SUPPLEMENTARY INFORMATION

Medial Frontal Cortex GABA Concentrations in Psychosis Spectrum and Mood Disorders: A Meta-Analysis of Proton Magnetic Resonance Spectroscopy Studies

Simmonite *et al.*

Voxel Classification

To classify the voxels from each publication, we first created a blank brain template onto which all voxels were to be placed. This template consisted of the outline of a mid-sagittal view of the brain and included the corpus collosum and anterior commissure as reference points. For each study, all information about voxel placement was extracted from the article. For publications that included a figure demonstrating placement, we digitally traced the voxel, corpus callosum, anterior commissure and outline of the brain, and used these landmarks to resize and place the voxel onto our template. If articles did not include a reference image, we reviewed the literature for other publications of the same dataset for such an image. If this was not available, we reviewed in-text information regarding voxel placement, and placed a voxel onto our template as best we could. We were able to find sufficient information to place voxels on the template image for all studies which met our inclusion criteria. Following placement of all voxels onto the template, we examined each to ensure that it was the correct size relative to others and adjusted where necessary. Since the figures featured voxels that were rendered on to brains of slightly different shapes/sizes, we wanted to ensure that on our template brain, a voxel that measured 3 x 3 x 3 cm^3 for example, was proportional to one measuring 4 x 4 x 4 cm^3.

We made preliminary assignments based on how voxels cluster, guided by the k = 3 cluster solution presented in de la Vega et al., (2016). Our rostral MFC subregion included the ventromedial prefrontal cortex and pregenual anterior cingulate cortex. The mid MFC subregion included the anterior ventral midcingulate cortex and dorsomedial prefrontal cortex. Finally, our posterior MFC subregion was comprised of the posterior ventral midcingulate cortex, posterior dorsal midcingulate cortex, and anterior dorsal midcingulate cortex.

Following initial classification, assignments were reviewed to ensure that at least two-thirds of the voxel was contained within the sub-region. Since a cluster of voxels straddled the rostral- and mid-regions of the MFC – i.e., encompassing the dorsomedial prefrontal cortex and pregenual anterior cingulate cortex - and were not easily classified into either sub-region, we creased a separate rostral-mid subregion and analysed them separately. We placed voxels from all eligible studies on to the template and classified them together, ensuring there were no differences in classifications between diagnoses. Co-registration of the voxels on to the template was performed by one author (C.J.S.) and reviewed by the others (M.S. and S.F.T.) Decisions regarding the classification of the voxels were performed by all authors in consensus.

Supplementary Results

To compare with our subregional meta-analyses, we also performed meta-analyses in which we included all voxels from across our four MFC subregions. Forest plots describing these meta-analyses are provided in Supplemental Figures 1- 4.

Schizophrenia

Meta-analysis including voxels from all subregions of the MFC revealed no significant GABA concentration differences in the full schizophrenia sample (SMD = -0.14, 95% CI = -0.32 to 0.05, $p = 0.14$) or acute subsample (SMD = -0.01, 95% CO = -0.33 to 0.32, $p = .97$), relative to healthy controls. GABA concentrations were significantly reduced in chronic patients (SMD = -0.26, 95% CI = -0.44 to -0.07, $p = 0.007$).

Depression

When combining across all subregions of the MFC, GABA concentrations were reduced in the full depression sample (SMD = -0.26, 95% CI = -0.48 to -0.04, $p = 0.02$), and the currently depressed subgroup (SMD = -0.30, 95% CI = -0.55 to -0.05, $p = 0.02$). There were no significant differences between the remitted subgroup and healthy controls (SMD = -0.01, 95% CI = -0.40 to -0.04, $p = 0.95$).

Bipolar Disorder

Meta-analysis revealed elevated GABA concentrations in patients with bipolar disorder relative to controls (SMD = 0.38, 95% CI = 0.11 to 0.65, $p = .0064$).

UHR

Combining across all regions of the MFC revealed no significant GABA differences between UHR individuals and healthy controls (SMD = -0.52, 95% CI = -1.58 to 0.54, $p = 0.33$).

