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Supplementary results

LEAVE-ONE-OUT SENSITIVITY ANALYSES

- 2. Unipolar depression vs healthy controls
- 2.1. Plasma GABA levels in unipolar depression

Leave-one-out analyses showed no marked difference in results, suggesting that they were not driven by one single study.

2.2. CSF GABA levels in unipolar depression

One study³⁵ included patients with treatment and two others^{33,37} included non-medicated samples. When excluding medicated samples from analyses, the significance of SMD was lost but the alpha risk remained at 6% (n=2 studies; 149 patients and 67 healthy controls; test for overall effect: SMD=-0.58, 95% CI: -1.17 to 0.02, p=0.06; test for heterogeneity: χ^2 =2.90, p=0.09).

2.3. MRS GABA levels in unipolar depression

Leave-one-out sensitivity analyses and meta-regression analyses did not contribute to give explanations to heterogeneity.

Despite the great heterogeneity of used ROIs, we gave results from subanalyses that should be interpreted cautiously. No change in MRS GABA levels was observed between euthymic patients and healthy controls (n=3 studies; 50 patients and 51 healthy controls; test for overall effect: SMD=-0.30, 95% CI: -0.95 to 0.35, p=0.37; test for heterogeneity: χ^2 =5.27, p=0.07). No change in MRS GABA levels between before and after treatment was observed (n=7 studies; test for overall effect: SMD=-0.27, 95% CI: -0.73 to 0.19, p=0.25; test for heterogeneity: χ^2 =14.14, p=0.03, I2=58%). I2,20,24-26,28 Importantly, "after treatment" states did not necessarily correspond to the definitions of treatment response or remission. For example, Valentine et al²⁸ reported mean "before" and "after treatment" HDRS scores of 26.8 and 19.2 respectively.

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3. Bipolar depression vs healthy controls

3.1. Plasma GABA levels in bipolar depression

Only one study⁴³ included patients without treatment and its exclusion from analyses leaded to the loss of significance (n=2 studies; 29 patients and 88 healthy controls; test for overall effect: SMD=-0.33, 95% CI: -0.75 to 0.09, p=0.13; test for heterogeneity: χ^2 =0.01, p=0.94), suggesting that mood stabilizers may contribute to normalize diminished plasma GABA levels in bipolar MDE. Exclusion of other studies did not markedly affect the present result.

Only one study assessed GABA levels in medicated sample and reported no difference between medicated bipolar patients and healthy controls.⁵² The exclusion of this medicated sample from analyses did not affect the present result (n=3 studies; 39 patients and 87 healthy controls; test for overall effect: SMD=-0.76, 95% CI: -1.16 to -0.36, p<0.001; test for heterogeneity: $\chi^2=1.08$, p=0.58).

3.2. CSF GABA levels in bipolar depression

One study assessed CSF GABA in medicated samples and reported diminished levels.³⁵ The two other studies,^{33,37} conducted in unmedicated patients revealed no difference between patients and controls (n=2 studies; 42 patients and 67 healthy controls; test for overall effect: SMD=-0.18, 95% CI: -0.98 to 0.61, p=0.65; test for heterogeneity: γ^2 =2.40, p=0.12).

The study by Berettini et al⁵³ reported no GABA change in CSF during euthymic states in bipolar patients, in comparison with healthy controls.

One study⁵⁰ reported no significant CSF GABA change before vs. after treatment by carbamazepine in patients with bipolar disorder.

4. Unipolar depression vs Bipolar depression

4.2. CSF GABA levels in unipolar depression vs bipolar depression

Leave-one-out analyses showed that the exclusion of either the study by Gerner et al³³ or the study by Mann et al³⁷ which included unmedicated samples, leaded to the loss of the significance, suggesting that medications may reduced the difference in CSF GABA levels between unipolar and bipolar depression.

