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Supplementary Material

**Widespread elevated hyperpolarized ^{13}C -lactate and ^{13}C -bicarbonate signal in
the brain of patients with brain metastases undergoing treatment**

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11 **Table S1.** Per patient summary of primary cancer type, types of systemic therapies used, estimated
12 duration on systemic therapy (potentially with breaks between different treatments), end of
13 systemic therapy relative to HP ¹³C imaging, and number of lines of systemic therapy.

Patient ID	Primary Cancer	Systemic Therapy Type	Duration (months)	End Relative to Imaging	No. Lines
1	NSCLC	NA	NA	NA	0
2	RCC	TKI, mAb	6	1-2 weeks	2
3	NSCLC	Alkylating agent	4	Unknown	2
4	Breast	Taxane	Unknown	1-2 weeks	2
5	NSCLC	Unknown	Unknown	Unknown	1
6	Breast	Anthracycline antibiotic, alkylating agent, taxane, mAb	5	Unknown	2
7	Breast	mAb, antimetabolite, microtubule inhibitor, hormone	60	0	3
8	Breast	Alkylating agent, antimetabolites, taxane, microtubule inhibitor, anthracycline antibiotic, hormone	72	4 weeks	6
9	Breast	Antimetabolite, anthracycline antibiotic, alkylating agent, mAb, hormone	72	0	2
10	Breast	Antimetabolite, mAb	Unknown	Unknown	2
11	Breast	Anthracycline antibiotic, alkylating agent, taxane, mAb, microtubule inhibitor	32	0	2
12	Breast	Antimetabolite, anthracycline antibiotic, alkylating agent, mAb, taxane, hormone	72	4 weeks	2

14 * mAb: monoclonal antibody; TKI: tyrosine kinase inhibitor

15 **Table S2.** List of SLANT brain region ID numbers and corresponding name and abbreviation.
16 Regions in italics were excluded from the analysis as they were either ventricles or below the
17 volumetric resolution of the ^{13}C images.

ID	Region	ID	Region
4	3rd Ventricle	138	Right MCgG middle cingulate gyrus
11	4th Ventricle	139	Left MCgG middle cingulate gyrus
23	Right Accumbens Area	140	Right MFC medial frontal cortex
30	Left Accumbens Area	141	Left MFC medial frontal cortex
31	Right Amygdala	142	Right MFG middle frontal gyrus
32	Left Amygdala	143	Left MFG middle frontal gyrus
35	Brain Stem	144	Right MOG middle occipital gyrus
36	Right Caudate	145	Left MOG middle occipital gyrus
37	Left Caudate	146	Right MOrG medial orbital gyrus
38	Right Cerebellum Exterior	147	Left MOrG medial orbital gyrus
39	Left Cerebellum Exterior	148	Right MPoG postcentral gyrus medial segment
40	Right Cerebellum White Matter	149	Left MPoG postcentral gyrus medial segment
41	Left Cerebellum White Matter	150	Right MPrG precentral gyrus medial segment
44	Right Cerebral White Matter	151	Left MPrG precentral gyrus medial segment
45	Left Cerebral White Matter	152	Right MSFG superior frontal gyrus medial segment
47	Right Hippocampus	153	Left MSFG superior frontal gyrus medial segment
48	Left Hippocampus	154	Right MTG middle temporal gyrus
49	Right Inf Lat Vent	155	Left MTG middle temporal gyrus
50	Left Inf Lat Vent	156	Right OCP occipital pole
51	Right Lateral Ventricle	157	Left OCP occipital pole
52	Left Lateral Ventricle	160	Right OFuG occipital fusiform gyrus
55	Right Pallidum	161	Left OFuG occipital fusiform gyrus
56	Left Pallidum	162	Right OpIFG opercular part of the inferior frontal gyrus
57	Right Putamen	163	Left OpIFG opercular part of the inferior frontal gyrus
58	Left Putamen	164	Right OrIFG orbital part of the inferior frontal gyrus
59	Right Thalamus Proper	165	Left OrIFG orbital part of the inferior frontal gyrus
60	Left Thalamus Proper	166	Right PCgG posterior cingulate gyrus
61	Right Ventral DC	167	Left PCgG posterior cingulate gyrus
62	Left Ventral DC	168	Right PCu precuneus
71	Cerebellar Vermal Lobules I-V	169	Left PCu precuneus
72	Cerebellar Vermal Lobules VI-VII	170	Right PHG parahippocampal gyrus
73	Cerebellar Vermal Lobules VIII-X	171	Left PHG parahippocampal gyrus
75	Left Basal Forebrain	172	Right PIns posterior insula
76	Right Basal Forebrain	173	Left PIns posterior insula
100	Right ACgG anterior cingulate gyrus	174	Right PO parietal operculum
101	Left ACgG anterior cingulate gyrus	175	Left PO parietal operculum
102	Right AIns anterior insula	176	Right PoG postcentral gyrus
103	Left AIns anterior insula	177	Left PoG postcentral gyrus
104	Right AOrG anterior orbital gyrus	178	Right POrG posterior orbital gyrus
105	Left AOrG anterior orbital gyrus	179	Left POrG posterior orbital gyrus
106	Right AnG angular gyrus	180	Right PP planum polare
107	Left AnG angular gyrus	181	Left PP planum polare
108	Right Calc calcarine cortex	182	Right PrG precentral gyrus
109	Left Calc calcarine cortex	183	Left PrG precentral gyrus
112	Right CO central operculum	184	Right PT planum temporale
113	Left CO central operculum	185	Left PT planum temporale
114	Right Cun cuneus	186	Right SCA subcallosal area