Supplementary Table 1: Characteristics of included Schizophrenia studies

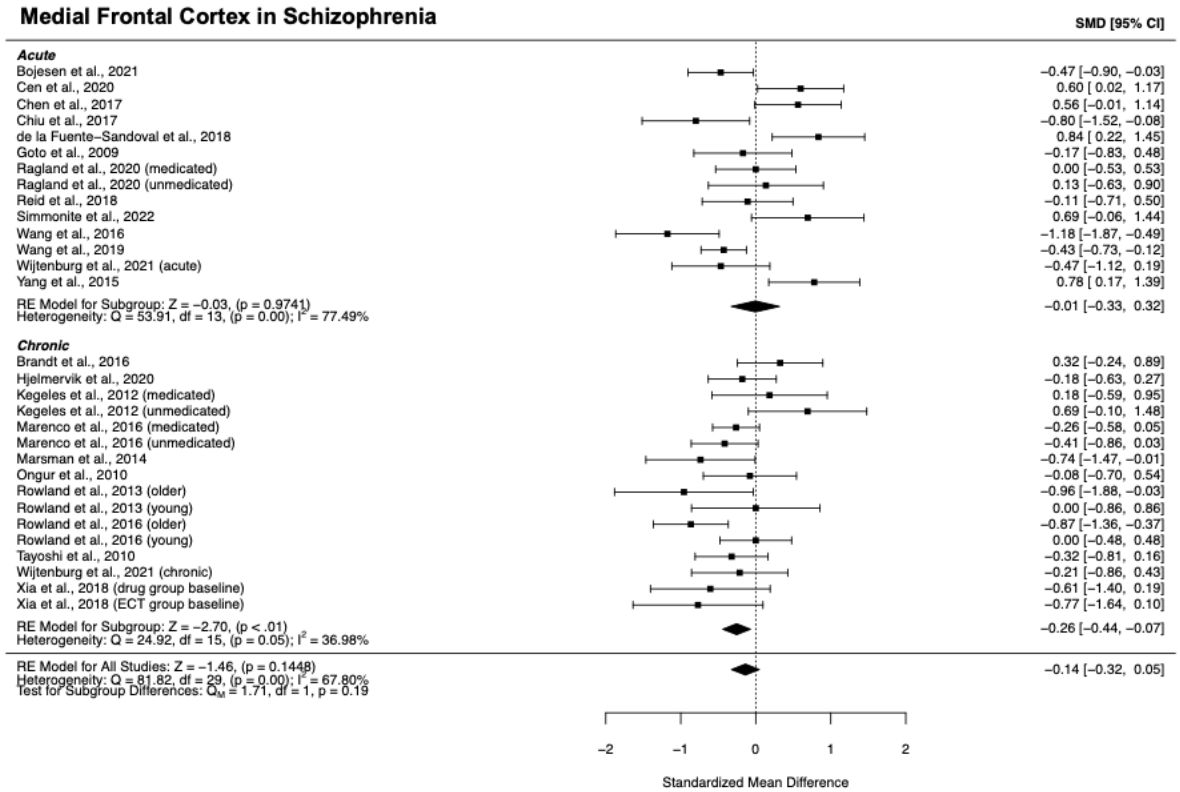
Study	Case		Control		Gender (%male)	Currently Medicated	Diagnosis	Illness duration	MRS technique	Field Strength	Reference Metabolite	Analysis software
	n	Mean age ± SD	n	Mean age ± SD								
Rostral MFC												
Cen et al., 2020 (1)	23	27.0 ± 6.5	26	25.9 ± 4.6	39.1	Unmed	10 FES, 10 SPF	Acute	MEGA-PRESS	3	Water	LCModel
Chen et al., 2017 (2)	24	28.8 ± 8.3	24	26.6 ± 4.7	41.7	Unmed	24 SZ	Acute	MEGA-PRESS	3	Water	LCModel
Chiu et al., 2018 (3)	19	29.1 ± 6.7	14	27.7 ± 5.9	57.4	Med	19 FES	Acute	MEGA-PRESS	3	Water	Gannet 2.0
De la Fuente-Sandoval et al., 2018 (4)	28	23.0 ± 6.1	18	23.0 ± 3.8	71.4	Unmed	28 FEP	Acute	J-editing	3	Water	Inhouse software
Kegeles et al., 2012 (medicated) (5)	16	32.0 ± 10.0	11	33.0 ± 8.0	68.8	Med	12 SZ, 4 SAD	Chronic	J-editing	3	Water	Inhouse software
Kegeles et al., 2012 (unmedicated) (5)	16	32.0 ± 11.0	11	33.0 ± 8.0	68.8	Unmed	10 SZ, 6 SAD	Chronic	J-editing	3	Water	Inhouse software
Ragland et al., 2020 (medicated) (6)	29	23.5 ± 4.6	25	24.2 ± 4.7	70.0	Med	29 SZ	Acute	MEGA-PRESS	3	Cr	jMRUI 4.0
Ragland et al., 2020 (unmedicated) (6)	9	23.5 ± 4.6	24	24.2 ± 4.7	70.0	Unmed	9 SZ	Acute	MEGA-PRESS	3	Cr	jMRUI 4.0
Simmonite et al., 2022 (7)	14	21.6 ± 2.6	15	21.6 ± 3.6	64.3	Mixed	14 FEP	Acute	MEGA-PRESS	3	Water	Gannet 3.0
Wang et al., 2016 (8)	16	22.1 ± 5.5	23	22.5 ± 5.5	50.0	Unmed	SZ, SPF	Acute	MEGA-PRESS	3	Water	LCModel
Xia et al., 2018 (drug group baseline) (9)	17	31.0 ± 7.7	10	30.9 ± 5.3	47.0	Med	17 SZ	Chronic	MEGA-PRESS	3	Cr	Gannet 2.0
Xia et al., 2018 (ECT group baseline) (9)	14	27.6 ± 7.3	9	30.9 ± 5.3	50.0	Med	14 SZ	Chronic	MEGA-PRESS	3	Cr	Gannet 2.0
Yang et al., 2015 (10)	22	26.1 ± 5.8	23	25.5 ± 4.4	40.9	Unmed	10 SZ, 12 SPF	Acute	MEGA-PRESS	3	Water	LCModel
Rostral-Mid MFC												
Marsman et al., 2014 (11)	13	27.6 ± 6.1	19	27.7 ± 5.3	76.5	Med	13 SZ	Chronic	MEGA-sLASER	7	Cr	Inhouse software
Rowland et al., 2013 (older) (12)	10	51.1 ± 4.0	10	49.4 ± 3.9	70.0	Med	10 SZ	Chronic	MEGA-PRESS	3	Water	csx3
Rowland et al., 2013 (young) (12)	11	30.2 ± 6.6	19	33.4 ± 6.5	81.8	Med	11 SZ	Chronic	MEGA-PRESS	3	water	csx3
Mid MFC												
Bojesen et al., 2021 (13)	37	22.7 ± 5.0	47	22.2 ± 4.1	42.9	Unmed	SZ, SAD, NOP, PP	Acute	MEGA-PRESS	3	Water	Gannet
Brandt et al., 2016 (14)	24	37.5 ± 26.7	24	36.6 ± 14.5	79.2	Med	SZ, SAD	Chronic	STEAM	7	Water	LCModel
Goto et al., 2009 (15)	18	29.0 ± 11.0	18	30.0 ± 11.0	50.0	Med	18 SZ	Acute	MEGA-PRESS	3	Cr	LCModel
Ongur et al., 2010 (16)	21	39.0 ± 10.8	19	36.3 ± 9.8	66.7	Med	21 SZ	Chronic	MEGA-PRESS	4	Cr	LCModel
Reid et al., 2019 (17)	21	23.3 ± 4.4	21	23.5 ± 4.4	76.2	Med	SZ, SAD	Acute	STEAM	7	Water	LCModel
Rowland et al., 2016 (older) (18)	31	48.3 ± 5.8	37	52.0 ± 6.0	61.3	Mixed	50 SZ, 10 SAD	Chronic	MEGA-PRESS	3	Water	Gannet 2.0
Rowland et al., 2016 (young) (18)	29	25.7 ± 4.3	40	25.3 ± 4.6	69.0	Mixed		Chronic	MEGA-PRESS	3	Water	Gannet 2.0
Wang et al., 2019 (19)	81	22.3 ± 4.4	91	25.3 ± 3.9	70.4	Med	81 FEP	Acute	STEAM	7	Water	LCModel
Wijtenburg et al., 2021 (acute) (20)	18	24.3 ± 3.9	19	NR	68.4	Med	18 SZ	Acute	STEAM	7	Water	LCModel
Wijtenburg et al., 2021 (chronic) (20)	21	43.1 ± 11.0	17	NR	47.6	Med	18 SZ	Chronic	STEAM	7	Water	LCModel
Posterior MFC												
Hjelmervik et al., 2020 (21)	37	29.8 ± 11.5	38	30.2 ± 10.2	NR	Mixed	37 SSD	Chronic	MEGA-PRESS	3	Water	LCModel
Marenco et al., 2016 (medicated) (22)	70	31.2 ± 9.2	92	30.6 ± 9.2	71.4	Med	56 SZ, 8 SAD, 6 OP	Chronic	J-editing	3	Cr	Inhouse software
Marenco et al., 2016 (unmedicated) (22)	25	28.4 ± 8.7	92	30.6 ± 9.2	72.0	Unmed	16 SZ, 3 SAD, 6 OP	Chronic	J-editing	3	Cr	Inhouse software
Tayoshi et al., 2010 (23)	38	34.0 ± 10.0	29	34.0 ± 10.2	52.6	Med	38 SZ	Chronic	MEGA-PRESS	3	Water	LCModel

