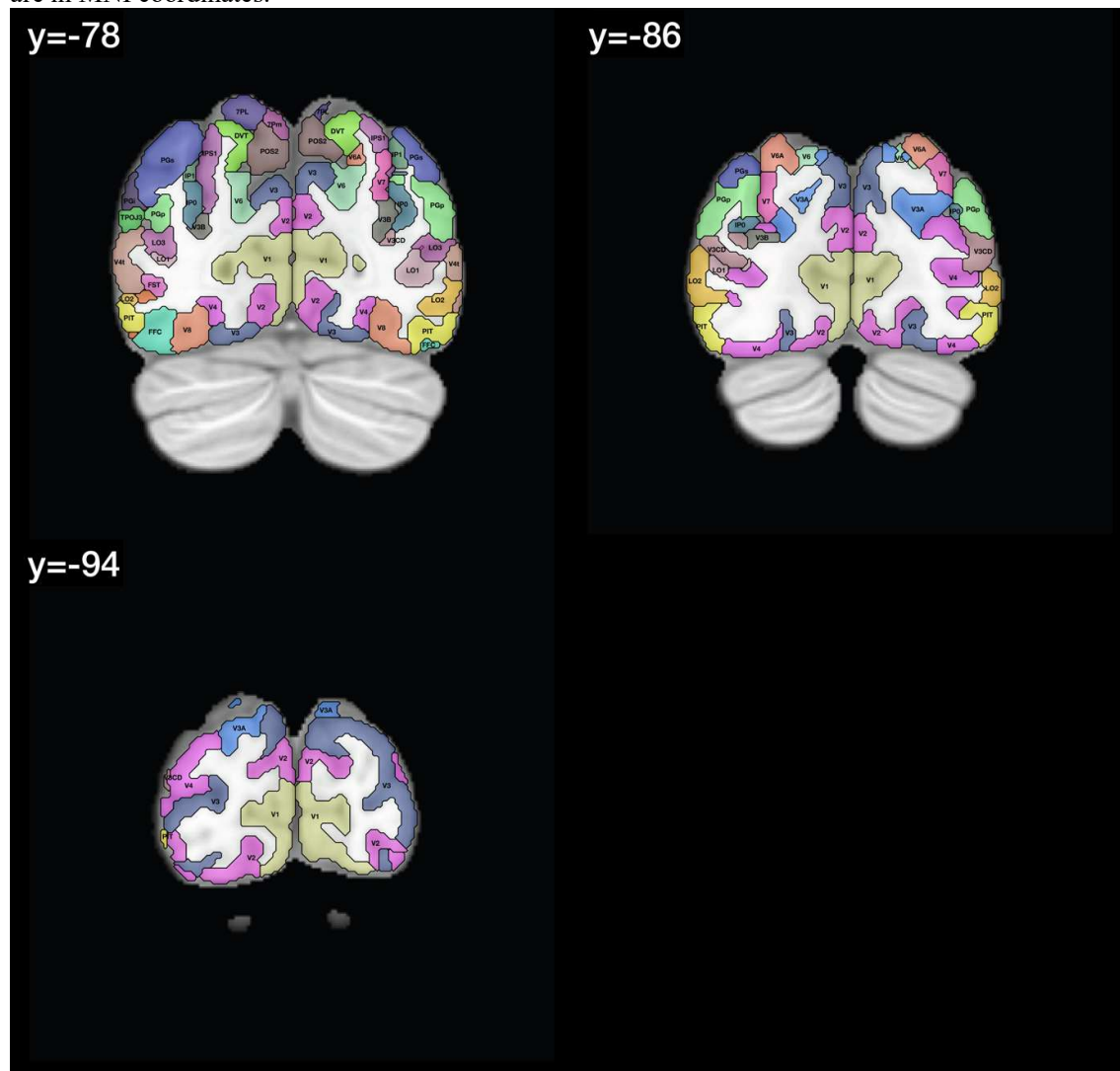
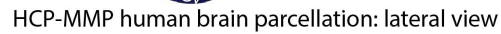


