

**Appendix 1** to Romeo B, Choucha W, Fossati P, et al. Meta-analysis of central and peripheral  $\gamma$ -aminobutyric acid levels in patients with unipolar and bipolar depression. *J Psychiatry Neurosci* 2017.

DOI: 10.1503/jpn.160228

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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 study<sup>35</sup> included patients with treatment and two others<sup>33,37</sup> 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:  $\chi^2=2.90$ , 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:  $\chi^2=5.27$ , p=0.07).<sup>21,27,29</sup> 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:  $\chi^2=14.14$ , p=0.03, I<sup>2</sup>=58%).<sup>12,20,24-26,28</sup> Importantly, "after treatment" states did not necessarily correspond to the definitions of treatment response or remission. For example, Valentine et al<sup>28</sup> 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 study<sup>43</sup> included patients without treatment and its exclusion from analyses led 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:  $\chi^2=0.01$ , 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.<sup>52</sup> 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.<sup>35</sup> The two other studies,<sup>33,37</sup> 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:  $\chi^2=2.40$ , p=0.12).

The study by Berettini et al<sup>53</sup> reported no GABA change in CSF during euthymic states in bipolar patients, in comparison with healthy controls.

One study<sup>50</sup> 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 al<sup>33</sup> or the study by Mann et al<sup>37</sup> which included unmedicated samples, led to the loss of the significance, suggesting that medications may reduce 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**).

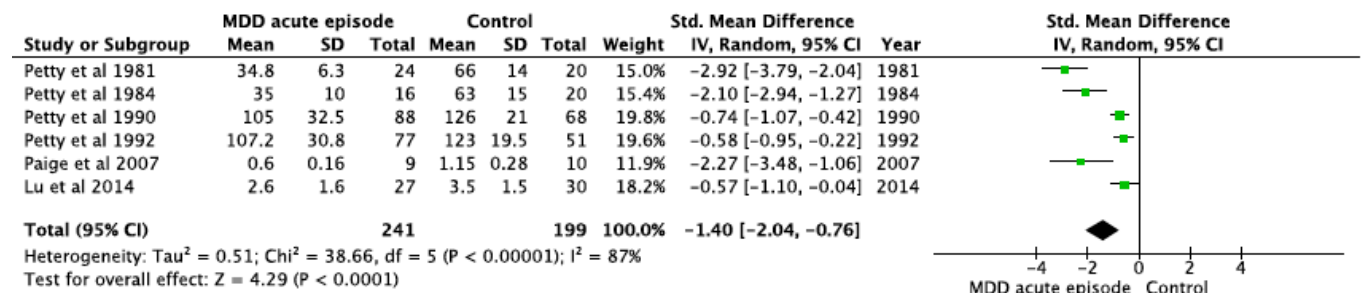
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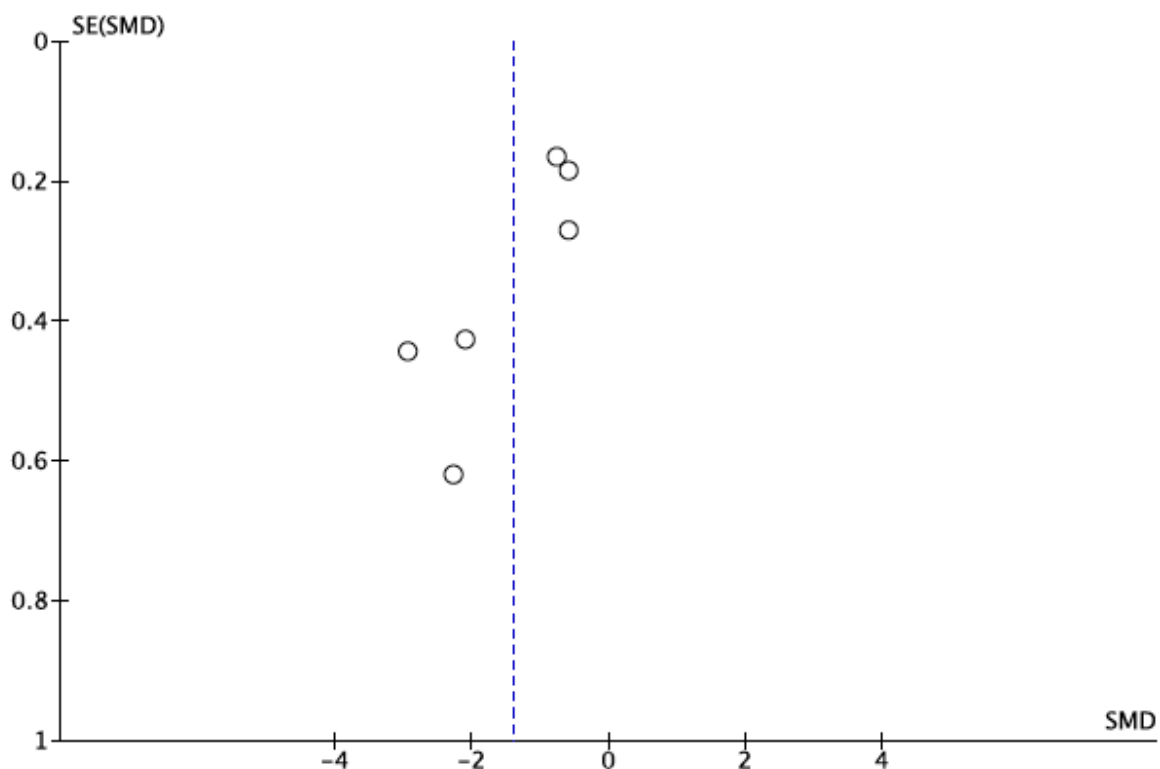
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**A**