Abbreviations: Cr, creatine; ECT, electroconvulsive therapy; FEP, first episode psychosis; Med, medicated; MEGA-PRESS, Mescher-Garwood point resolved spectroscopy; MEGA-sLASER, Mescher-Garwood-semi-localized by adiabatic selective refocusing; MFC, medial frontal cortex; NOP, non-organic psychosis; OP, psychosis not otherwise specified; PP, paranoid psychosis; PRESS, point resolved spectroscopy; SAD, schizoaffective disorder; SD, standard deviation; SSD, schizophrenia spectrum disorder; SFP, schizophreniform disorder; STEAM, stimulated echo acquisition mode; SZ, schizophrenia; NR, not reported; Unmed, unmedicated.

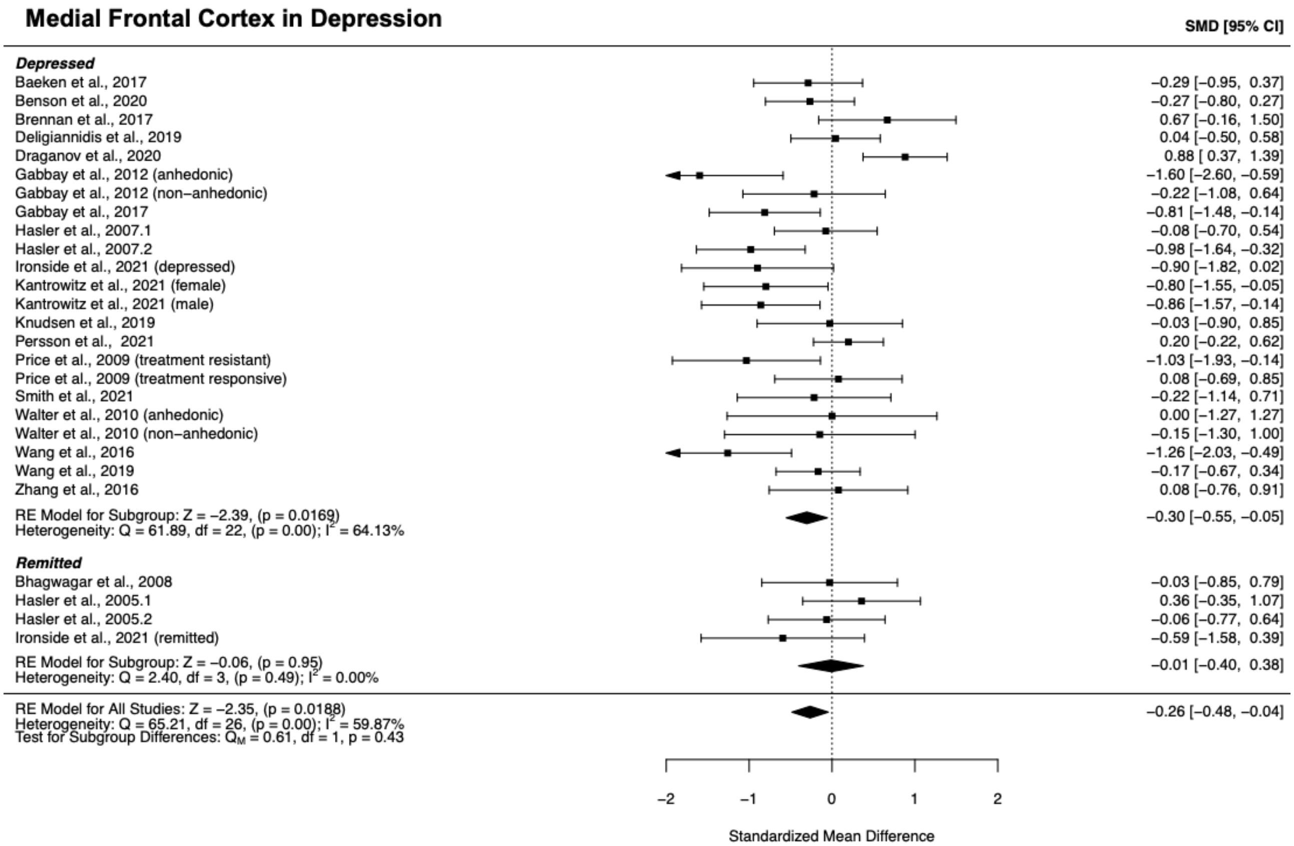
Supplementary Table 2: Characteristics of included Depression studies										
Study	Case		Control		Gender (%male)	Currently Medicated	MRS technique	Field Strength	Reference Metabolite	Analysis software
	n	Mean age ± SD	n	Mean age ± SD						
Rostral MFC										
Brennan et al., 2017 (24)	17	38.5 ± 12.2	9	38.4 ± 14.1	57.9	Unmedicated	MEGA-PRESS	3	Cr	LCModel
Gabbay et al., 2012 (anhedonic) (25)	10	18 ± 1.9	10	16.2 ± 1.6	40.0	Mixed	J-editing	3	Water	Inhouse software
Gabbay et al., 2012 (non-anhedonic) (25)	10	15.3 ± 2.7	11	16.2 ± 1.6	40.0	Mixed	J-editing	3	Water	Inhouse software
Gabbay et al., 2017 (26)	24	16.1 ± 2.6	15	15.3 ± 2.7	54.2	Unmedicated	J-editing	3	Water	Inhouse software
Hasler et al., 2005 (27)	16	41 ± 11.6	15	41.7 ± 12.4	33.3	Unmedicated	J-editing	3	Water	MRUI
Hasler et al., 2007 (28)	20	34 ± 11.2	20	34.8 ± 12.4	35.0	Unmedicated	J-editing	3	Water	Inhouse software
Ironside et al., 2021 (depressed) (29)	17	21.1 ± 1.8	7	21.5 ± 2.5	0.0	Unmedicated	MEGA-PRESS	3	Water	LCModel
Ironside et al., 2021 (remitted) (29)	13	21.1 ± 2.12	6	21.5 ± 2.5	0.0	Unmedicated	MEGA-PRESS	3	Water	LCModel
Kantrowitz et al., 2021 (female) (30)	12	35 ± 10.4	19	36.9 ± 9.7	0.0	Unmedicated	PROBE-P/PROBE-J	3	NAA	Gannet
Kantrowitz et al., 2021 (male) (30)	22	38.4 ± 11	13	30.7 ± 5.1	100.0	Unmedicated	PROBE-P/PROBE-J	3	NAA	Gannet