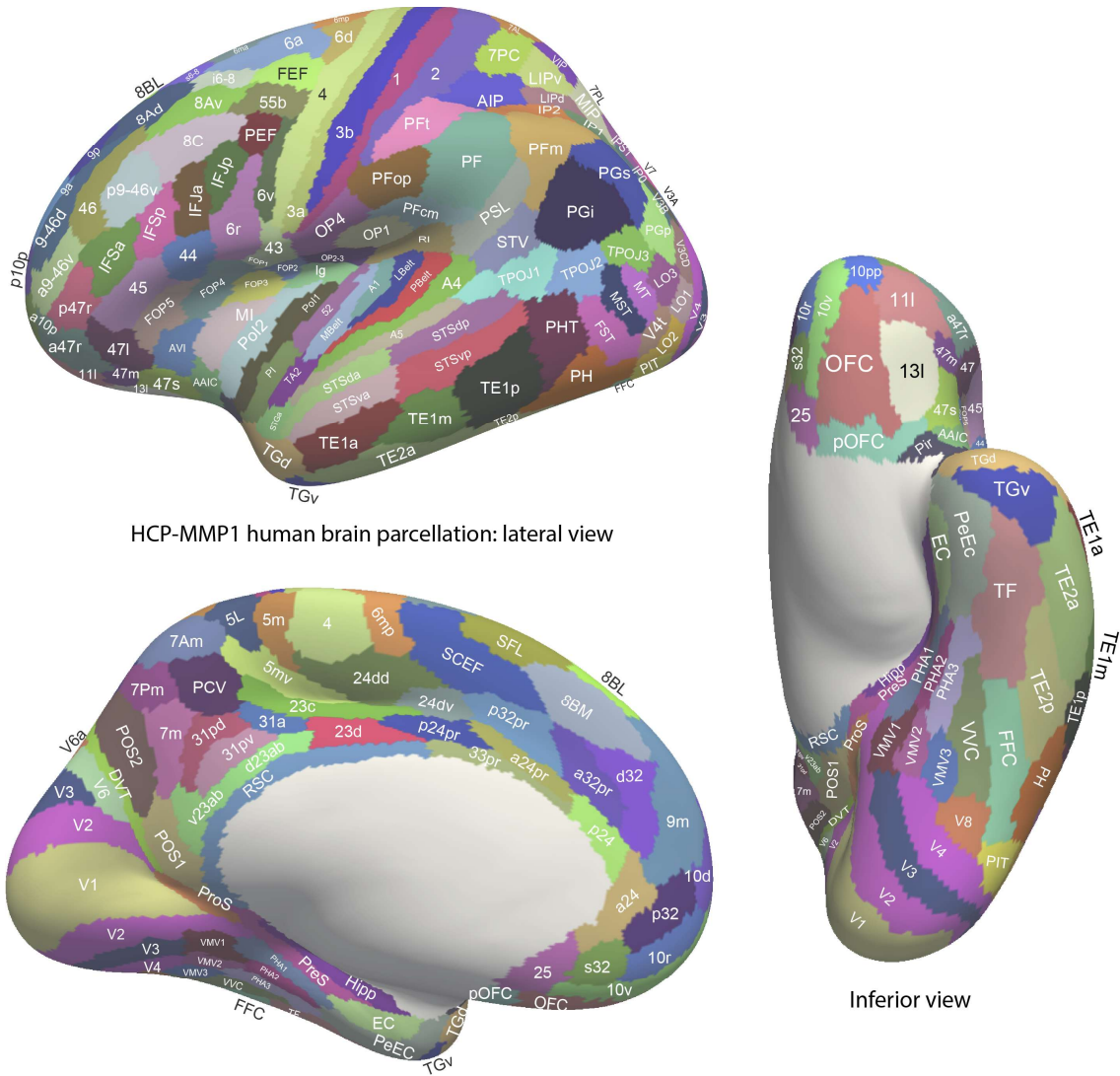
Fig. S1-4. Example coronal slices showing regions defined in the HCPex atlas and added subcortical regions (Huang et al., 2022). The abbreviations are as in Table S1. The y values for the coronal slices are in MNI coordinates.





HCP-MMP human brain parcellation: medial view

Fig. S1-5. Anatomical regions of the human visual and other cortical regions. Regions are shown as defined in the HCP-MMP atlas (Glasser et al., 2016), and in its extended version HCPex (Huang et al., 2022). The regions are shown on images of the human brain without the sulci expanded to show which cortical HCP-MMP regions are normally visible, for comparison with Fig. 1. (The ICBM153 MNI T1 image was used to prepare this figure.) Abbreviations are provided in Table S1.



