Supplementary Online Content

Bossong MG, Antoniades M, Azis M, et al. Association of hippocampal glutamate levels with adverse outcomes in individuals at clinical high risk for psychosis. *JAMA Psychiatry*. Published online November 14, 2018. doi:10.1001/jamapsychiatry.2018.3252

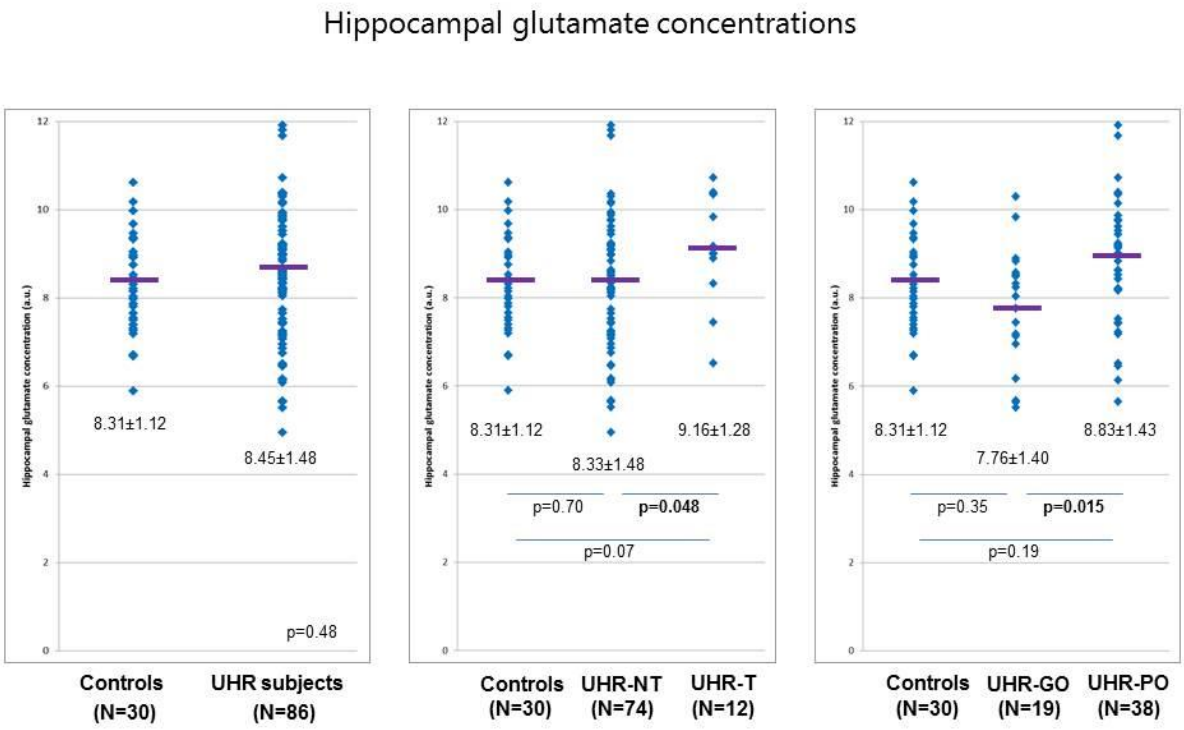
This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. ^{1}H-MRS Data Processing