**B**



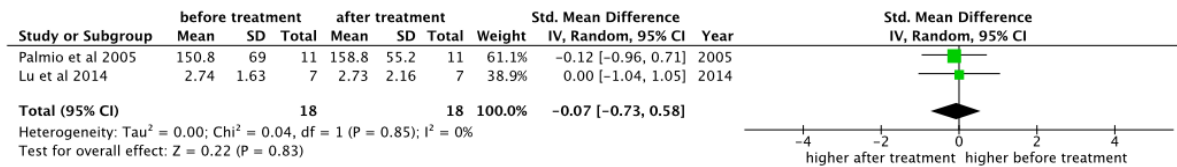
**Figure S1.** (A) Standardized Mean Difference (SMD) of plasma GABA level between Unipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI). (B) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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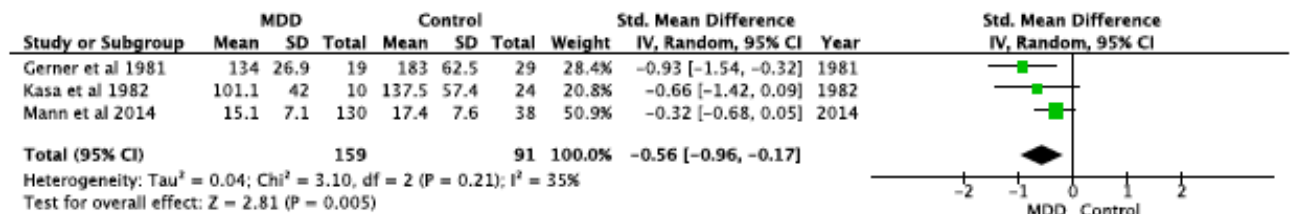
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**Figure S2.** Standardized Mean Difference (SMD) of plasma GABA level before and after treatment in Unipolar current MDE. Error bars indicate 95% confidence interval (95% CI).