Price et al., 2009 (treatment resistant) (31)	12	46.8 ± 11.8	10	37.3 ± 13.5	56.3	Unmedicated	J-editing	3	Water	Inhouse software
Price et al., 2009 (treatment responsive) (31)	16	38.3 ± 12.3	11	37.3 ± 13.5	66.7	Unmedicated	J-editing	3	Water	Inhouse software
Walter et al., 2010 (anhedonic) (32)	4	40 ± NR	6	34.6 ± NR	42.1	Unmedicated	J-PRESS	3	Cr	ProFit
Walter et al., 2010 (non-anhedonic) (32)	5	40 ± NR	7	34.6 ± NR	42.1	Unmedicated	J-PRESS	3	Cr	ProFit
Wang et al., 2019 (33)	19	47.7 ± 1.9	71	46.8 ± 2.0	0.0	NR	MEGA-PRESS	3	Water	TARQUIN
Zhang et al., 2016 (34)	11	34.1 ± 8.8	11	33.6 ±7.2	0.0	Mixed	MEGA-PRESS	3	Water	LCModel
Rostral-Mid MFC										
Deligiannidis et al., 2019 (35)	25	28.6 ± 4.9	28	29.0 ± 5.0	0	Unmedicated	MEGA-PRESS	3	Cr	Gannet
Draganov et al., 2020 (36)	23	37.3 ± 10.8	54	41.8 ± 10.1	41.9	Unmedicated	PRESS	3	Water	TARQUIN
Hasler et al., 2005 (27)	16	41.0 ± 11.6	15	41.7 ± 12.4	33.3	Unmedicated	J-editing	3	Water	MRUI
Hasler et al., 2007 (28)	20	34.0 ± 11.2	20	34.8 ± 12.4	35.0	Unmedicated	J-editing	3	Water	Inhouse software
Knudsen et al., 2019 (37)	10	38.4 ± 10.9	10	38.8 ± 10.8	40.0	Medicated	SPECIAL	3	Cr	LCModel
Mid MFC										
Baeken et al., 2017 (38)	18	47.2 ± 12.5	18	45.8 ± 12.3	33.3	Mixed	PRESS	3	Water	jMRUI 5.1
Benson et al., 2020 (39)	41	33.2 ± 14.4	20	33.9 ± 14.6	19.5	Unmedicated	MEGA-PRESS	4	Cr	LCModel
Bhagwagar et al., 2008 (40)	12	40.6 ± 4.2	11	34.3 ± 4.1	33.3	Unmedicated	MEGA-PRESS	3	Cr	LCModel
Persson et al., 2021 (41)	42	29.2 ± 9.4	45	29.5 ± 11.2	50.0	Mixed	MEGA-PRESS	3	Cr	Gannet 3.0
Smith et al., 2021 (42)	9	70.0 ± 7.0	9	67.0 ± 7.0	44.4	Medicated	STEAM	7	Cr	LCModel
Wang et al., 2016 (43)	19	53.9 ± 2.6	13	52.6 ± 2.18	0	Unmedicated	MEGA-PRESS	3	Water	Gannet
Abbreviations: Cr, creatine; MEGA-PRESS, Mescher-Garwood point resolved spectroscopy; MFC, medial frontal cortex; PRESS, point resolved spectroscopy; SD, standard deviation; SPECIAL, spin echo full intensity-acquired localized spectroscopy; STEAM, stimulated echo acquisition mode; NAA, N-acetyl aspartate; NR, not reported.										