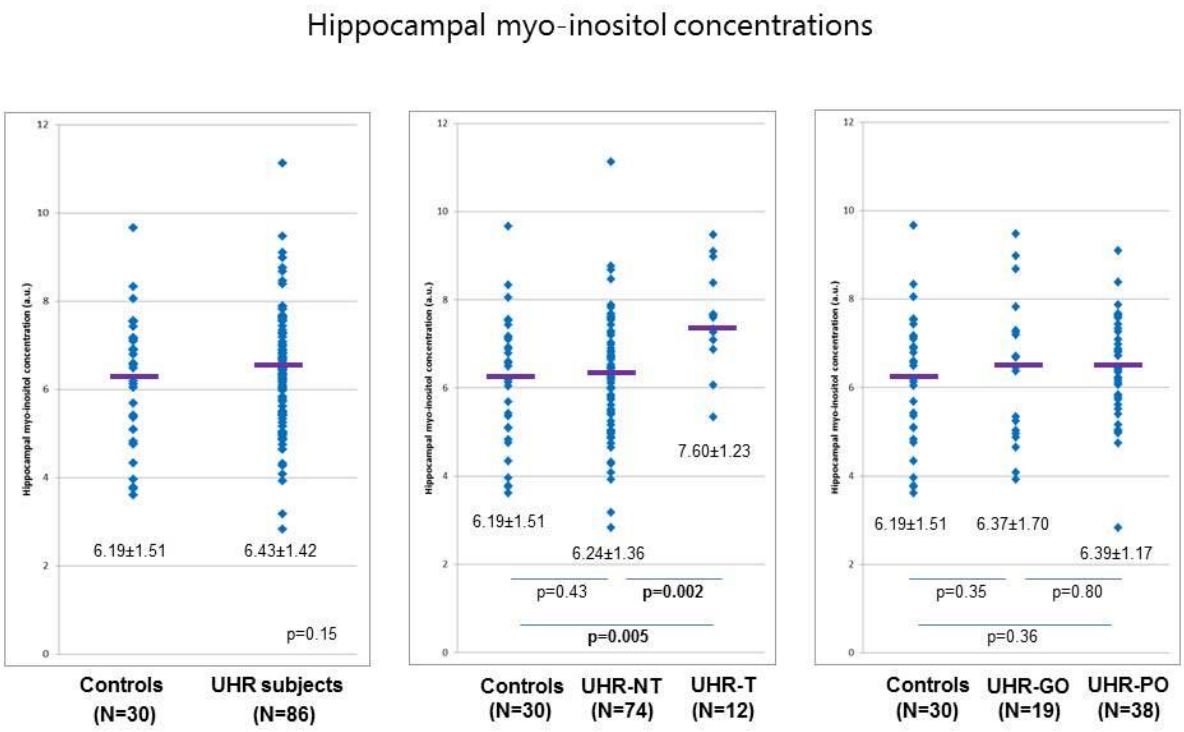
^{1}H-MRS Data Processing

Water-scaled glutamate, Glx, myo-inositol, creatine, choline and NAA values were corrected for voxel tissue composition using the formula Mcorr = M*(WM+1.28GM+1.55CSF)/(WM+GM), where M is the uncorrected metabolite value, and WM, GM and CSF are the white matter, grey matter and CSF fractions of the voxel, respectively. The denominator (WM+GM) is the same as (1-CSF), which is the part of the equation that corrects the concentrations for the CSF content in the voxel. Since the concentrations are scaled by the water signal and concentration, the numerator is a measure of the water concentration in the voxel, which is 43300*GM+ 35880*WM+55556*CSF, where 43300 mM, 35880 mM and 55556 mM are the water concentrations of grey matter, white matter and CSF, respectively (http://s-provencher.com/pub/LCModel/manual/manual.pdf). By default, calculations in LCModel are performed for a voxel that completely consists of white matter, and therefore the corrected concentrations need to be divided by 35880, which provides the numerator of 1.28GM+WM+1.55CSF.