S2. Diffusion Tractography for Streamline Number and Fractional Anisotropy

Diffusion-weighted images were obtained with the following parameters: repetition time (TR) = 9400 ms; echo time (TE) = 89.0 ms; field of view (FOV) = 256×256 mm²; matrix size = 122×122 ; slice thickness = 2.0 mm; slice number = 70; and b-values of 0/1000 s/mm². Diffusion MRI data were collected with reverse phase-encoding pairs (anterior-posterior [AP] and posterior-anterior [PA]). The AP acquisition included 64 diffusion-weighted directions and 5 b0 images, and the reverse PA acquisition included 6 diffusion directions and 5 b0 images. The PA b0 images were used for susceptibility distortion correction.

A Multi-Shell Multi-Tissue Constrained Spherical Deconvolution (MSMT-CSD) combined with anatomically constrained tractography (ACT) was performed to reconstruct fibre orientation distribution (FOD) using the iFOD2 method. A dynamic seeding algorithm was employed, generating 20 million streamlines (maximum tract length = 250 mm, minimal tract length = 5 mm, FOD amplitude = 0.05, curve angle = 45°) (Smith et al., 2015; Tournier et al., 2010). The registered 5t image was used as prior biological information to ensure that the streamlines terminated at the GM-WM interface (Smith et al., 2012). To improve the estimation of structural connection density and to reduce false-positive streamlines, the spherical-deconvolution informed filtering of tractography (SIFT) was then applied, resulting in 2 million streamlines per participant (Smith et al., 2013). Further details are in the Supplementary Material. Because we wished to measure the Connection Distance (CD) of the streamlines between pairs of cortical regions, the SIFT2 algorithm that we used in our previous work (Huang et al., 2021) was not considered. SIFT2 weights down the streamlines' connection densities rather than eliminating streamlines likely to be false positive based on FOD. Thus, this approach is not applicable in the case when calculating average fiber length; therefore, we used a slightly different method, as in Yu et al (2025). The correlation between the two methods for the number of streamlines was 0.98, showing excellent consistency. Structural connectomes were generated based on the HCPex atlas, which contains 360 cortical regions and 66 subcortical regions. The atlas was transformed into DWI native space. The number of streamlines between each pair of brain regions were measured, producing two 426 x 426 matrices for each individual.

For the DTI dataset, a total of 434 participants had diffusion data available with both AP and PA directions and successfully completed preprocessing. After applying a mean head motion threshold of 2, 20 subjects were excluded, leaving 414 subjects in total (HC: 235; MDD: 179). The HCPex parcellation (Huang et al., 2022) was used.

For fractional anisotropy, no differences between MDD patients and controls were found.

S3. Reliability analysis for the temporal variability V_k of the functional connectivity.

Because the temporal variability V_k of the functional connectivity was estimated from five non-overlapping windows, a leave-one-window-out analysis was performed to directly evaluate the reliability of the temporal variability estimates. For each participant, temporal variability was recalculated after removing one of the five windows in turn, and the correlation between the original V_k estimate and each leave-one-window-out estimate was calculated across participants. This analysis showed high reproducibility of the temporal variability estimates, with the average ROI-level reliability being $r=0.915$ in the right hemisphere and 0.917 in the left hemisphere. The key regions involved in the main findings also showed high reliability, including right OFC ($r=0.907$), right 10r ($r=0.945$), right 10v ($r=0.945$), right 47l ($r=0.910$), right EC ($r=0.897$), and right hippocampus ($r=0.920$).

S4. Reproducibility of the temporal variability of the functional connectivity results at a longer window length.

If the temporal variability is measured with a window length shorter than the lowest retained component of the timeseries, then that might provide a source of spurious apparent fluctuation in connectivity (Leonardi and Van De Ville, 2015). The data in this investigation were band-pass filtered at 0.01-0.08 Hz, so the slowest retained component has a period of 100 s, whereas the 35-TR window is 87.5 s. Additional analyses were therefore performed with a 40-TR window for which the window is 100 s. In one additional analysis, the participant-averaged 180-ROI temporal-variability vectors were

highly correlated between the 35- and 40-TR windows ($r > 0.997$) in both hemispheres. In further additional analyses, the temporal variability with the 40-TR window length was confirmed to be higher in the MDD group than the HC group for the Anterior Cingulate and Medial Prefrontal Division ($t = 2.39$, $p_{\text{fdr}} = 0.05$) and for the Medial Temporal Division ($t = 2.54$, $p_{\text{fdr}} = 0.05$). In addition, the analyses with a window of 40 TR confirmed that the right key group of cortical regions for emotion and depression (10r, 10v, p32, OFC) showed significantly greater temporal variability in the MDD than the HC group ($t = 2.98$, $p_{\text{fdr}} = 0.009$), and so did the right episodic-memory key group (Hipp, EC, 31pd, 31pv, 7m) ($t = 2.68$, $p_{\text{fdr}} = 0.011$).