Supplementary Table 3: Characteristics of included bipolar disorder studies										
Study	Case		Control		Gender (%male)	Currently Medicated	MRS technique	Field Strength	Reference Metabolite	Analysis software
	n	Mean age ± SD	n	Mean age ± SD						
Rostral MFC										
Brady et al., 2013 (medicated) (44)	10	32.6 ± 13.6	7	36.9 ± 10.4	57.1	Medicated	MEGA-PRESS	4	Cr	LCModel
Brady et al., 2013 (unmedicated) (44)	4	32.6 ± 13.6	7	36.9 ± 10.4	57.1	Unmedicated	MEGA-PRESS	4	Cr	LCModel
Godlewska et al., 2014 (45)	13	23.8 ± 3.6	11	21.9 ± 2.7	46.2	Unmedicated	SPECIAL	3	Cr	LCModel 6.2-2B
Wang et al., 2006 (46)	15	35.7 ± 11.4	6	41.7 ± 21.2	80.0	Mixed	J-editing	3	Cr	SAGE
Mid MFC										
Huber et al., 2018 (47)	19	17.5 ± 2.6	10	19.0 ± 1.6	31.6	NR	J-PRESS	3	Water	ProFit
Priscandaro et al., 2017 (48)	18	36.3 ± 11.4	15	38.0 ± 11.1	55.0	Mixed	J-RES	3	Water	ProFit
Soeiro-de-Souza et al., 2015 (49)	50	31.7 ± 9.1	38	25.7 ± 5.7	38.0	Mixed	J-PRESS	3	Cr	ProFit
Abbreviations: Cr, creatine; MEGA-PRESS, Meschler-Garwood point resolved spectroscopy; MFC, medial frontal cortex; PRESS, point resolved spectroscopy; SD, standard deviation; SPECIAL, spin echo full intensity-acquired localized spectroscopy; NR, not reported										

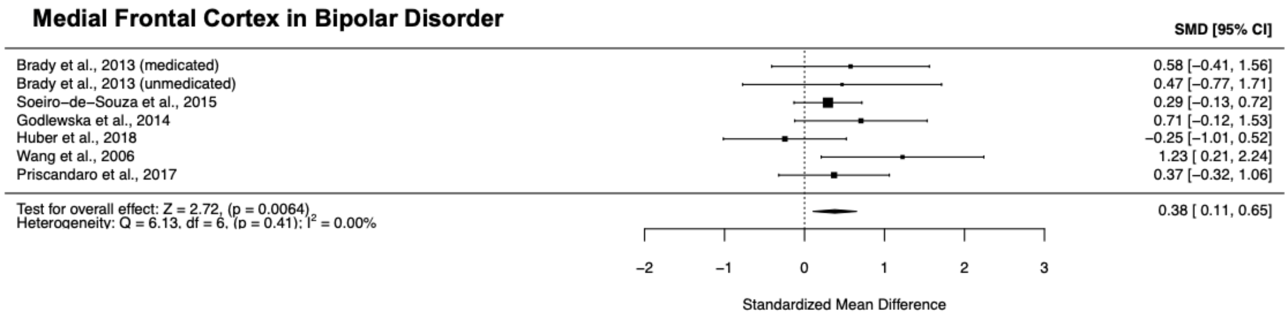
Supplementary Table 4: Characteristics of included Ultra High-Risk studies										
Study	Case		Control		Gender (%male)	Currently Medicated	MRS technique	Field Strength	Reference Metabolite	Analysis software
	n	Mean age ± SD	n	Mean age ± SD						
Rostral MFC										
De la Fuente-Sandoval et al., 2015 (50)	23	20.7 ± 4.1	24	21.4 ± 3.3	65.22	Unmedicated	J-editing	3	Water	Inhouse software
Menschikov et al., 2016 (51)	21	NR	26	NR	100.0	NR	MEGA-PRESS	3	Cr	jMRUI 5.1a
Simmonite et al., 2022 (7)	7	19.9 ± 3.6	15	21.6 ± 21.6	71.43	Mixed	MEGA-PRESS	3	Water	Gannet 3.1
Wang et al., 2016 (8)	21	21.1 ± 5.7	23	22.5 ± 22.5	57.14	Unmedicated	MEGA-PRESS	3	Water	LCModel
Mid MFC										
Wenneberg et al., 2020 (medicated) (52)	54	23.9 ± 4.2	26	25.3 ± 5.2	N.R.	Medicated	MEGA-PRESS	3	Water	Gannet 3.0
Wenneberg et al., 2020 (unmedicated) (52)	47	23.9 ± 4.2	27	25.3 ± 5.2	N.R.	Unmedicated	MEGA-PRESS	3	water	Gannet 3.0
Posterior MFC										
Da Silva et al., 2019 (53)	35	20.6 ± 1.6	18	21.3 ± 2.0	54.3	Mixed	MEGA-PRESS	3	Water	Gannet
Modinos et al., 2018 (54)	21	22.2 ± 3	20	23.7 ± 2.7	100.0	Unmedicated	MEGA-PRESS	3	Cr	LCModel6.3-1L
Abbreviations: Cr, creatine; JRES, J-resolved; MEGA-PRESS, Mescher-Garwood point resolved spectroscopy; MFC, medial frontal cortex; SD, standard deviation; NR, not reported										