eFigure 1. Hippocampal Glutamate Concentrations

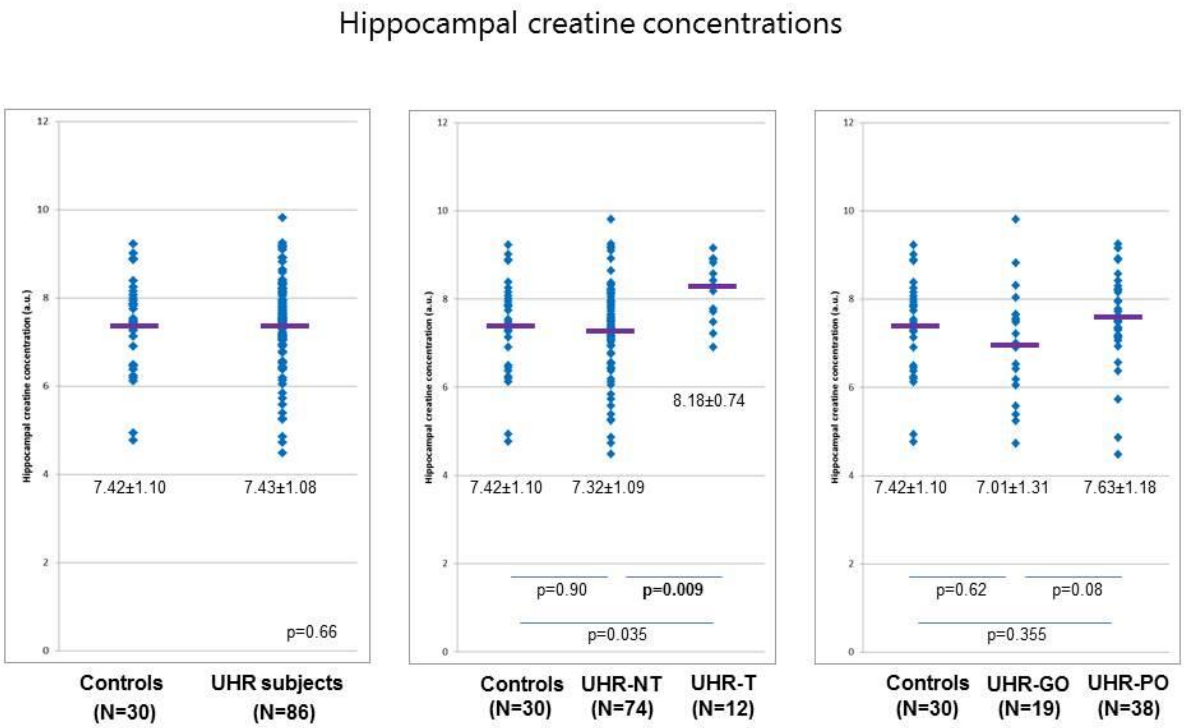


eFigure 2. Hippocampal Myo-inositol Concentrations



Corrected for age and tobacco use

eFigure 3. Hippocampal Creatine Concentrations



eTable 1 Scan Quality Parameters and Voxel Tissue Composition: Healthy Controls vs Clinical High-Risk Subjects

Measure	Healthy controls N=30		Clinical High Risk N=86		Analysis	
	Mean	SD	Mean	SD	t	p
SNR	13.9	2.8	13.3	2.9	1.10	0.27
Line width	8.43	2.24	8.47	1.92	-0.10	0.93
FWHM	0.07	0.02	0.07	0.02	-0.10	0.93
Voxel GM	0.64	0.07	0.64	0.07	-0.09	0.93
Voxel WM	0.33	0.08	0.33	0.08	0.29	0.77
Voxel CSF	0.03	0.02	0.04	0.02	-0.80	0.43
Glutamate % CRLB	9.1	1.3	9.5	1.9	-1.00	0.32
Glx % CRLB	10.0	2.5	10.2	2.6	-0.44	0.66
Myo-inositol % CRLB	6.0	1.6	5.8	1.5	0.64	0.53
NAA % CRLB	3.9	0.9	3.9	1.3	-0.16	0.87
Total choline % CRLB	3.9	0.9	4.2	2.1	-0.76	0.45
Creatine % CRLB	3.8	0.7	4.0	0.9	-0.68	0.50

CRLB, Cramer-Rao Lower Bounds; CSF, cerebrospinal fluid; FWHM, full-width-half-maximum; Glx, combined measure of glutamine and glutamate; GM, grey matter; NAA, N-acetylaspartate; SNR, signal to noise ratio; WM: white matter.

eTable 2. Scan Quality Parameters and Voxel Tissue Composition: Healthy Controls (HC) vs CHR Non-Transition (CHR-NT) vs CHR Transition (CHR-T)

Measure	HC N=30		CHR-NT N=74		CHR-T N=12		Analysis					
							CHR-NT vs CHR-T		HC vs CHR-T		HC vs CHR-NT	
	Mean	SD	Mean	SD	Mean	SD	t	p	t	p	t	p
SNR	13.9	2.8	13.3	3.0	12.9	2.1	0.46	0.65	1.14	0.26	0.96	0.34
Line width	8.43	2.24	8.58	1.95	7.78	1.58	1.34	0.19	0.90	0.37	-0.34	0.73
FWHM	0.07	0.02	0.07	0.02	0.06	0.01	1.34	0.19	0.90	0.37	-0.34	0.73
Voxel GM	0.64	0.07	0.64	0.07	0.65	0.08	-0.39	0.70	-0.33	0.74	-0.01	0.99
Voxel WM	0.33	0.08	0.33	0.08	0.31	0.08	0.52	0.61	0.57	0.57	0.18	0.86
Voxel CSF	0.03	0.02	0.03	0.02	0.04	0.02	-0.59	0.56	-1.12	0.27	-0.67	0.51
Glutamate % CRLB	9.1	1.3	9.5	2.0	9.3	1.7	0.22	0.83	-0.54	0.59	-1.20	0.31
Glx % CRLB	10.0	2.5	10.2	2.7	10.3	2.6	-0.17	0.86	-0.43	0.67	-0.39	0.69
Myo-inositol % CRLB	6.0	1.6	5.9	1.6	5.3	1.1	1.40	0.17	1.60	0.12	0.34	0.74
NAA % CRLB	3.9	0.9	3.9	1.3	4.2	0.7	-0.77	0.44	-1.00	0.33	0.01	1.00
Total choline % CRLB	3.9	0.9	4.3	2.2	3.8	0.8	0.86	0.39	0.60	0.55	-0.89	0.24
Creatine % CRLB	3.8	0.7	4.0	0.9	3.8	0.6	0.86	0.39	0.36	0.72	-0.82	0.41