115	Left Cun cuneus	187	Left SCA subcallosal area
116	Right Ent entorhinal area	190	Right SFG superior frontal gyrus
117	Left Ent entorhinal area	191	Left SFG superior frontal gyrus
118	Right FO frontal operculum	192	Right SMC supplementary motor cortex
119	Left FO frontal operculum	193	Left SMC supplementary motor cortex
120	Right FRP frontal pole	194	Right SMG supramarginal gyrus
121	Left FRP frontal pole	195	Left SMG supramarginal gyrus
122	Right FuG fusiform gyrus	196	Right SOG superior occipital gyrus
123	Left FuG fusiform gyrus	197	Left SOG superior occipital gyrus
124	Right GRe gyrus rectus	198	Right SPL superior parietal lobule
125	Left GRe gyrus rectus	199	Left SPL superior parietal lobule
128	Right IOG inferior occipital gyrus	200	Right STG superior temporal gyrus
129	Left IOG inferior occipital gyrus	201	Left STG superior temporal gyrus
132	Right ITG inferior temporal gyrus	202	Right TMP temporal pole
133	Left ITG inferior temporal gyrus	203	Left TMP temporal pole
134	Right LiG lingual gyrus	204	Right TrIFG triangular part of the inferior frontal gyrus
135	Left LiG lingual gyrus	205	Left TrIFG triangular part of the inferior frontal gyrus
136	Right LOrG lateral orbital gyrus	206	Right TTG transverse temporal gyrus
137	Left LOrG lateral orbital gyrus	207	Left TTG transverse temporal gyrus

Table S3. Per patient summary of the number of brain regions and volume excluded due to involvement with tumor or hyperintensity on T2w FLAIR images. Reported is the total brain volume, number of tumors, total tumor volume (and percent of the total brain volume involved with tumor), number of tumor and hyperintensity involved brain regions, and the total volume excluded by those region (followed by the percent of the total brain volume excluded).

Patient ID	Total Brain Volume (mL)	No. Tumors	Total Tumor Volume (mL)	No. Excluded Brain Regions (Tumor + FLAIR = Total)	Excluded Brain Volume (mL) (Tumor + FLAIR = Total)
1	1157.9	2	1.5 (0.13%)	5 + 3 = 8	123.4 + 353.7 = 477.1 (41.2%)
2	1345.5	1	3.9 (0.29%)	3 + 1 = 4	93.5 + 6.4 = 99.9 (7.4%)
3	994.0	1	0.6 (0.06%)	3 + 0 = 3	175.7 + 0 = (17.7%)
4	1043.5	5	7.7 (0.74%)	15 + 16 = 31	473.4 + 97.7 = (54.7%)
5	1163.4	1	28.4 (2.5%)	3 + 0 = 3	92.4 + 0 = 92.4 (7.9%)
6	1208.7	4	11.8 (0.98%)	18 + 0 = 18	381.7 + 0 = 381.7 (31.6%)
7	1136.9	1	3.9 (0.34%)	6 + 0 = 6	206.0 + 0 = 206.0 (18.1%)
8	1187.1	1	1.8 (0.15%)	4 + 1 = 5	81.5 + 9.6 = (7.7%)
9	1071.9	2	4.4 (0.41%)	6 + 0 = 6	252.0 + 0 = 252.0 (23.5%)
10	1207.8	1	0.8 (0.07%)	6 + 2 = 8	219.6 + 22.9 = 242.5 (20.1%)
11	1084.5	2	11.0 (1.0%)	15 + 4 = 19	420.6 + 14.1 = 434.7(40.1%)
12	1202.0	3	5.9 (0.49%)	11 + 5 = 16	303.3 + 35.0 = 338.3 (28.1%)