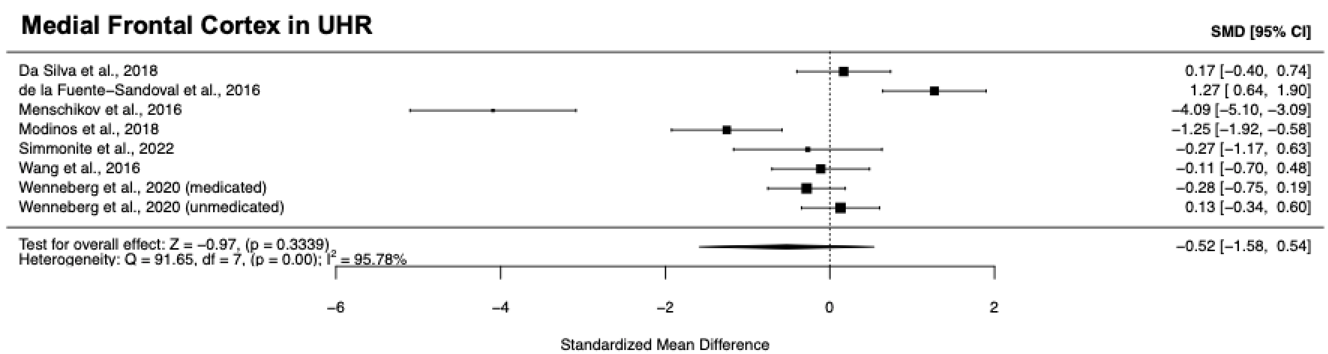
Supplementary Figure 1: Forest plots showing summary effect sizes between individuals with schizophrenia and healthy controls for all voxels within the MFC. Negative SMDs denote lower GABA concentrations in patients in comparison with controls and positive SMDs denote higher GABA concentrations in patients relative to controls. Abbreviations: SMD – standardized mean difference, CI – confidence interval, RE – Random effects, df – degrees of freedom.



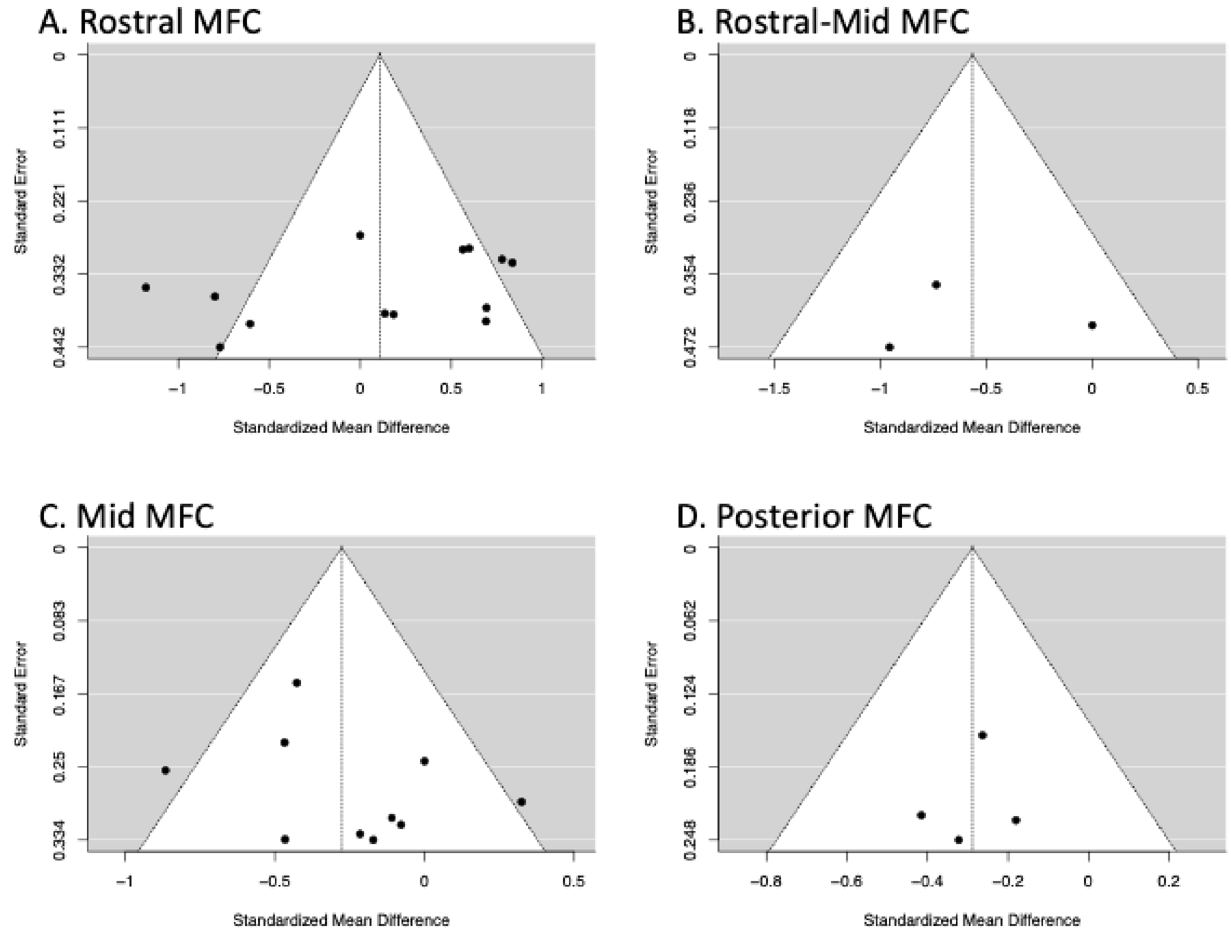
Supplementary Figure 2: Forest plots showing summary effect sizes between individuals with depression and healthy controls for all voxels within the MFC. Negative SMDs denote lower GABA concentrations in patients in comparison with controls and positive SMDs denote higher GABA concentrations in patients relative to controls. Abbreviations: SMD – standardized mean difference, CI – confidence interval, RE – Random effects, df – degrees of freedom.