CRLB, Cramer-Rao Lower Bounds; CSF, cerebrospinal fluid; FWHM, full-width-half-maximum; Glx, combined measure of glutamine and glutamate; GM, grey matter; NAA, N-acetylaspartate; SNR, signal to noise ratio; WM: white matter.

eTable 3. Scan Quality Parameters and Voxel Tissue Composition: Healthy Controls (HC) vs Good Functional Outcome (CHR-GO) vs Poor Functional Outcome (CHR-PO)

Measure	HC N=30		CHR-GO N=19		CHR-PO N=38		Analysis					
							CHR-GO vs CHR-PO		HC vs CHR-GO		HC vs CHR-PO	
	Mean	SD	Mean	SD	Mean	SD	t	p	t	p	t	p
SNR	13.9	2.8	12.0	3.0	13.1	2.3	-1.49	0.14	2.28	0.03	1.37	0.18
Line width	8.43	2.24	8.98	2.15	8.76	1.79	0.41	0.69	-0.86	0.40	-0.69	0.50
FWHM	0.07	0.02	0.07	0.02	0.07	0.01	0.41	0.69	-0.86	0.40	-0.69	0.50
Voxel GM	0.64	0.07	0.63	0.06	0.62	0.07	0.08	0.94	0.59	0.56	0.77	0.45
Voxel WM	0.33	0.08	0.33	0.07	0.34	0.08	-0.41	0.68	-0.22	0.83	-0.70	0.48
Voxel CSF	0.03	0.02	0.04	0.03	0.03	0.02	1.18	0.24	-1.12	0.27	-0.11	0.91
Glutamate % CRLB	9.1	1.3	10.9	2.4	9.0	1.5	3.14	0.004	-2.96	0.01	0.34	0.74
Glx % CRLB	10.0	2.5	12.0	3.1	9.7	2.0	3.01	0.01	-2.55	0.01	0.52	0.60
Myo-inositol % CRLB	6.0	1.6	6.3	1.8	5.8	1.3	0.97	0.34	-0.94	0.62	0.62	0.54
NAA % CRLB	3.9	0.9	4.5	1.9	3.9	1.0	1.48	0.15	-1.51	0.14	-0.23	0.82
Total choline % CRLB	3.9	0.9	5.0	2.6	4.2	2.4	1.00	0.32	-1.941	0.06	-0.66	0.52
Creatine % CRLB	3.8	0.7	4.5	1.3	3.9	0.7	1.96	0.06	-2.02	0.05	-0.21	0.83

CRLB, Cramer-Rao Lower Bounds; CSF, cerebrospinal fluid; FWHM, full-width-half-maximum; Glx, combined measure of glutamine and glutamate; GM, grey matter; NAA, N-acetylaspartate; SNR, signal to noise ratio; WM: white matter.

eTable 4. Participant Demographic, Clinical, and Medication Data at Baseline: Healthy Controls (HC) vs CHR Non-Transition (CHR-NT) vs CHR Transition (CHR-T)