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

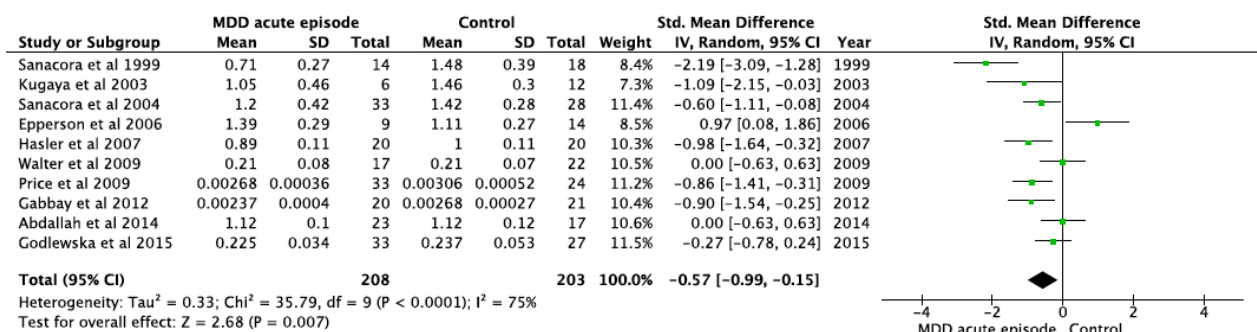
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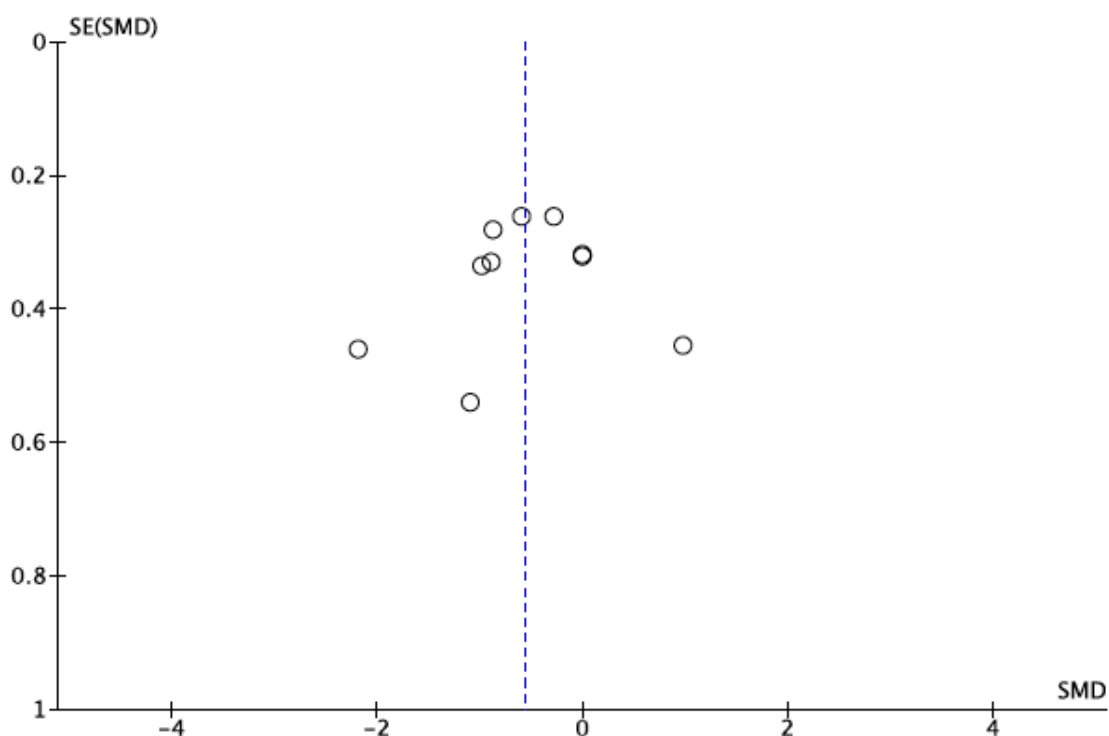
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**A**