Table S4. Estimated percent differences in ^{13}C -pyruvate, ^{13}C -lactate, ^{13}C -bicarbonate, ^{13}C -lac/pyr ratio, ^{13}C -bic/pyr ratio, brain region volume and GMV between patients and controls. Uncorrected p-values are reported. ^{13}C -metabolite signals and ratios and brain region volume p-values should be compared to a Bonferroni corrected significance level of $\alpha_B = 0.05/86 = 0.00058$. GMV p-values should be compared to a Bonferroni corrected significance level of $\alpha_B = 0.05/82 = 0.0006$.

^{13}C -pyruvate			^{13}C -lactate			^{13}C -bicarbonate		
Region	$\Delta\%$	p-value	Region	$\Delta\%$	p-value	Region	$\Delta\%$	p-value
120	-36.1	0.0002	58	73.7	1.7E-05	106	62.8	0.002
199	-27.8	0.006	147	70.4	2.9E-05	200	54.4	0.005
190	-27.6	0.008	179	64.7	7.9E-05	157	53.6	0.005
192	-25.5	0.01	108	61.3	0.0002	201	53.4	0.006
193	-25.3	0.01	197	59.3	0.0002	144	52.7	0.006
198	-24.9	0.01	145	58.4	0.0002	108	52.1	0.007
194	-24.5	0.02	122	58.0	0.0003	115	52.0	0.007
143	-23.8	0.02	157	57.9	0.0003	179	51.7	0.007
162	-23.7	0.02	48	57.7	0.0003	168	51.2	0.008
182	-23.2	0.03	103	57.0	0.0003	107	49.9	0.008
37	-21.6	0.04	57	56.8	0.0003	196	49.4	0.008
142	-21.5	0.04	160	56.7	0.0003	198	49.4	0.009
115	-21.4	0.04	109	56.0	0.0004	37	49.3	0.009
191	-21.3	0.04	101	55.9	0.0004	169	49.2	0.01
177	-21.2	0.04	161	55.8	0.0004	114	48.6	0.01
121	-20.9	0.05	134	55.6	0.0004	103	48.3	0.01
114	-20.7	0.05	169	54.2	0.0005	109	47.0	0.01
196	-20.7	0.05	171	53.8	0.0006	154	46.3	0.01
169	-20.4	0.06	115	53.7	0.0006	113	45.8	0.01
154	-20.0	0.06	114	53.7	0.0006	134	45.6	0.01
146	-19.6	0.06	45	53.6	0.00097	128	45.3	0.01
204	-19.4	0.06	133	53.3	0.0007	191	44.2	0.02
39	-18.9	0.08	168	52.8	0.0007	60	44.0	0.02
168	-18.6	0.08	44	52.6	0.001	197	43.9	0.02
152	-18.1	0.09	36	52.5	0.001	162	43.9	0.02
183	-18.0	0.08	121	52.2	0.001	101	43.7	0.02
100	-17.5	0.09	107	51.8	0.001	195	43.1	0.02
176	-17.4	0.1	60	51.0	0.001	199	42.9	0.02
178	-17.1	0.1	62	51.0	0.001	44	42.8	0.03
71	-16.1	0.1	166	50.4	0.001	166	42.6	0.02
153	-15.2	0.2	47	49.7	0.001	139	42.0	0.02
202	-14.8	0.2	113	49.6	0.001	167	41.9	0.02