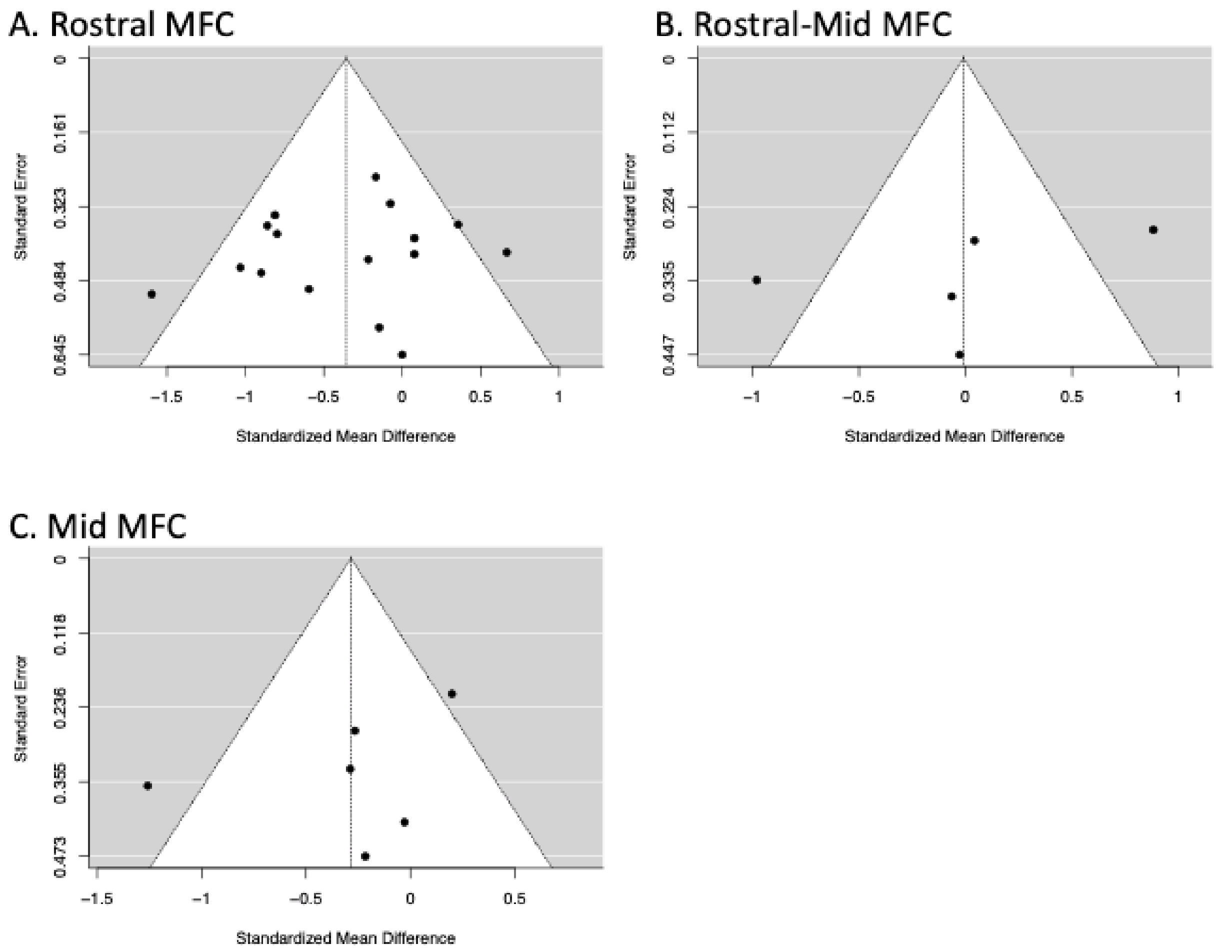
Supplementary Figure 3: Forest plots showing summary effect sizes between individuals with bipolar disorder and healthy controls for all voxels within the MFC. Negative SMDs denote lower GABA concentrations in patients in comparison with controls and positive SMDs denote higher GABA concentrations in patients relative to controls. Abbreviations: SMD – standardized mean difference, CI – confidence interval, df – degrees of freedom.