**B**



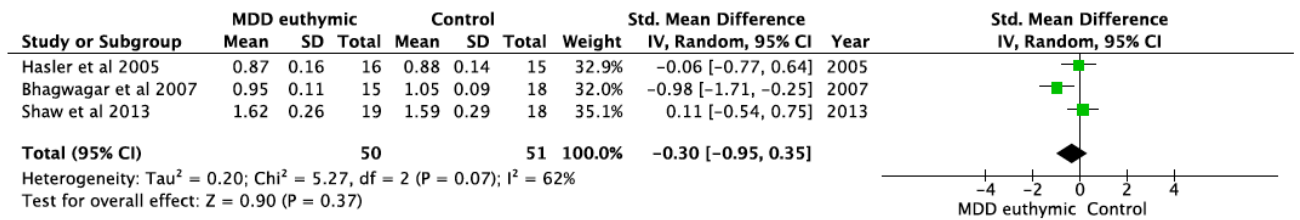
**Figure S4.** (A) Standardized Mean Difference (SMD) of MRS GABA level between Unipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI). (B) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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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).

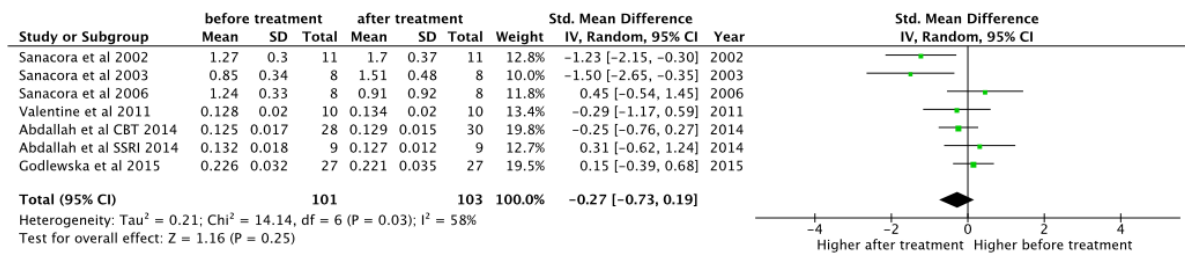
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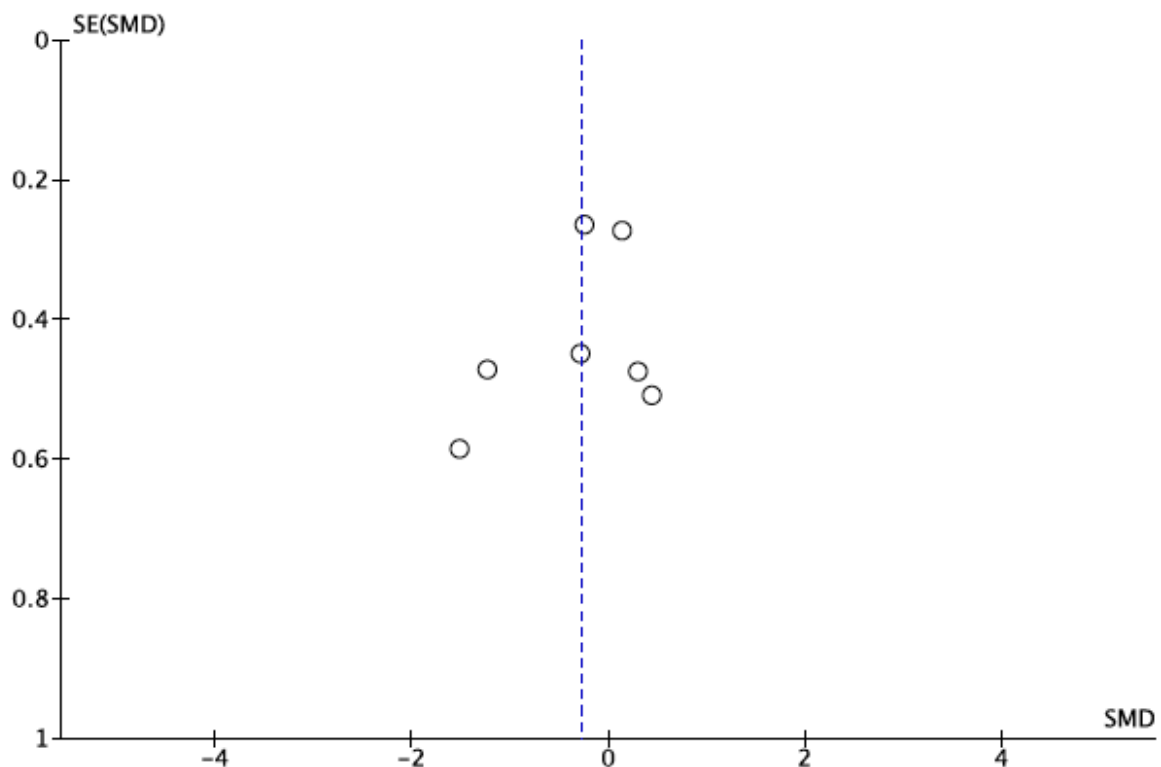
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**A**