112	-14.8	0.2	71	49.4	0.001	112	41.9	0.02
200	-14.7	0.2	112	49.2	0.001	147	41.5	0.02
179	-14.6	0.2	129	48.9	0.001	129	41.4	0.02
195	-14.1	0.2	106	48.8	0.001	160	41.2	0.02
167	-14.1	0.2	196	48.5	0.001	121	40.8	0.02
102	-14.0	0.2	135	48.4	0.001	156	40.7	0.02
144	-13.3	0.2	59	48.3	0.001	132	40.7	0.02
138	-13.1	0.2	144	48.1	0.001	57	40.7	0.02
107	-13.0	0.2	153	48.0	0.002	163	40.5	0.02
60	-12.8	0.2	201	47.6	0.002	155	40.4	0.03
166	-12.6	0.2	200	47.2	0.002	62	40.2	0.03
106	-12.5	0.2	102	47.1	0.002	205	39.9	0.03
203	-12.4	0.3	156	47.1	0.002	122	39.7	0.03
36	-11.5	0.3	132	47.0	0.002	45	39.7	0.04
205	-11.4	0.3	167	46.9	0.002	145	39.3	0.03
45	-11.2	0.4	195	46.6	0.002	153	38.9	0.03
109	-11.2	0.3	38	46.4	0.003	176	38.5	0.03
147	-11.1	0.3	199	46.2	0.002	102	37.5	0.04
156	-11.1	0.3	61	46.2	0.002	190	37.4	0.04
155	-11.0	0.3	37	46.1	0.002	58	37.1	0.04
145	-10.6	0.3	128	45.5	0.002	182	37.1	0.04
61	-10.4	0.3	154	45.4	0.002	194	36.6	0.04
123	-10.2	0.4	155	45.3	0.002	142	36.2	0.04
59	-9.8	0.4	176	45.1	0.002	177	36.1	0.04
103	-9.7	0.4	193	44.8	0.002	192	35.9	0.04
44	-9.7	0.4	123	44.7	0.003	171	35.7	0.05
201	-9.3	0.4	177	44.7	0.003	178	35.0	0.05
35	-9.1	0.4	163	44.5	0.003	193	34.9	0.05
197	-9.0	0.4	204	44.5	0.003	183	34.3	0.05
62	-8.8	0.4	139	44.2	0.003	138	34.0	0.05
38	-8.5	0.5	191	43.9	0.003	152	33.9	0.06
101	-8.4	0.4	183	43.8	0.003	36	32.8	0.06
41	-8.1	0.5	198	43.5	0.003	161	32.8	0.06
128	-7.6	0.5	170	43.2	0.003	204	32.6	0.06
163	-7.4	0.5	182	42.4	0.004	38	32.3	0.08
135	-7.4	0.5	152	41.9	0.004	48	31.9	0.07
40	-6.8	0.6	205	41.7	0.004	135	31.4	0.07
113	-6.7	0.5	203	41.6	0.005	143	30.9	0.07
171	-5.9	0.6	194	41.2	0.005	123	29.3	0.09
47	-5.4	0.6	41	41.1	0.005	39	28.9	0.1
48	-5.2	0.6	162	40.9	0.005	35	28.6	0.1
139	-5.1	0.6	178	40.7	0.005	133	28.5	0.1
108	-3.8	0.7	143	40.3	0.005	146	28.0	0.1
129	-3.4	0.8	138	40.0	0.006	71	25.0	0.1
133	-3.2	0.8	100	39.7	0.006	202	24.9	0.1

58	-3.0	0.8	142	39.7	0.006	203	23.2	0.2
157	-1.4	0.9	190	38.3	0.008	120	22.8	0.2
134	-1.2	0.9	39	38.2	0.009	59	21.8	0.2
170	-0.6	1.0	192	36.9	0.009	41	20.1	0.2
57	0.6	1.0	146	36.5	0.01	40	16.7	0.3
160	4.4	0.7	35	36.0	0.01	100	16.2	0.3
132	4.5	0.7	40	35.7	0.01	170	14.1	0.4
122	5.3	0.7	202	33.7	0.02	47	12.1	0.4
161	9.2	0.4	120	23.4	0.08	61	6.6	0.7

