Supplementary Material

MRS Acquisition and Spectral Fitting

A two-dimensional sagittal anatomical image (37 slices, TR = 8000 ms, TE = 70 ms, flip-angle (α) = 120°, thickness = 3.5 mm, field of view = 240×191 mm) was used as reference to prescribe a 2.0 x 2.0 x 2.0 cm (8 cm^3) ^{1}H-MRS voxel on the bilateral dorsal ACC (Supplementary Figure 1). Voxel positioning was set by having the posterior end of the voxel coinciding with the precentral gyrus and the caudal face of the voxel coinciding with the most caudal positioning that was not part of the corpus callosum. Voxel angle was set to be tangential to the corpus callosum. A semi-LASER ^{1}H-MRS sequence (TR = 7500 ms, TE = 100 ms, bandwidth = 6000 Hz, N = 2048) was used to acquire 32 channel-combined, VAPOR (Tkáč *et al.*, 2005) water-suppressed spectra as well as a water-unsuppressed spectrum to be used for spectral post-processing, fitting and quantification. During scan, participants were asked to rest by fixing their gaze on a white cross on a 50% gray background.

Using the tools outlined in Near et al. (Near *et al.*, 2015), the 32 spectra were phase and frequency corrected before being averaged into a single spectrum to be used for all subsequent analyses. QUECC (Bartha *et al.*, 2000) and HSVD (van den Boogaart *et al.*, 1994) were applied to the spectrum for lineshape deconvolution and removal of residual water signal, respectively. Spectral

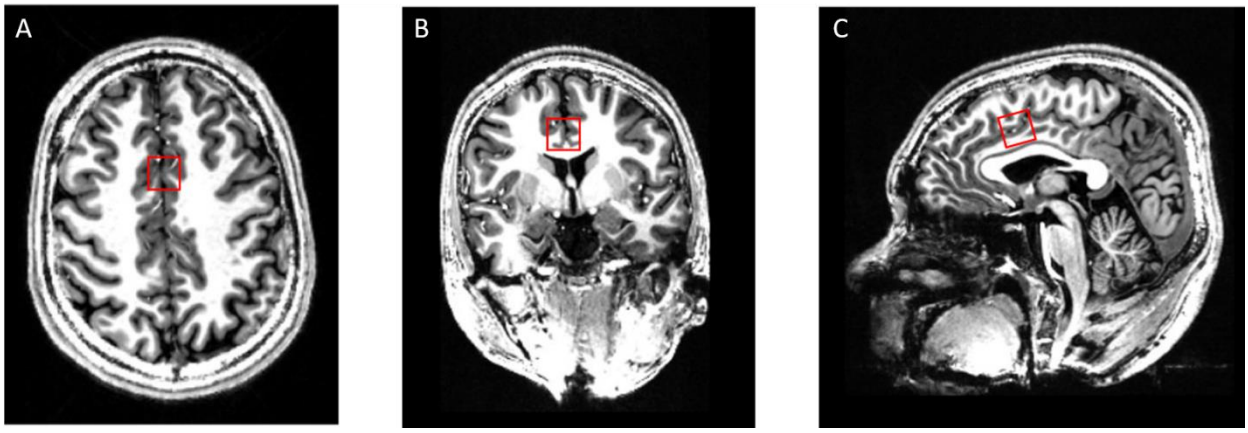
fitting was done using fitMAN (Bartha *et al.*, 1999), a time-domain fitting algorithm that uses a non-linear, iterative Levenberg-Marquardt minimization algorithm to estimate the chemical shift, amplitude, linewidth and phase (0^{th} and 1^{st} order) of echo time-specific prior knowledge templates. The metabolite fitting template included 17 brain metabolites: alanine, aspartate, choline, creatine, γ-aminobutyric acid (GABA), glucose, glutamate, glutamine, glutathione, glycine, lactate, myo-inositol, N-acetyl aspartate, N-acetyl aspartyl glutamate, phosphorylethanolamine, scyllo-inositol, and taurine. No significant macromolecule contribution was expected due to the long echo time and hence was omitted from the metabolite template. Metabolite quantification was then performed using Barstool (Wong, 2019) with corrections made for tissue-specific (gray matter, white matter, CSF) T_1 and T_2 relaxations through partial volume segmentation calculations of voxels mapped onto T_1-weighted images acquired using a 0.75 mm isotropic MP2RAGE sequence (TR = 6000 ms, TI_1 = 800 ms, TI_2 = 2700 ms, flip-angle 1 (α_1) = 4°, flip-angle 2 (α_2) = 5°, FOV = 350 mm × 263 mm × 350 mm, T_{acq} = 9 min 38 s, $iPAT_{PE}$ = 3 and 6/8 partial k-space). All spectral fit underwent visual quality inspection as well as Cramer-Rao lower bounds (CRLB) assessment for each metabolite.