Measure	HC N=30		CHR-NT N=74		CHR-T N=12		Analysis					
							CHR-NT vs CHR-T		HC vs CHR-T		HC vs CHR-NT	
	Mean	SD	Mean	SD	Mean	SD	Statistic	p	Statistic	p	Statistic	p
Age (years)	24.7	3.8	22.5	3.7	22.1	2.8	t_{84}=0.38	0.71	t_{40}=2.11	0.04	t_{102}= 2.70	0.01
NART IQ	104.8	13.6	104.7	12.0	99.3	12.5	t_{76}=1.37	0.17	t_{37}=1.61	0.25	t_{93}=0.04	0.97
Years of education	15.8	3.3	14.6	2.1	14.3	2.5	t_{80}=0.37	0.71	t_{38}=1.30	0.20	t_{100}=2.23	0.03
CAARMS												
Positive score			10.0	4.4	11.3	3.3	t_{82}=-0.99	0.33				
Negative score			5.4	4.1	6.1	4.9	t_{82}=-0.49	0.63				
Total score			42.8	21.7	48.9	22.9	t_{80}=-0.87	0.39				
GAF score	93.0	5.1	58.4	9.5	53.6	7.6	t_{79}=1.64	0.11	t_{32}=18.1	<0.001	t_{89}=16.25	<0.001
HAM-A score	3.6	4.2	17.0	10.3	27.3	12.1	t_{61}=-2.55	0.01	t_{31}=-8.5	<0.001	t_{78}= -6.32	<0.001
HAM-D score	1.7	3.6	16.4	10.9	24.4	8.2	t_{61}=-1.96	0.05	t_{31}=-11.2	<0.001	t_{78}= -6.46	<0.001
Tobacco (cigarettes/day)	1.9	3.3	6.1	8.9	1.83	3.6	t_{84}=1.63	0.11	t_{40}=0.03	0.98	t_{102}= -2.53	0.01
Alcohol (units/day)	1.6	2.2	1.6	3.4	0.83	0.7	t_{80}=0.78	0.44	t_{40}=1.23	0.23	t_{98}= 0.05	0.96
Cannabis (median)[a]	0		0		0		χ^2 =1.68	0.79	χ^2 =2.59	0.63	χ^2 =2.21	0.70
	N	%	N	%	N	%	Statistic	P	Statistic	p	Statistic	p
Antipsychotic medication	0	0	10	13	1	0.08	χ^2 =0.23	0.63	χ^2 =2.73	0.10	χ^2 =4.71	0.03
Male	14	47	42	60	7	58	χ^2=0.004	0.95	χ^2 =0.46	0.50	χ^2 = 0.99	0.32
Right-handed	29	94	60	80	11	92	χ^2 =0.94	0.33	χ^2 =0.05	0.83	χ^2 =3.00	0.08

[a] 0=never, 1=experimental use, 2=occasional use, 3=moderate use, 4=severe use.

CAARMS, Comprehensive Assessment for the At-Risk Mental State; CHR, clinical high risk; CHR-NT, clinical high risk non-transition; CHR-T, clinical high risk transition; GAF, Global Assessment of Functioning scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; NART, National Adult Reading Test; SD, standard deviation.

eTable 5. Participant Demographic, Clinical, and Medication Data at Baseline: Healthy Controls (HC) vs Good Functional Outcome (CHR-GO) vs Poor Functional Outcome (CHR-PO)

Measure	HC N=30		CHR-GO N=19		CHR-PO N=38		Analysis					
							CHR-GO vs CHR-PO		HC vs CHR-GO		HC vs CHR-PO	
	Mean	SD	Mean	SD	Mean	SD	t	p	t	p	t	p
Age (years)	24.7	3.8	22.1	3.3	23.3	3.9	t_{55}=-1.19	0.24	t_{47}=2.44	0.02	t_{66}=1.46	0.15
NART IQ	104.8	13.6	106.3	9.2	105.2	13.3	t_{51}=0.31	0.76	t_{44}=-0.41	0.69	t_{61}=-0.12	0.90
Years of education	15.8	3.3	14.8	2.3	14.3	2.1	t_{52}=0.76	0.45	t_{47}=1.15	0.26	t_{63}=2.17	0.03
CAARMS												
Positive score			10.2	4.2	10.5	4.3	t_{54}=-0.32	0.75				
Negative score			6.4	3.9	5.5	4.3	t_{55}=0.78	0.44				
Total score			45.5	19.9	42.7	20.8	t_{53}=0.48	0.63				
GAF score	93.0	5.1	56.8	8.9	54.8	9.6	t_{53}=0.72	0.48	t_{38}=16.2	<0.001	t_{57}=17.2	<0.001
HAM-A score	3.6	4.2	18.3	12.8	20.6	11.8	t_{40}=-0.57	0.57	t_{38}=-5.36	<0.001	t_{50}=-6.82	<0.001
HAM-D score	1.7	3.6	15.5	10.3	19.6	11.9	t_{40}=-1.10	0.28	t_{38}=-6.18	<0.001	t_{50}=-7.22	<0.001
Tobacco (cigarettes/day)	1.9	3.3	6.7	10.0	5.7	8.5	t_{55}=0.39	0.70	t_{47}=-2.46	0.02	t_{66}=-2.35	0.02
Alcohol (units/day)	1.6	2.2	1.4	1.0	1.5	4.0	t_{53}=-0.12	0.91	t_{47}=0.40	0.69	t_{64}=0.13	0.90
Cannabis (median)[a]	0		1		0		χ^2 =4.83	0.31	χ^2 =5.13	0.27	χ^2 =2.27	0.52
	N	%	N	%	N	%	Statistic	P	Statistic	P	Statistic	p
Antipsychotic medication	0	0	3	15.8	2	0.06	χ^2 =1.75	0.19	χ^2 =5.37	0.02	χ^2 =1.73	0.19
Male	15	50	9	47.4	23	63.9	χ^2 =0.89	0.35	χ^2 =0.001	0.97	χ^2 =1.31	0.25
Right-handed	29	96.7	17	89.5	29	80.6	χ^2 =1.41	0.24	χ^2 =0.27	0.61	χ^2 =3.78	0.05