S5. Null model for the temporal variability of the functional connectivity using a surrogate-data comparison

To investigate whether the higher temporal variability of the functional connectivity is related to a stationary process with the same static connectivity structure, a participant-specific multivariate phase-randomized surrogate time series was generated. For each participant, the BOLD time series were transformed into the frequency domain, and a common random phase shift was applied to all cortical regions at each frequency. The corresponding conjugate phase was applied to the negative-frequency component to preserve real-valued time series. This procedure preserved the power spectrum of each region and the participant-specific cross-spectral and static FC structure while randomizing the absolute temporal phase organization. A total of 1,000 surrogate realizations were generated. For each realization, temporal variability was recalculated using the same five non-overlapping 35-TR windows and the same analysis pipeline as in the primary analysis. Division-level MDD–HC group comparisons were then repeated using linear models controlling for age, sex, education, and mean FD, producing a stationary null distribution of group t-statistics for each division. Empirical p-values were calculated from the upper and lower tails of each division-specific null distribution.

The analysis confirmed that the measured temporal variability of the functional connectivity in the MDD group was higher than in the HC group when compared to the null surrogate for the most important Division in this investigation as it includes ventromedial prefrontal cortex regions, the Anterior Cingulate and Medial Prefrontal Division ($p = 0.009$). The implication is that the temporal variability of the functional connectivity is higher in this cortical division in the MDD group even compared to what might be expected because of any difference in static functional connectivity. For the other five divisions, the p values were as follows, consistent with the hypothesis that the differences in temporal variability of functional connectivity are somewhat reduced if the differences in static functional connectivity are taken into account: Orbital_and_Polar_Frontal ($p = 0.13$); Medial_Temporal ($p = 0.33$); Inferior_Frontal ($p = 0.13$); Inferior_Parietal ($p = 0.003$); and Auditory_Association ($p = 0.06$). However, as noted in the Introduction, a difference in the temporal variability of the functional connectivity as measured is of interest as it is a dynamic property of the brain even if it is related to some extent to the static functional connectivity.

S6. Removal of the Global Signal was not applied.

Analysis of the data with GSR is not reported in this paper for several reasons. First, the use of GSR is controversial because it leads to difficulties in interpreting negative correlations (Cheng et al., 2016; Gotts et al., 2013; Murphy et al., 2009; Saad et al., 2012) and indeed can introduce artifactual negative and other correlations (Nalci et al., 2017; Saad et al., 2012). Second, it has been shown that the impact of GSR on the temporal variability of functional connectivity is spatially heterogeneous across the brain, with some cortical regions especially affected by the use of GSR (Xu et al., 2018). Third, GSR may obscure differences between patients and other groups that may be important, such as a higher global signal in schizophrenia (Yang et al., 2014). For these reasons, regressing out the GS could reduce the temporal variability effects of interest in this investigation, and obscure some important results in which we find that especially some cortical regions show higher temporal variability in the functional connectivity in depression. For those reasons, it is we believe not appropriate to present the temporal variability of functional connectivity results with GSR in this paper.

However, we note that, as expected given what has just been said, in depression the global signal was a little lower in depression though not significantly so (Welch $t=-1.45$, $df=347$, $p=0.15$), and again consistent with what has just been written, after GSR, the temporal variability of the functional connectivity effects were no longer significant at the division level after correction for multiple comparisons. That is consistent with the other analyses in this paper showing that the higher temporal variability of certain cortical divisions and regions is related, but only in part, to the reduced functional connectivity. In addition, we again emphasise the important point made in the third paragraph of the Introduction that altered temporal variability may or may not be associated with a difference in functional connectivity.

S7. Left-hemisphere results.

Whereas significantly higher temporal variability of the functional connectivity was clearly evident in the right hemisphere for a number of cortical systems including ventromedial prefrontal cortex and medial temporal lobe cortex in the right hemisphere, fewer differences were found in the left hemisphere. At the 35-TR window length, the left-hemisphere analysis of the variability of functional connectivity showed fewer significantly high values in the MDD than the HC group than in the right hemisphere. Significantly higher ($p<0.05$) temporal variability in MDD was found in the Ventral Stream Visual, Medial Temporal, Orbital and Polar Frontal, and Somatosensory and Motor Cortical Divisions, but these differences in the left hemisphere were no significant after FDR correction. At the individual-region level, 15 regions showed significantly higher temporal variability in the FC in MDD—Ig, FFC, 7AL, OP2–3, 5L, 6ma, PHA3, VVC, PHA1, TE2p, 3a, 10v, VMV2, 3b, and A5, but these were not significant after FDR correction for multiple comparisons across the 180 left-hemisphere regions. Of the three predefined composite measures, the hippocampal spatial-input composite comprising VMV1–3, VVC, and PHA1–3 showed significantly higher temporal variability in MDD ($t(403)=2.53$, $p=0.012$) in the left hemisphere.