Spectral Fit Quality and Metabolite Quantification

Spectral fit quality for each metabolite in our template was assessed by Cramer-Rao lower bound (CRLB) percentage values (Supplementary Table 1). Out of 17 metabolites included in the fitting template, eight metabolites are reported here that met the individual CRLB cut-off of 50%. A sample fitted spectrum outlining all metabolites included in our template is presented in Supplementary Figure 2.

Supplementary Figure 1

(A) Axial, (B), coronal, and (C) sagittal views of MRS voxel (red square) in the dorsolateral anterior cingulate cortex (ACC) for myo-inositol measurements.



Supplementary Table 1

Mean Metabolite Concentration and CRLB

	$[HC]_{baseline}$	$[HC]_{FUP}$	$CRLB_{HC\_baseline}$	$CRLB_{HC\_FUP}$	$[FES]_{baseline}$	$[FES]_{FUP}$	$CRLB_{FES\_baseline}$	$CRLB_{FES\_FUP}$
NAA	11.37 (2.03)	10.82 (1.05)	1.03 (0.34)	0.93 (0.20)	10.44 (1.03)	10.71 (1.77)	1.26 (1.08)	1.01 (0.29)
Creatine	9.31 (1.32)	8.77 (0.80)	1.28 (0.33)	1.34 (0.29)	8.85 (0.82)	9.08 (1.50)	1.28 (0.39)	1.38 (0.34)
Choline	2.64 (0.49)	2.54 (0.28)	1.90 (0.66)	1.97 (0.47)	2.47 (0.29)	2.61 (0.50)	1.81 (0.48)	1.95 (0.58)
Myo-inositol	5.45 (0.99)	5.02 (0.61)	3.94 (1.39)	4.26 (1.07)	4.62 (0.64)	5.01 (1.11)	4.21 (1.12)	4.37 (1.04)
Scyllo-inositol	0.34 (0.13)	0.33 (0.12)	18.42 (3.21)	19.83 (5.36)	0.35 (0.11)	0.37 (0.23)	17.07 (4.84)	21.54 (10.94)
Glutamate	7.25 (1.34)	6.86 (0.73)	3.43 (1.27)	3.55 (0.89)	6.51 (0.64)	6.49 (1.29)	3.52 (1.20)	3.96 (1.12)
Glutamine	1.10 (0.36)	0.98 (0.31)	20.89 (7.01)	24.93 (11.56)	1.06 (0.32)	1.09 (0.40)	19.67 (7.18)	22.91 (9.56)
Glutathione	1.71 (0.36)	1.75 (0.23)	10.92 (5.67)	9.55 (1.18)	1.64 (0.25)	1.63 (0.32)	9.99 (3.37)	10.75 (2.60)

