

Appendix 1 to Da Silva T, Hafizi S, Rusjan PM, et al. GABA levels and TSPO expression in people at clinical high risk for psychosis and healthy volunteers: a PET-MRS study. *J Psychiatry Neurosci* 2018.

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SUPPLEMENTARY METHODS

¹H-MRS Acquisition and Analysis

Glx was acquired from the same imaging session and acquisition as GABA and is therefore among the identical population with reported GABA+ measures. Briefly, the frequencies of these editing RF pulses were centered to suppress the C3 resonance of GABA (at 1.9 ppm) in the ‘on’ condition and at 7.5 ppm in the ‘off’ condition. This editing RF pulse pair inhibits and allows J-modulation of the coupled GABA spin system such that upon subtraction of the two sub-spectra yields the J-edited GABA C4 resonance at 3.03ppm and Glx C2 at 3.71 ppm. All post-processing and analysis were performed with Gannet. The ratio of Glx and unsuppressed water peak areas were reported. Spectra that exceeded a full-width at half maximum (FWHM) of unsuppressed water resonance greater than 10 Hz were excluded from further analysis. Quality control parameters are the same for both GABA+ and Glx, and are shown in Supplementary Table 2 below.

Levels of *N*-acetylaspartate (NAA), choline (tCho), and creatine (tCr) were acquired from the editing-off pulses, and processed through LCModel. Metabolites were reported as ratio to creatine since descriptive analyses demonstrated no change in Cr in our cohorts. Data was excluded if % standard deviation (%SD) was >15%.

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SUPPLEMENTARY TABLES

Supplementary Table 1: TSPO genotype and PET parameters in clinical high risk (CHR) and healthy volunteers (HV).

		HV (n=15)	CHR (n=29)	Test value	<i>p</i> value
TSPO genotype	HAB	11	16	$\chi^2=0.91$	<i>p</i> = 0.34
	MAB	4	13		
PET parameters (SD)	Specific activity (mCi/ μ mol)	1398.47 \pm 912.74	1474.64 \pm 839.09	F= 0.08	<i>p</i> = 0.78
	Mass injected (μ g)	1.94 \pm 1.35	1.94 \pm 1.60	F= 0.00	<i>p</i> = 1.00
	Amount injected (mCi)	4.95 \pm 0.36	5.09 \pm 0.25	F= 2.33	<i>p</i> = 0.13
	[¹⁸ F]FEPPA V_T	10.94 \pm 4.00	9.31 \pm 3.81	F= 0.62	<i>p</i> = 0.44

Abbreviations: CHR, Clinical high risk; HAB, high affinity binder; HV, healthy volunteer; MAB, mixed affinity binder; PET, positron emission tomography; SD, standard deviation; TSPO, translocator protein 18kDa; V_T , total distribution volume.

Supplementary Table 2: Mean and standard deviations of GABA+ levels in mPFC corrected and uncorrected for CSF, FWHM, and tissue fraction composition of the MRS voxel in clinical high risk (CHR) and healthy volunteers (HV).

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		HV (n=18)	CHR (n=35)	Test value	p value
	GABA+ in mPFC (SD)	2.34 x 10 ⁻⁵ (3.11 x 10 ⁻⁶)	2.39 x 10 ⁻⁵ (2.48 x 10 ⁻⁶)	F=0.00	1.00
	FWHM, Hz (SD)	7.39 (0.85)	7.57 (1.14)	F=0.36	0.55
Tissue Fraction % (SD)	Gray Matter	63.33 (3.15)	63.29 (3.60)	F=0.004	0.95
	White Matter	20.77 (3.07)	19.57 (2.90)	F=1.94	0.17
	CSF	15.89 (4.33)	17.15 (4.35)	F=1.00	0.32

Abbreviations: CHR, Clinical high risk; CSF, cerebrospinal fluid; GABA, γ -aminobutyric acid; FWHM, frequency width at half maximum intensity; HV, healthy volunteer; mPFC, medial prefrontal cortex; SD, standard deviation.

Supplementary Table 3: Correlations between GABA+ levels in mPFC and symptom severity and cognition in clinical high risk (CHR).

SOPS	Positive Symptoms		Negative Symptoms		Disorganization Symptoms		General Symptoms		Total Symptoms	
	r	p	r	p	r	p	r	p	r	p
GABA+ levels	0.04	0.82	-0.12	0.50	-0.007	0.97	0.04	0.82	-0.05	0.77

RBANS	Immediate Memory		Visuospatial memory		Language		Attention		Delayed memory		Total Scale	
	r	p	r	p	r	p	r	p	r	p	r	p
GABA+ levels	0.03	0.88	-0.006	0.97	-0.29	0.09	0.11	0.52	0.06	0.74	-0.08	0.64

Abbreviations: CHR, Clinical high risk; GABA, γ -aminobutyric acid; mPFC, medial prefrontal cortex; p, statistical value; r, correlation coefficient; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SOPS, Scale of Prodromal Syndrome.