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FUNNEL PLOTS

SMDs, 95% CIs (**A**) and funnel plots if there are more than 4 studies (**B**) were given in details for each Unipolar disorder analyze (**Figure S1-S6 A & B**). SMDs, 95% CIs (**A**) and funnel plots if there are more than 4 studies (**B**) were given in details for each bipolar disorder analyze (**Figure S7-S11 A & B**). SMDs, 95% CIs were given in details for each comparison between unipolar and bipolar disorder (**Figure S12-S13**).

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	MDD ac	ute epi	sode	C	ontrol		:	Std. Mean Difference		Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI		
Petty et al 1981	34.8	6.3	24	66	14	20	15.0%	-2.92 [-3.79, -2.04]	1981			
Petty et al 1984	35	10	16	63	15	20	15.4%	-2.10 [-2.94, -1.27]	1984			
Petty et al 1990	105	32.5	88	126	21	68	19.8%	-0.74 [-1.07, -0.42]	1990	*		
Petty et al 1992	107.2	30.8	77	123	19.5	51	19.6%	-0.58 [-0.95, -0.22]	1992	→		
Paige et al 2007	0.6	0.16	9	1.15	0.28	10	11.9%	-2.27 [-3.48, -1.06]	2007			
Lu et al 2014	2.6	1.6	27	3.5	1.5	30	18.2%	-0.57 [-1.10, -0.04]	2014	-		
Total (95% CI)			241			199	100.0%	-1.40 [-2.04, -0.76]		•		
Heterogeneity: Tau ² =	= 0.51; Ch	$i^2 = 38.6$	-	-4 -2 0 2 4								
Test for overall effect	: Z = 4.29	(P < 0.0)	0001)							MDD acute episode Control		

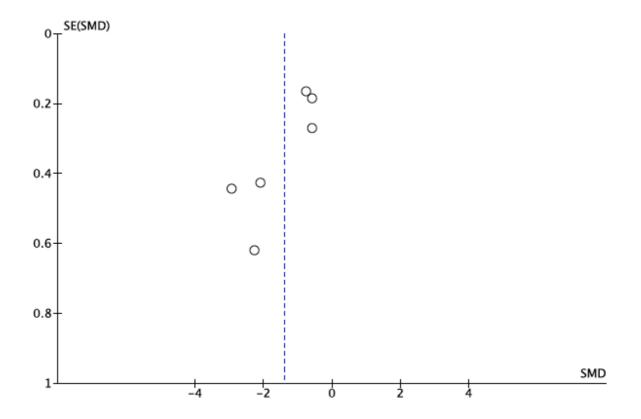


Figure S1. (**A**) Standardized Mean Difference (SMD) of plasma GABA level between Unipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI). (**B**) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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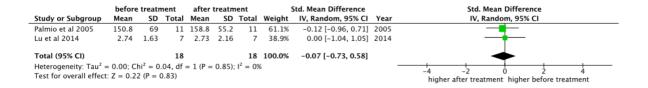


Figure S2. Standardized Mean Difference (SMD) of plasma GABA level before and after treatment in Unipolar current MDE. Error bars indicate 95% confidence interval (95% CI).

	MDD Control				1	Std. Mean Difference		Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Gerner et al 1981	134	26.9	19	183	62.5	29	28.4%	-0.93 [-1.54, -0.32]	1981	
Kasa et al 1982	101.1	42	10	137.5	57.4	24	20.8%	-0.66 [-1.42, 0.09]	1982	
Mann et al 2014	15.1	7.1	130	17.4	7.6	38	50.9%	-0.32 [-0.68, 0.05]	2014	
Total (95% CI)			159			91	100.0%	-0.56 [-0.96, -0.17]		•
Heterogeneity: Tau ² = Test for overall effect:				-2 -1 0 1 2 MDD Control						

Figure S3. Standardized Mean Difference (SMD) of csf GABA level between Unipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI).