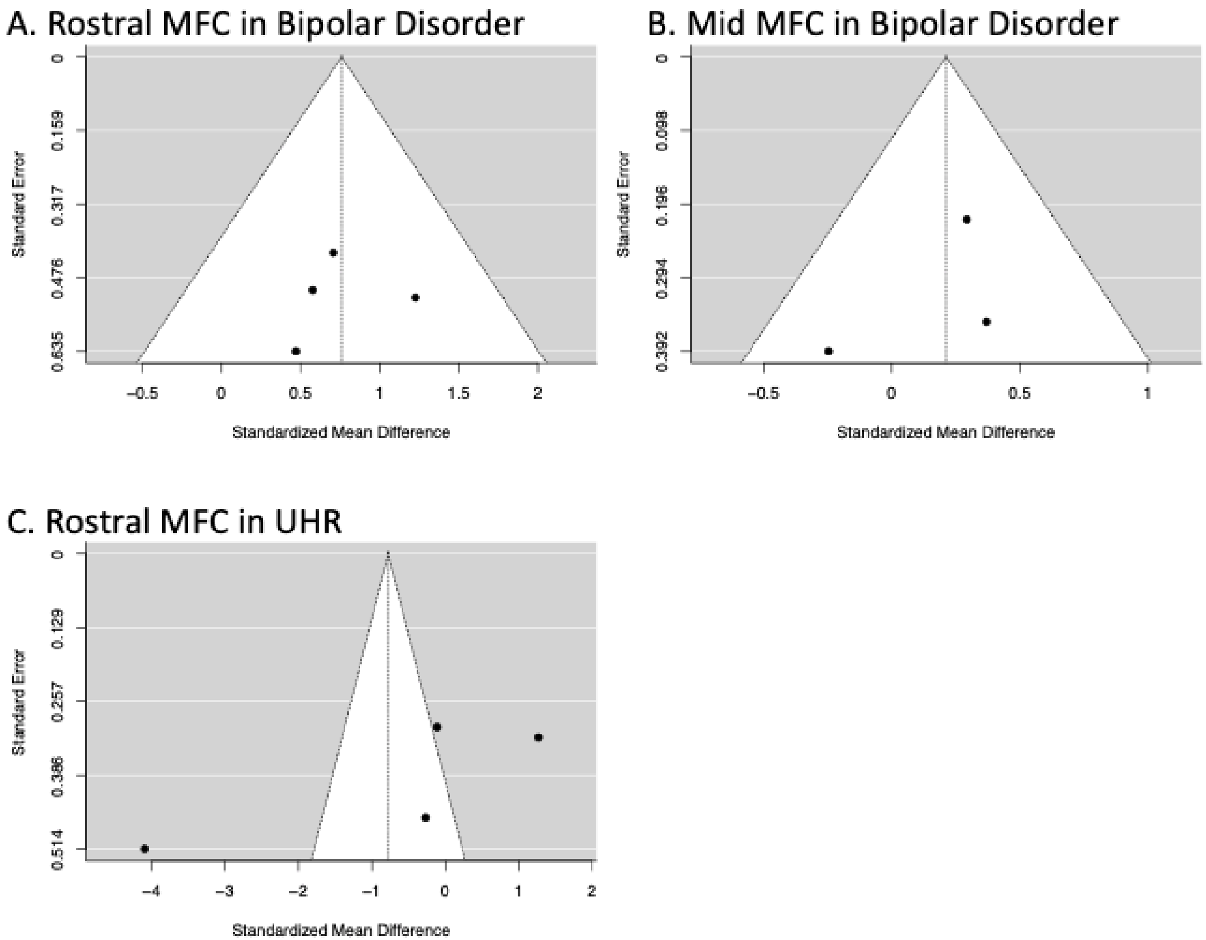
Supplementary Figure 4: Forest plots showing summary effect sizes between UHR individuals and healthy controls for all voxels within the MFC. Negative SMDs denote lower GABA concentrations in UHR individuals in comparison with controls and positive SMDs denote higher GABA concentrations in UHR individuals relative to controls. Abbreviations: SMD – standardized mean difference, CI – confidence interval, df – degrees of freedom.



Supplementary Figure 5: Funnel plots for studies on Schizophrenia in the A) rostral MFC; B) rostral-mid MFC; C) mid MFC; and Posterior MFC showing the relationship between the standardized mean difference and standard error for each included study. Egger's test is not significant for the rostral MFC (p = .14), rostral-mid MFC (p = .99), mid MFC (p = .31) or posterior MFC (p = .85).



Supplementary Figure 6: Funnel plots for studies on depression in the A) rostral MFC; B) rostral-mid MFC; C) mid MFC, showing the relationship between the standardized mean difference and standard error for each included study. Egger's test is not significant for the rostral MFC (p = .55), rostral-mid MFC (p = .44) or mid MFC (p = .50)



Supplementary Figure 7: Funnel plots for studies on bipolar disorder in the A) rostral MFC and B) mid MFC, and C, studies of individuals meeting ultra-high risk (UHR) criteria in the mid MFC, showing the relationship between the standardized mean difference and standard error for each included study. Egger's test is not significant for the rostral MFC (p = .50) or mid MFC (p = .47) in bipolar disorder, or the rostral MFC in UHR (p = .06)

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