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Supplementary Table 4: Mean and standard deviations of Glx levels, inhibitory index and other conventional metabolites in mPFC in clinical high risk (CHR) and healthy volunteers (HV).

		HV (n=18)	CHR (n=35)	Test value	p value
	Glx/H₂O (SD)	1.66 x 10 ⁻⁵ (2.41 x 10 ⁻⁶)	1.67 x 10 ⁻⁵ (2.43 x 10 ⁻⁶)	F= 0.00	p = 1.00
'Inhibitory Index' (SD)	GABA+/ [(GABA+)+ Glx]	0.58 ± 0.03	0.58 ± 0.04	F= 0.17	p = 0.68
	NAA/Cr (SD)	1.15 ± 0.12	1.16 ± 0.08	F= 0.04	p = 0.84
	Cho/Cr (SD)	0.24 ± 0.02	0.25 ± 0.03	F= 0.05	p = 0.82

Abbreviations: Cho, choline; Cr, creatine; GABA, γ -aminobutyric acid; Glx, glutamate+glutamine; NAA, N-acetylaspartate; V_T, total distribution volume.

Supplementary Table 5: Association between TSPO expression and Glx (glutamate+glutamine), inhibitory index and other conventional metabolites controlling for TSPO polymorphism.

		[¹⁸F]FEPPA V_T in mPFC	
		Test value	p value
	Glx/H₂O	F=0.13	0.72
'Inhibitory Index'	GABA+/ [(GABA+) +Glx]	F=3.26	0.08
	NAA/Cr	F=0.51	0.48

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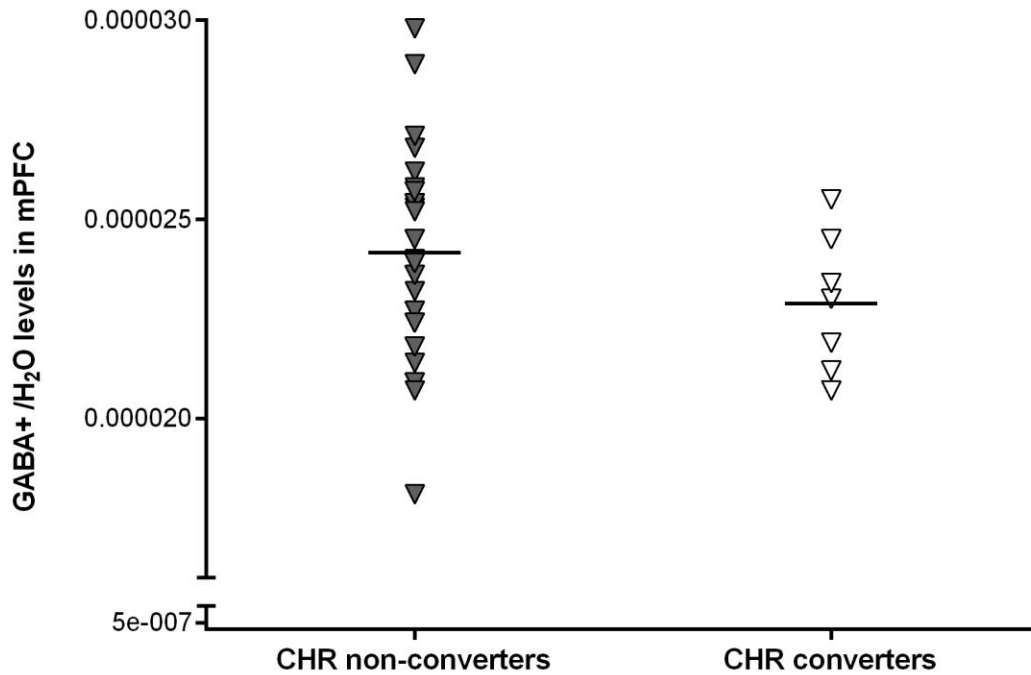
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	Cho/Cr	F=2.97	0.09
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Abbreviations: Cho, choline; Cr, creatine; GABA, γ -aminobutyric acid; Glx, glutamate+glutamine; NAA, N-acetylaspartate; V_T , total distribution volume.

SUPPLEMENTARY FIGURES

Supplementary Figure 1: GABA⁺/H₂O levels in mPFC in clinical high risk (CHR) non-converters (n=28) and CHR converters (n=7).