¹³ C-lac/pyr ratio			¹³ C-bic/pyr ratio		
Region	Δ%	p-value	Region	Δ%	p-value
199	95.7	3.0E-07	198	93.1	8.28E-05
115	88.6	1.2E-06	199	92.4	0.0001
193	87.2	1.0E-06	120	88.5	0.0001
169	87.0	1.6E-06	115	86.6	0.0002
114	86.9	1.6E-06	190	83.7	0.0003
120	86.9	1.1E-06	37	83.0	0.0003
121	86.3	1.5E-06	196	82.3	0.0003
179	86.0	1.5E-06	162	82.1	0.0003
147	85.0	1.8E-06	169	81.5	0.0004
198	84.5	1.6E-06	114	81.1	0.0004
190	84.4	2.4E-06	168	80.3	0.0005
168	81.2	4.2E-06	106	80.1	0.0004
194	80.7	4.6E-06	191	77.6	0.0006
196	80.7	3.1E-06	192	76.8	0.0005
37	79.4	4.7E-06	154	76.6	0.0007
182	79.1	5.0E-06	121	75.4	0.0007
162	78.4	4.7E-06	194	75.4	0.0008
143	77.7	6.3E-06	193	74.8	0.0007
192	77.6	5.4E-06	200	74.5	0.0008
177	77.3	6.7E-06	182	73.0	0.0009
191	76.5	9.4E-06	179	71.3	0.001
154	75.4	1.1E-05	144	70.9	0.001
204	73.1	1.2E-05	142	68.1	0.002
58	72.6	1.5E-05	177	67.5	0.002
142	71.8	1.8E-05	107	66.6	0.002
71	71.8	1.8E-05	143	66.2	0.002
145	71.0	2.0E-05	201	63.2	0.003
176	69.7	2.2E-05	176	63.1	0.003
109	69.6	2.6E-05	195	61.0	0.003
183	69.3	2.4E-05	109	60.7	0.004
112	69.0	2.9E-05	112	60.1	0.004
197	68.9	3.5E-05	204	59.6	0.004

153	68.6	3.7E-05	167	59.4	0.004
107	68.4	3.2E-05	60	59.3	0.004
103	67.7	3.1E-05	153	59.0	0.005
152	67.2	4.7E-05	183	58.4	0.004
45	67.0	1.4E-04	152	58.2	0.005
60	67.0	3.6E-05	166	58.2	0.005
200	66.5	4.6E-05	103	58.1	0.005
36	66.2	4.1E-05	178	57.0	0.005
166	66.1	4.8E-05	156	55.7	0.007
102	65.1	5.9E-05	108	54.4	0.008
144	65.0	5.1E-05	146	54.3	0.008
167	64.9	6.0E-05	39	54.1	0.009
195	64.8	5.3E-05	147	54.1	0.008
39	64.7	9.0E-05	157	53.8	0.008
101	64.3	6.7E-05	102	53.8	0.008
106	64.2	5.9E-05	197	53.2	0.009
146	64.0	7.0E-05	128	53.1	0.009
178	63.7	6.4E-05	205	52.8	0.009
100	63.6	6.6E-05	44	52.7	0.02
44	63.1	0.0003	155	52.2	0.01
108	62.1	0.0001	45	51.8	0.02
48	60.7	0.0001	101	51.6	0.01
156	60.2	0.0001	145	51.0	0.01
62	59.8	0.0001	113	50.1	0.01
59	58.6	0.0002	138	49.1	0.01
171	57.7	0.0003	62	48.5	0.01
155	57.6	0.0002	163	46.7	0.02
61	57.5	0.0002	139	44.4	0.02
201	57.0	0.0002	36	44.3	0.02
203	55.9	0.0003	71	43.5	0.02
138	55.5	0.0003	129	42.6	0.03
123	55.4	0.0004	134	42.4	0.03
157	55.3	0.0003	202	41.0	0.03
135	54.6	0.0004	38	40.2	0.06
38	54.6	0.001	171	39.4	0.04
113	54.6	0.0003	123	38.7	0.04
205	54.4	0.0004	135	36.7	0.05
133	52.9	0.0007	35	36.6	0.05
47	52.7	0.0006	100	36.3	0.05
128	52.1	0.0006	58	35.9	0.06
134	51.9	0.0007	203	35.5	0.06
202	51.3	0.0007	48	34.8	0.06
163	50.7	0.0007	57	34.2	0.06
57	50.2	0.0008	160	31.6	0.09
129	49.0	0.001	59	30.2	0.09