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	MDD a	IDD acute episode Control						Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Sanacora et al 1999	0.71	0.27	14	1.48	0.39	18	8.4%	-2.19 [-3.09, -1.28]	1999	
Kugaya et al 2003	1.05	0.46	6	1.46	0.3	12	7.3%	-1.09 [-2.15, -0.03]	2003	
Sanacora et al 2004	1.2	0.42	33	1.42	0.28	28	11.4%	-0.60 [-1.11, -0.08]	2004	
Epperson et al 2006	1.39	0.29	9	1.11	0.27	14	8.5%	0.97 [0.08, 1.86]	2006	
Hasler et al 2007	0.89	0.11	20	1	0.11	20	10.3%	-0.98 [-1.64, -0.32]	2007	
Walter et al 2009	0.21	0.08	17	0.21	0.07	22	10.5%	0.00 [-0.63, 0.63]	2009	
Price et al 2009	0.00268	0.00036	33	0.00306	0.00052	24	11.2%	-0.86 [-1.41, -0.31]	2009	
Gabbay et al 2012	0.00237	0.0004	20	0.00268	0.00027	21	10.4%	-0.90 [-1.54, -0.25]	2012	
Abdallah et al 2014	1.12	0.1	23	1.12	0.12	17	10.6%	0.00 [-0.63, 0.63]	2014	
Godlewska et al 2015	0.225	0.034	33	0.237	0.053	27	11.5%	-0.27 [-0.78, 0.24]	2015	
Total (95% CI)			208			203	100.0%	-0.57 [-0.99, -0.15]		•
Heterogeneity: Tau ² = Test for overall effect:			f = 9 (P	< 0.0001)	$I^2 = 75\%$				-	-4 -2 0 2 4 MDD acute episode Control

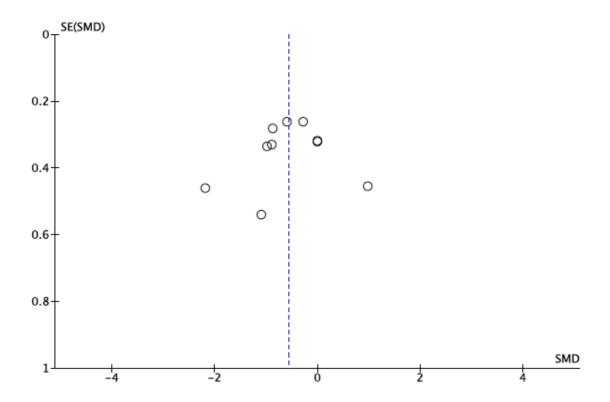


Figure S4. (A) Standardized Mean Difference (SMD) of MRS GABA level between Unipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI). (B) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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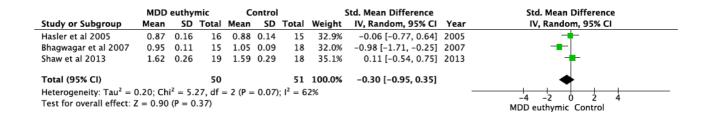


Figure S5. Standardized Mean Difference (SMD) of MRS GABA level between Unipolar euthymic vs controls. Error bars indicate 95% confidence interval (95% CI).

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	befor	e treatr	nent	after	treatm	ent	9	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Sanacora et al 2002	1.27	0.3	11	1.7	0.37	11	12.8%	-1.23 [-2.15, -0.30]	2002	
Sanacora et al 2003	0.85	0.34	8	1.51	0.48	8	10.0%	-1.50 [-2.65, -0.35]	2003	
Sanacora et al 2006	1.24	0.33	8	0.91	0.92	8	11.8%	0.45 [-0.54, 1.45]	2006	
Valentine et al 2011	0.128	0.02	10	0.134	0.02	10	13.4%	-0.29 [-1.17, 0.59]	2011	
Abdallah et al CBT 2014	0.125	0.017	28	0.129	0.015	30	19.8%	-0.25 [-0.76, 0.27]	2014	
Abdallah et al SSRI 2014	0.132	0.018	9	0.127	0.012	9	12.7%	0.31 [-0.62, 1.24]	2014	
Godlewska et al 2015	0.226	0.032	27	0.221	0.035	27	19.5%	0.15 [-0.39, 0.68]	2015	-
Total (95% CI)			101			103	100.0%	-0.27 [-0.73, 0.19]		•
Heterogeneity: $Tau^2 = 0.2$ Test for overall effect: $Z = 0.2$				(P = 0.	03); I ² =	= 58%			_	-4 -2 0 2 4 Higher after treatment Higher before treatment