Suppl

ementary Figure 2: Brain region composition within the prescribed MRS voxel. Using FSL5.0, the T1 brain image was extracted, co-registered and warped to the MNI152_T1_1mm template. The corresponding ROI voxel mask was then warped using the

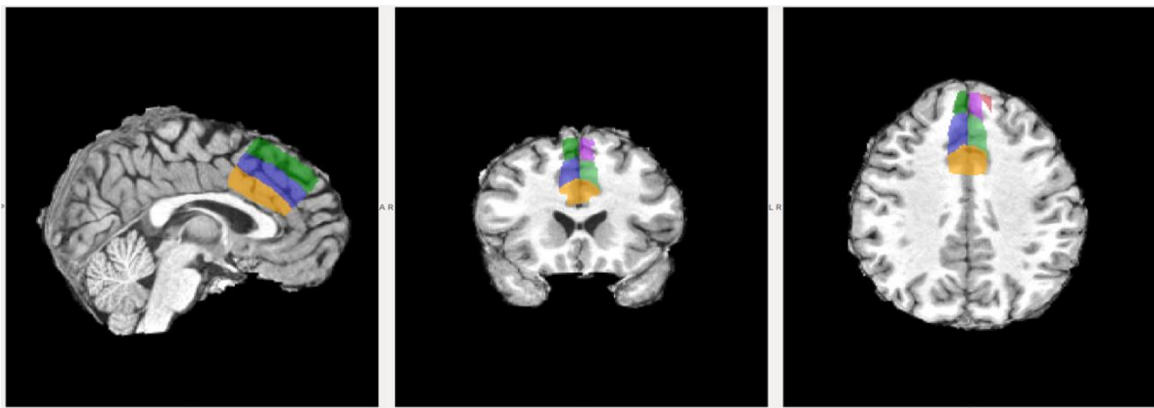
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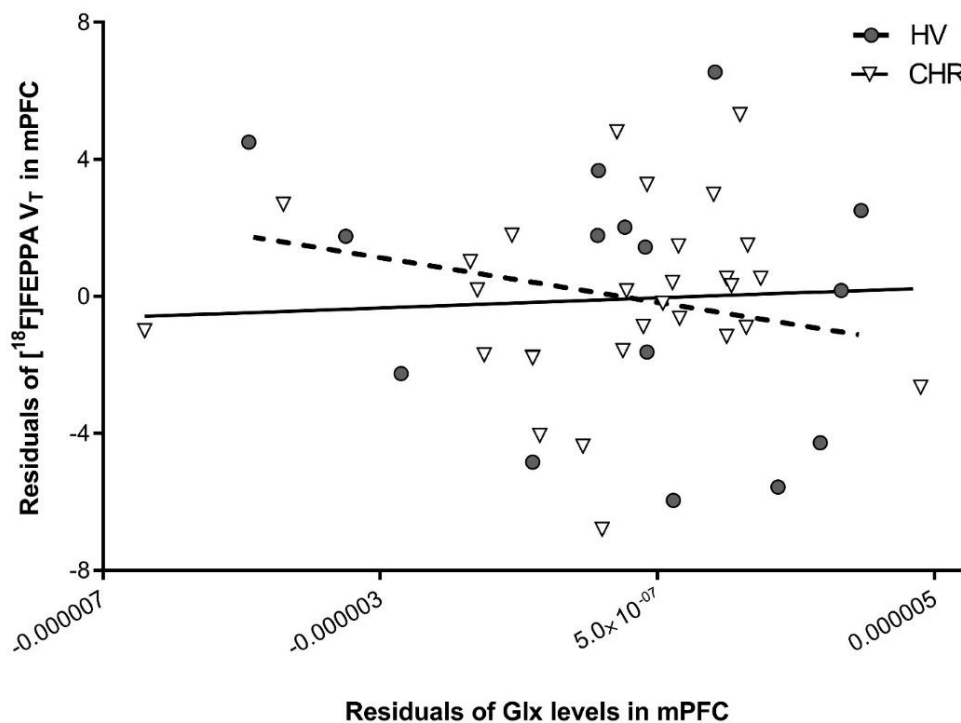
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same warping coefficients as the T1 image. The regions within the warped ROI mask were extracted from the Harvard Oxford cortical structural atlas. The 24cc MRS voxel called medial prefrontal cortex (mPFC) composes of 65% cingulate gyrus (purple and yellow) and 28% superior frontal gyrus (green).



Supplementary Figure 3: Association between TSPO expression and Glx in clinical high risk

and (CHR) healthy



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volunteers (HV).

Supplementary Figure 4: Association between TSPO expression and inhibitory index in clinical high risk (CHR) and healthy volunteers (HV).

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