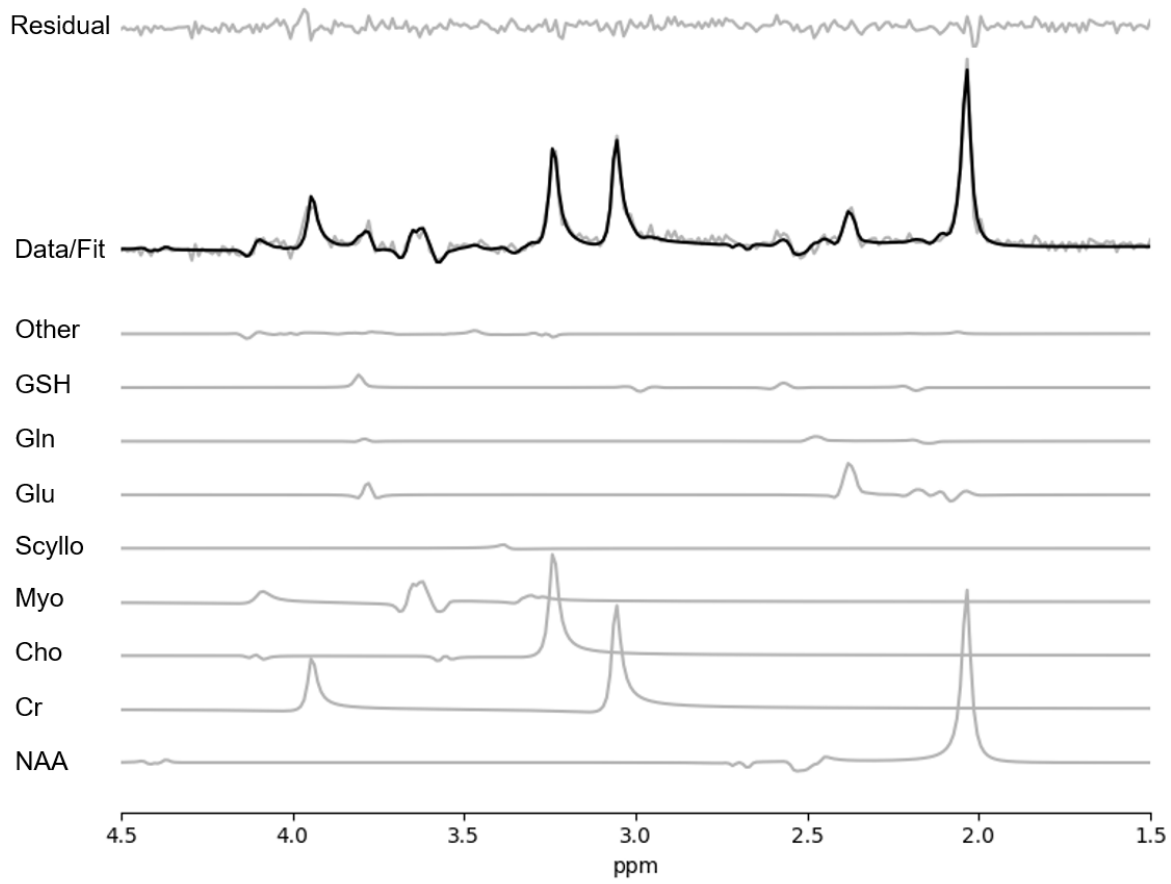
CRLB Cramer-Rao Lower Bound, *HC* healthy controls, *FES* first-episode schizophrenia, *FUP* follow-up, *NAA* N-acetyl aspartate, *SD* standard deviation

Note: Mean (SD) concentration and CRLB (SD) units are measured in mM and %, respectively. Only those metabolites with CRLB ≤ 50% were included in this table (all CRLB outliers of ≥ 50% were removed).

Supplementary Figure 2

Sample fitted spectrum of a single participant. Fit spectrum (bolded) is overlaid on the raw spectrum with the residual spectrum displayed above. Individual component spectra of the 8 metabolites reported in Supplementary Table 1 are displayed below.

Abbreviation: GSH, glutathione; Gln, glutamine; Glu, glutamate; Scyllo, scyllo-inositol; Myo, myo-inositol; Cho, choline; Cr, creatine; NAA, N-acetyl aspartate.



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