**B**



**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.

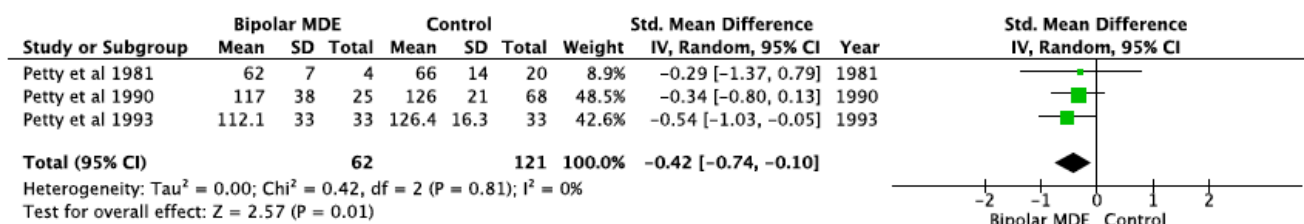


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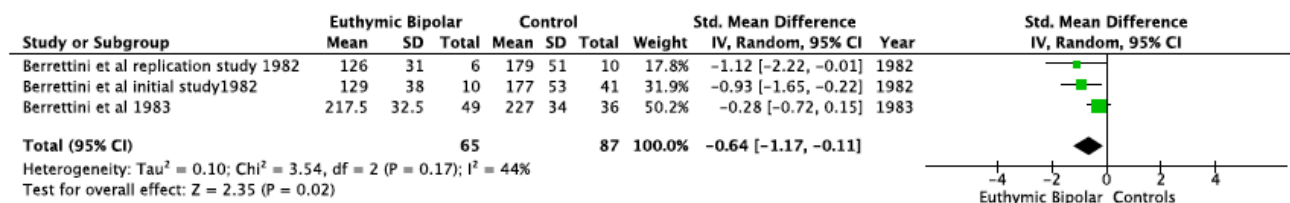
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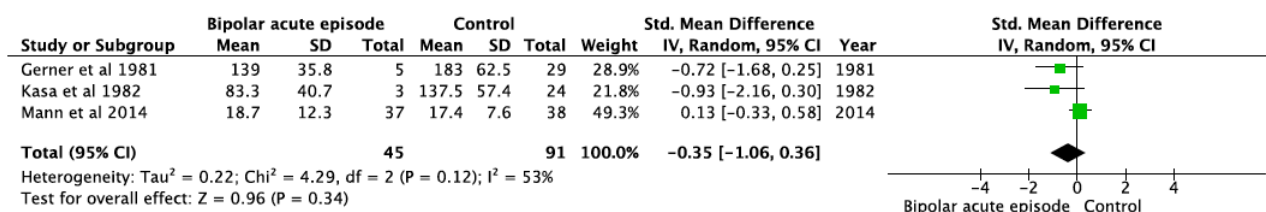
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**Figure S7.** Standardized Mean Difference (SMD) of plasma GABA level between Bipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI).