41	48.0	0.002	132	29.9	0.1
139	46.7	0.001	133	28.0	0.1
160	45.1	0.002	122	27.8	0.1
122	44.7	0.002	41	25.8	0.2
35	44.4	0.003	40	20.7	0.2
40	40.6	0.005	161	17.4	0.3
170	39.1	0.006	61	14.8	0.4
161	37.7	0.007	47	14.4	0.4
132	35.7	0.01	170	10.9	0.5

Volume			GMV		
Region	$\Delta\%$	p-value	Region	$\Delta\%$	p-value
106	-19.1	2.1E-05	204	-19.1	0.0003
204	-18.9	2.6E-05	106	-18.8	0.0004
205	-15.0	0.00095	120	-18.5	0.0005
153	-14.8	0.001	57	-16.1	0.003
157	-13.7	0.003	153	-16.0	0.004
143	-13.7	0.003	58	-15.5	0.005
100	-13.3	0.003	205	-14.9	0.006
163	-13.1	0.003	157	-14.9	0.007
152	-12.3	0.008	121	-14.1	0.010
120	-11.8	0.008	36	-13.0	0.01
58	-11.4	0.01	143	-13.0	0.02
57	-11.2	0.01	100	-12.7	0.02
122	-11.0	0.02	163	-12.3	0.02
107	-10.7	0.02	37	-12.1	0.03
142	-10.7	0.02	152	-12.0	0.03
36	-10.6	0.02	142	-10.5	0.06
103	-10.4	0.02	59	-10.0	0.06
123	-10.3	0.03	122	-10.0	0.07
145	-10.2	0.02	107	-10.0	0.07
167	-9.8	0.03	145	-9.8	0.07
200	-9.6	0.03	176	-9.2	0.09
102	-9.3	0.04	167	-9.1	0.1
144	-8.7	0.05	168	-9.1	0.1
146	-8.7	0.06	191	-8.9	0.1
154	-8.6	0.07	144	-8.8	0.1
201	-8.6	0.06	146	-8.5	0.1
112	-8.5	0.06	123	-8.2	0.1
191	-8.5	0.07	169	-7.4	0.2
113	-8.4	0.06	177	-7.4	0.2
37	-8.2	0.07	60	-7.3	0.2
190	-8.0	0.09	166	-7.0	0.2
168	-7.6	0.1	190	-6.9	0.2

179	-7.2	0.1	201	-6.8	0.2
166	-7.1	0.1	103	-6.7	0.2
169	-6.9	0.1	147	-6.7	0.2
132	-6.9	0.1	179	-6.5	0.2
177	-6.5	0.2	114	-6.4	0.3
38	-6.1	0.3	134	-6.1	0.3
195	-5.9	0.2	200	-6.1	0.3
176	-5.9	0.2	154	-5.9	0.3
139	-5.9	0.2	113	-5.8	0.3
101	-5.8	0.2	156	-5.6	0.3
60	-5.8	0.2	38	-5.4	0.4
155	-5.6	0.2	132	-5.2	0.4
182	-5.6	0.2	196	-5.1	0.3
192	-5.5	0.2	192	-5.1	0.4
147	-5.3	0.2	101	-5.1	0.4
202	-5.3	0.3	115	-5.0	0.4
59	-5.2	0.2	47	-4.9	0.4
39	-4.3	0.4	39	-4.7	0.4
203	-4.2	0.4	182	-4.7	0.4
134	-3.9	0.4	139	-4.6	0.4
115	-3.8	0.4	71	-4.4	0.4
61	-3.8	0.4	102	-4.4	0.4
162	-3.7	0.4	112	-4.4	0.4
156	-3.7	0.4	195	-4.0	0.5
48	-3.4	0.5	129	-3.7	0.5
47	-3.3	0.5	155	-3.7	0.5
121	-3.2	0.5	135	-3.5	0.5
194	-3.1	0.5	61	-3.4	0.5
62	-3.0	0.5	160	-3.3	0.6
45	-2.9	0.6	203	-3.2	0.6
40	-2.8	0.6	202	-3.1	0.6
196	-2.7	0.5	48	-2.8	0.6
161	-2.5	0.6	197	-2.4	0.7
135	-2.4	0.6	198	-2.3	0.7
129	-2.3	0.6	138	-1.9	0.7
138	-1.8	0.7	62	-1.9	0.7
114	-1.8	0.7	183	-1.7	0.8
183	-1.7	0.7	161	-1.6	0.8
198	-1.2	0.8	194	-1.6	0.8
171	-1.1	0.8	162	-1.3	0.8
160	-0.9	0.9	128	-0.8	0.9
170	-0.8	0.9	108	-0.6	0.9
71	-0.7	0.9	171	-0.5	0.9
133	-0.6	0.9	199	0.0	1.0
35	-0.6	0.9	109	0.2	1.0