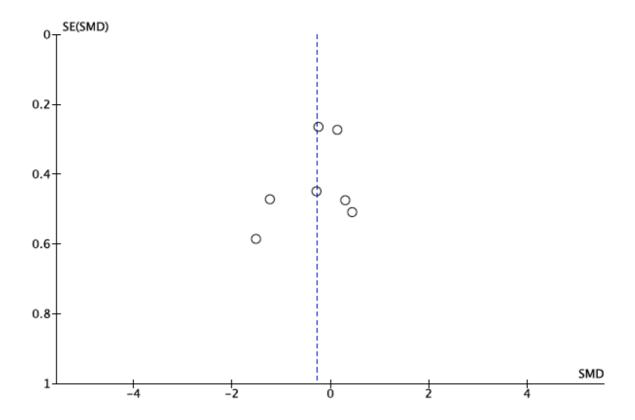


Figure S6. (A) Standardized Mean Difference (SMD) of MRS GABA level between before and after treatment in Unipolar current MDE. Error bars indicate 95% confidence interval (95% CI). (B) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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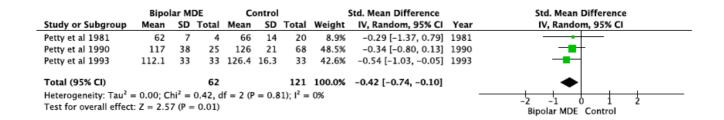


Figure S7. Standardized Mean Difference (SMD) of plasma GABA level between Bipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI).

	Euthy	Euthymic Bipolar				d		Std. Mean Difference		Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI			
Berrettini et al replication study 1982	126	31	6	179	51	10	17.8%	-1.12 [-2.22, -0.01]	1982				
Berrettini et al initial study1982	129	38	10	177	53	41	31.9%	-0.93 [-1.65, -0.22]	1982				
Berrettini et al 1983	217.5	32.5	49	227	34	36	50.2%	-0.28 [-0.72, 0.15]	1983	=			
Total (95% CI)			65			87	100.0%	-0.64 [-1.17, -0.11]		•			
	Heterogeneity: Tau ² = 0.10; Chi ² = 3.54, df = 2 (P = 0.17); I ² = 44%												
Test for overall effect: $Z = 2.35$ (P = 0.0	02)									Euthymic Bipolar Controls			

Figure S8. Standardized Mean Difference (SMD) of plasma GABA level between Bipolar euthymic vs controls. Error bars indicate 95% confidence interval (95% CI).

	Bipolar a	cute epi	sode	Co	ontrol		9	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Gerner et al 1981	139	35.8	5	183	62.5	29	28.9%	-0.72 [-1.68, 0.25]	1981	
Kasa et al 1982	83.3	40.7	3	137.5	57.4	24	21.8%	-0.93 [-2.16, 0.30]	1982	
Mann et al 2014	18.7	12.3	37	17.4	7.6	38	49.3%	0.13 [-0.33, 0.58]	2014	•
Total (95% CI)			45			91	100.0%	-0.35 [-1.06, 0.36]		•
Heterogeneity: Tau ² = Test for overall effect			-4 -2 0 2 4 Bipolar acute episode Control							

Figure S9. Standardized Mean Difference (SMD) of csf GABA level between Bipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI).