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



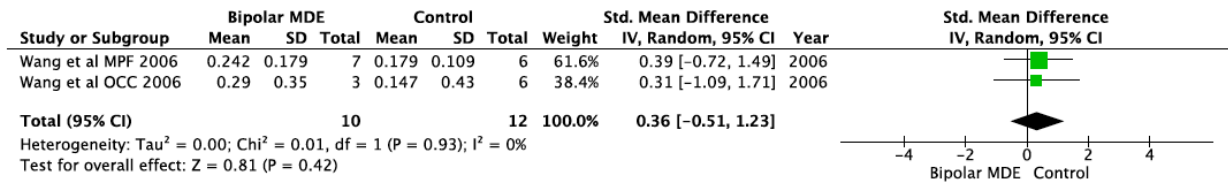
**Figure S9.** Standardized Mean Difference (SMD) of csf GABA level between Bipolar current MDE vs controls. Error bars indicate 95% confidence interval (95% CI).

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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).

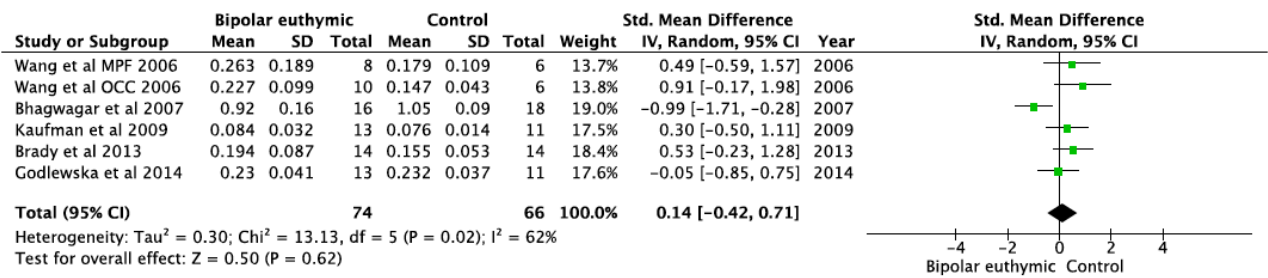
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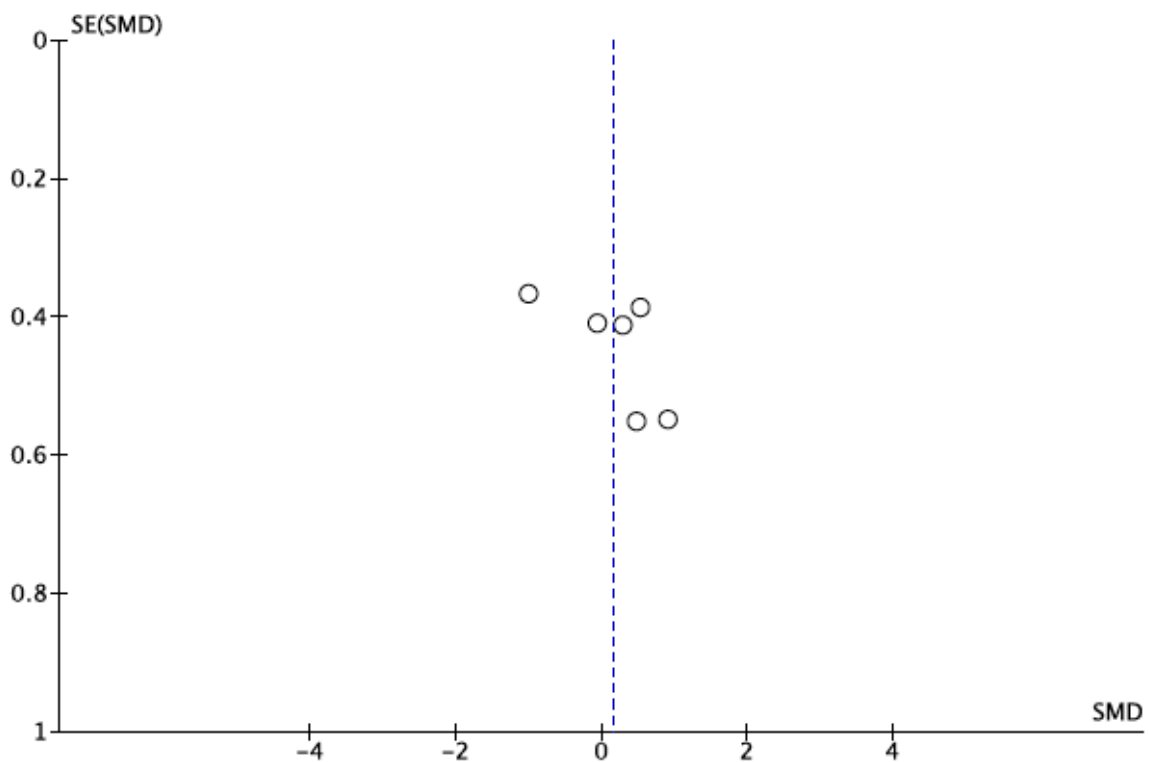
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**A**