[a] 0=never, 1=experimental use, 2=occasional use, 3=moderate use, 4=severe use.

CAARMS, Comprehensive Assessment for the At-Risk Mental State; CHR, clinical high risk; CHR-NT, clinical high risk non-transition; CHR-T, clinical hig h risk transition; GAF, Global Assessment of Functioning scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; NART, National Adult Reading Test; SD, standard deviation.

eTable 6. Hippocampal Metabolite Concentrations and Transition to Psychosis: Healthy Controls (HC) vs CHR Non-Transition (CHR-NT) vs CHR Transition (CHR-T).

Metabolite	HC N=30	CHR-NT N=74	CHR-T N=12	CHR-NT vs CHR-T	CHR-T vs HC	CHR-NT vs HC
				p (effect size)	p (effect size)	p (effect size)
Glutamate	8.31 (1.12)	8.33 (1.48)	9.16 (1.28)	**0.048** (0.57)	0.07 (0.73)	0.70 (0.01)
Glx	11.61 (2.23)	11.43 (2.48)	12.44 (2.16)	0.18 (0.41)	0.32 (0.38)	0.89 (0.07)
Myo-Inositol	6.19 (1.51)	6.24 (1.36)	7.60 (1.23)	**0.002** (1.01)	**0.005** (0.98)	0.43 (0.04)
Creatine	7.42 (1.10)	7.32 (1.09)	8.18 (0.74)	**0.009** (0.82)	0.035 (0.75)	0.90 (0.09)
Choline	2.30 (0.40)	2.40 (0.43)	2.59 (0.21)	0.06 (0.47)	0.020 (0.81)	0.35 (0.23)
NAA	9.34 (1.43)	9.34 (1.18)	9.49 (0.80)	0.63 (0.13)	0.66 (0.12)	0.92 (0.07)

Glx, combined measure of glutamine and glutamate; NAA, N-acetylaspartate. Significant differences between groups are indicated in bold.

eTable 7. Hippocampal Metabolite Concentrations and Functional Outcome: Healthy Controls (HC) vs Good Functional Outcome (CHR-GO) vs Poor Functional Outcome (CHR-PO).

Metabolite	HC N=30	CHR-GO N=19	CHR-PO N=38	CHR-GO vs CHR-PO	CHR-PO vs HC	CHR-GO vs HC
				p (effect size)	p (effect size)	p (effect size)
Glutamate	8.31 (1.12)	7.76 (1.40)	8.83 (1.43)	**0.015** (0.75)	0.19 (0.40)	0.35 (0.45)
Glx	11.61 (2.23)	10.78 (2.11)	11.90 (2.38)	0.09 (0.49)	0.59 (0.13)	0.21 (0.38)
Myo-Inositol	6.19 (1.51)	6.37 (1.70)	6.39 (1.17)	0.80 (0.01)	0.36 (0.15)	0.35 (0.11)
Creatine	7.42 (1.10)	7.01 (1.31)	7.63 (1.18)	0.08 (0.51)	0.55 (0.18)	0.62 (0.35)
Choline	2.30 (0.40)	2.36 (0.56)	2.40 (0.37)	0.90 (0.09)	0.48 (0.26)	0.28 (0.13)
NAA	9.34 (1.43)	8.84 (0.97)	9.28 (1.06)	0.16 (0.43)	0.65 (0.05)	0.41 (0.39)

Glx, combined measure of glutamine and glutamate; NAA, N-acetylaspartate. Significant differences between groups are indicated in bold.