S8. Further evidence that differences in residual transient head motion did not account for the higher temporal variability of the functional connectivity in the MDD (depression) group compared to the control group (HC).

To assess whether residual transient head motion accounted for the temporal variability findings, volume-wise framewise displacement (FD) and DVARS were calculated for each participant. (DVARS is calculated as the root mean square across voxels of the change in the BOLD signal intensity between successive volumes in the BOLD signal intensity timeseries.) In addition to mean FD, the number and proportion of high-motion volumes using FD thresholds of 0.2 and 0.3 mm were quantified, as well as mean DVARS and the number and proportion of DVARS outlier volumes. These motion measures were compared between MDD and HC groups. As an additional sensitivity analysis, the primary temporal variability analysis was repeated after applying a more stringent participant-level exclusion criterion of mean $FD < 0.2$ mm, compared with the original threshold of 0.3 mm.

Transient-motion measures did not indicate greater motion contamination in the MDD group. The number and proportion of high-FD volumes did not differ significantly between groups at either the 0.2- or 0.3-mm threshold, and the number and proportion of DVARS outliers were also comparable between groups. Mean DVARS was slightly lower in MDD than HC (22.72 ± 3.58 vs. 23.23 ± 3.15 ; $t = -2.72$, $p = 0.048$). Further, with a strict mean $FD < 0.2$ mm exclusion criterion, all six right-hemisphere divisions identified in the primary analysis remained significant after FDR correction (all $p_{\text{fdr}} \leq 0.05$). (Again, no significant division-level effects were detected in the left hemisphere after correction for multiple comparisons.) These findings indicate that the primary right-hemisphere temporal variability effects were robust to stricter participant-level motion exclusion.

S9. Education as a covariate.

Given the somewhat lower educational attainment in the MDD group (Table 1) and the possibility that the educational difference may partly reflect consequences of illness in this young first-

episode cohort, a sensitivity analysis was performed in which education was omitted from the covariate set. The main temporal variability of functional connectivity analyses were therefore repeated using a model including group, age, sex, and mean FD as predictors, and the results were compared with those from the original model additionally including education. This sensitivity analysis was performed at the cortical ROI, division, and post hoc composite levels.

The main temporal variability of functional connectivity findings were robust to exclusion of education from the covariate set. All six right-hemisphere divisions that were significant in the original analysis remained significant after FDR correction when education was omitted as a covariate, with generally increased statistical strength: Anterior_Cingulate_and_Medial_Prefrontal ($t = 2.72$, $p_{\text{fdr}} = 0.023$); Orbital_and_Polar_Frontal ($t = 2.70$, $p_{\text{fdr}} = 0.023$); Medial_Temporal ($t = 2.77$, $p_{\text{fdr}} = 0.023$); Inferior_Frontal ($t = 2.74$, $p_{\text{fdr}} = 0.023$); Inferior_Parietal ($t = 2.56$, $p_{\text{fdr}} = 0.029$), and Auditory_Association ($t = 3.10$, $p_{\text{fdr}} = 0.023$). The right-hemisphere vmPFC/OFC, episodic-memory, and hippocampal ventral visual stream spatial-input composites were all significant after education was omitted as a covariate. As before, no division-level effect survived FDR correction in the left hemisphere. These results indicate that the principal right-hemisphere temporal variability of functional connectivity findings are not dependent on adjustment for educational attainment.

S10. Correlations of the temporal variability of the functional connectivity with the symptoms.

Within the MDD group, associations between temporal variability at the ROI, cortical-division, and prespecified composite levels and the HAM-D-17 total and item scores and BDI-21 total and item scores were tested using separate linear regression models adjusted for age, sex, education, and mean FD. For each model, the temporal-variability of functional connectivity effect was summarized using the t-statistic, and p-value. Benjamini–Hochberg FDR correction was applied within each prespecified analysis family: across ROIs or cortical divisions for each clinical measure, and across the 17 HAM-D items or 21 BDI items for each composite. No association survived the applicable FDR correction.

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