**B**



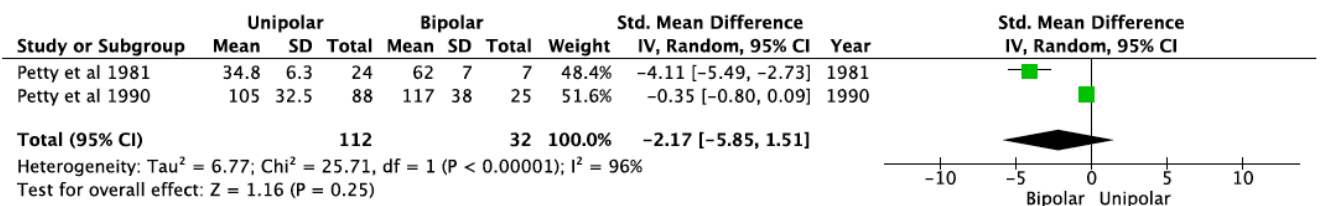
**Figure S11.** (A) Standardized Mean Difference (SMD) of MRS GABA level between Bipolar euthymic vs controls. Error bars indicate 95% confidence interval (95% CI). (B) Funnel plot graph for the meta-analysis corresponding. Which plot the standard error (SE) of each SMD.

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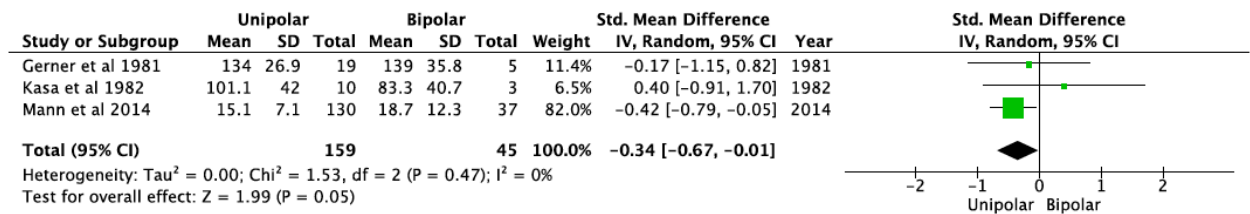
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**Figure S12.** Standardized Mean Difference (SMD) of plasma GABA level between Unipolar and Bipolar current MDE. Error bars indicate 95% confidence interval (95% CI).



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

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