193	-0.3	0.9	170	0.5	0.9
44	-0.1	0.99	193	0.6	0.9
178	0.7	0.9	178	1.5	0.8
197	0.9	0.9	133	1.8	0.8
128	1.1	0.8	35	7.9	0.2
41	1.7	0.7			
199	1.8	0.7			
109	3.6	0.5			
108	6.6	0.2			

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33

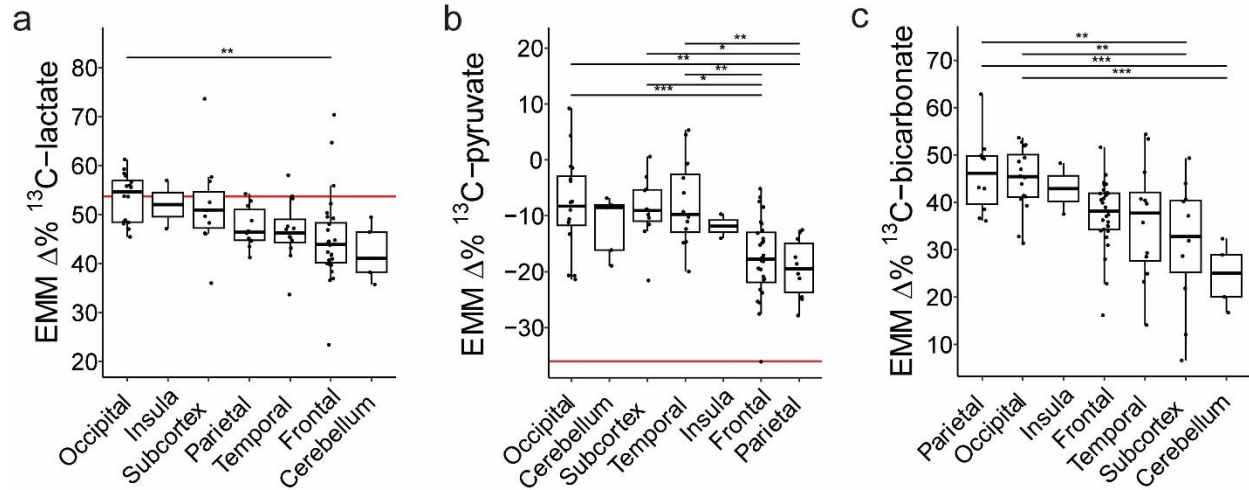
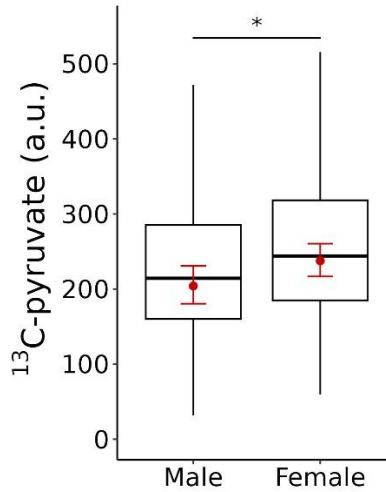


Fig. S5. Estimated percentage change in the (a) ^{13}C -lactate, (b) ^{13}C -pyruvate and (c) ^{13}C -bicarbonate signals between patients and controls versus neuroanatomical regions. Boxplots are organized from highest to lowest median. The red line indicates Bonferroni corrected significance threshold. Regions above the red line in (a) show significant elevations, while regions below the red line in (b) show significant reductions. Significance between regions was determined using ANOVA followed by Tukey's post-hoc test. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. EMM: estimated marginal means.



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44 **Fig. S6.** Sex difference in ^{13}C -pyruvate signal. Boxplots show the raw ^{13}C -pyruvate signal across
 45 all participants (controls and patients) and brain regions. Overlaid on the boxplots are the estimated
 46 marginal mean ^{13}C -pyruvate signals from the regression model as red dots and 95% confidence
 47 intervals. Significance was evaluated from mixed effects linear regression: * $p < 0.05$.