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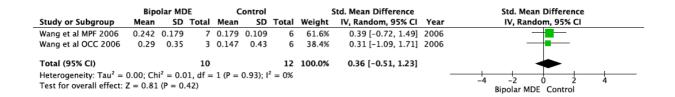


Figure S10. Standardized Mean Difference (SMD) of MRS GABA level between Bipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI).

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	Bipola	ar euthy	/mic	Control			9	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Wang et al MPF 2006	0.263	0.189	8	0.179	0.109	6	13.7%	0.49 [-0.59, 1.57]	2006	
Wang et al OCC 2006	0.227	0.099	10	0.147	0.043	6	13.8%	0.91 [-0.17, 1.98]	2006	 •
Bhagwagar et al 2007	0.92	0.16	16	1.05	0.09	18	19.0%	-0.99 [-1.71, -0.28]	2007	-
Kaufman et al 2009	0.084	0.032	13	0.076	0.014	11	17.5%	0.30 [-0.50, 1.11]	2009	- -
Brady et al 2013	0.194	0.087	14	0.155	0.053	14	18.4%	0.53 [-0.23, 1.28]	2013	 • -
Godlewska et al 2014	0.23	0.041	13	0.232	0.037	11	17.6%	-0.05 [-0.85, 0.75]	2014	+
Total (95% CI)			74			66	100.0%	0.14 [-0.42, 0.71]		•
Heterogeneity: Tau ² = 0	0.30; Ch	$i^2 = 13$.	13, df =	= 5 (P =	0.02); I	$^{2} = 629$	6		-	_4 _3 0 3 4
Test for overall effect: 2	Z = 0.50	(P = 0.6)	62)							Bipolar euthymic Control

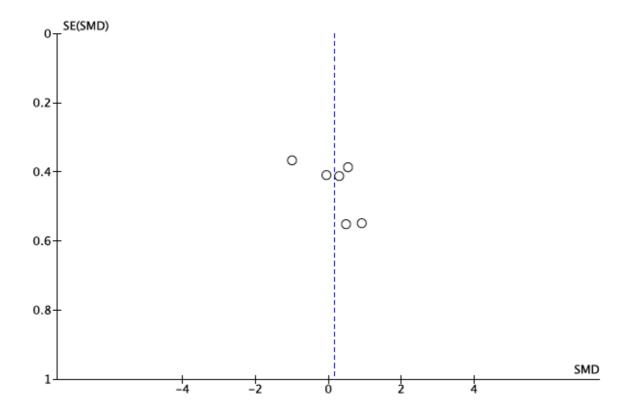


Figure S11. (**A**) Standardized Mean Difference (SMD) of MRS GABA level between Bipolar euthymic vs controls. Error bars indicate 95% confidence interval (95% CI). (**B**) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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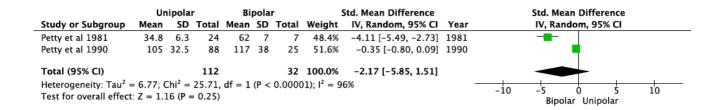


Figure S12. Standardized Mean Difference (SMD) of plasma GABA level between Unipolar and Bipolar current MDE. Error bars indicate 95% confidence interval (95% CI).

	Ur	nipolai	r	Bipolar				Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Gerner et al 1981	134	26.9	19	139	35.8	5	11.4%	-0.17 [-1.15, 0.82]	1981	
Kasa et al 1982	101.1	42	10	83.3	40.7	3	6.5%	0.40 [-0.91, 1.70]	1982	
Mann et al 2014	15.1	7.1	130	18.7	12.3	37	82.0%	-0.42 [-0.79, -0.05]	2014	-
Total (95% CI)			159			45	100.0%	-0.34 [-0.67, -0.01]		•
Heterogeneity: Tau ² = Test for overall effect	-				-2 -1 0 1 2					
rest for overall effect	. Z = 1.5	9 (F =	0.05)							Unipolar Bipolar

Figure S13. Standardized Mean Difference (SMD) of csf GABA level between Unipolar and Bipolar current MDE. Error bars indicate 95% confidence interval (95%

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