Meta-analysis of central and peripheral \(\gamma\)-aminobutyric acid levels in patients with unipolar and bipolar depression

Bruno Romeo, MD; Walid Choucha, MD; Philippe Fossati, MD, PhD; Jean-Yves Rotge, MD, PhD

Introduction

Major depression is a highly prevalent disorder with important functional and health consequences.\(^1\) It mainly involves abnormal cooperation between emotional and cognitive networks, resulting in impaired emotional and cognitive regulation. Although the neural circuits implicated in the pathophysiology of depression are now better identified, the cellular and molecular changes that cause impairment in these emotional and cognitive networks and their association with depressive symptoms have yet to be determined.

\(\gamma\)-Aminobutyric acid (GABA) is the most important inhibitor of neurotransmitters in the central nervous system. The hypothesis of GABA dysfunction has long been considered in individuals with depression and affective disorders.\(^2\) Expression of genes implicated in the function and identification of the GABA components of local cell circuits suggest primary deficits affecting the GABA system, with human postmortem studies reporting a downregulation of gene expression in specific brain regions in depressed patients compared with healthy controls.\(^3-6\) Moreover, GABAergic interneurons have been proposed as major players in local and regional brain changes in individuals with depression and have been associated with rumination and increased self-focus in depressed patients.\(^7\) However, beyond cellular and gene expression, direction of change in GABA concentration in plasma and brain need to be clearly defined in individuals with mood disorders. The GABA levels may be measured by peripheral dosages in plasma and central dosages in cerebrospinal fluid (CSF) or in some brain regions using proton magnetic resonance spectroscopy (MRS). Results of studies assessing GABA levels in individuals with depression appear highly variable according to the type of measure (plasma, CSF, or MRS) or to clinical characteristics of the included samples. For example, MRS studies have reported GABA diminution,\(^8-10\) no GABA change,\(^11-13\) or GABA increase in participants with depression compared with healthy participants.\(^14\) Furthermore, many authors have described specific
implications of GABA neurotransmission according to different clinical characteristics of depression, such as pharmacological resistance, anhedonia, melancholia or unipolar or bipolar depression.

To provide a quantitative evaluation of GABA levels according to the type of measurement (plasma, CSF, or MRS) or to the clinical characteristics of depression, we performed a meta-analysis of studies assessing GABA levels in patients with major depression. We further assessed GABA changes according to clinical states (major depressive episode [MDE] and euthymic state) and to the exposure to treatment.

Methods

Data sources and study selection process

We searched the MEDLINE and PsycINFO databases through June 2015, without limits on year of publication, using the keywords “γ-aminobutric acid” or “GABA” or “inhibitory amino acid” and “magnetic resonance spectroscopy” or “MRS” or “CSF” or “plasma” and “major depressive disorder” or “depressive disorder” or “affective disorder” or “bipolar depression” or “unipolar depression.” Studies were included if they were published in English in a peer-reviewed journal, if they reported GABA levels, if they included patients with a current or a previous diagnosis of unipolar or bipolar depression, or if they compared patients with current MDE or in a euthymic state with healthy controls, or if they compared GABA levels before and after treatment. Studies that did not fulfill all 4 criteria were not included in the analyses. To obtain additional data, we created an email alert after June 2015 in MEDLINE containing the same keywords to identify putative publications of interest. Study selection was performed by one of us (B.R.) and verified by one of us (J.-Y.R.).

Data extraction

For each study, we obtained the means and standard deviations (SDs) for GABA concentrations and for demographic and clinical variables. It was necessary to contact several authors to obtain missing data (see Acknowledgements); however, 1 research team explicitly refused to provide the requested data. The GABA concentrations were measured in MRS studies in millimoles per kilogram, in millimoles per litre, in parts per million, or via the ratios GABA:creatine or GABA:w, with w being the voxel tissue water resonance.

Regarding demographic and clinical variables, we extracted the percentage of women, the mean age of participants, the mean duration of illness, the mean number of lifetime episodes, the percentage of melancholic episodes and the mean episode duration. Data extraction was performed by one of us (B.R.) and verified by one of us (J.-Y.R.).

Statistical analysis

Data analyses were performed using RevMan version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration). For MRS, plasma, or CSF studies, we calculated standardized mean differences (SMDs) in GABA concentrations in patients with current MDE versus controls, in euthymic patients versus controls, and in patients with current MDE before versus after treatment. The SMDs were defined as the difference between group means divided by the pooled SD. All analyses were performed with a random-effects model, which considered both between-study and within-study variability. We considered the SMDs to be significant when the 95% confidence interval (CI) excluded 0 and at p < 0.05.

To assess the putative influence of treatment in GABA changes, we considered studies having reported results in medication-free samples.

For MRS studies, we calculated SMDs for the following regions of interest (ROIs) independently: the occipital cortex, the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (dlPFC), the ventromedial prefrontal cortex (vmPFC) and the left inferior frontal gyrus.

We estimated study heterogeneity using the Q statistic when SMDs were significant. The I² index, an estimate of the total variation across included studies that was due to heterogeneity rather than chance, was determined by the equation I² = [(Q – df) / Q] × 100%. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity was considered unimportant for an I² between 0% and 40%, moderate for an I² between 30% and 60%, substantial for an I² between 50% and 90%, or considerable for an I² between 75% and 100%. Moreover, to ensure that the overall results were not influenced by a single study, we performed “leave-one-out” sensitivity analyses by repeating the analyses with the consecutive exclusion of each study. We created funnel plots, plotting the standard error of each SMD against the SMD calculated of each included study when at least 5 individual studies contributed to an overall result, and their asymmetry was analyzed to assess the possible influence of publication and location biases. Results from leave-one-out sensitivity analyses and funnel plots are included in Appendix 1, available at jpn.ca/160228-a1.

Finally, we conducted meta-regression analyses based on linear regression models for assessing the influence of the clinical heterogeneity of study populations on meta-analysis effect sizes. We performed regression analyses when SMDs or heterogeneity were significant and when a reasonable number of data points were available (≥4).

Results

Our search identified 45 studies: 26 studies for the comparison of patients with current MDE versus healthy controls, 12 studies for the comparison of patients with current MDE before treatment versus after treatment, and 11 for the comparison of euthymic patients and controls. Figure 1 depicts the study selection process, and the included plasma, CSF and MRS studies are described in Table 1, Table 2 and Table 3, respectively. We excluded 3 studies assessing plasma GABA levels and 5 studies assessing CSF GABA levels from our analyses because clinical samples included patients with unipolar and bipolar depression, and no independent analysis was reported.
Patients with unipolar depression versus healthy controls

Plasma GABA levels

Although SMD significantly indicated a decrease in GABA levels in patients with current unipolar MDE compared with healthy controls, heterogeneity was significant across studies (6 studies including a total of 241 patients and 199 healthy controls; test for overall effect: SMD $-1.40$, $95\%$ CI $-2.04$ to $-0.76$, $p < 0.001$; test for heterogeneity: $\chi^2 = 38.66$, $p < 0.001$, $I^2 = 87\%$). Only 1 study included patients without treatment, reporting diminished GABA levels in those with depression; its exclusion from analyses did not affect the result.

Plasma GABA levels during euthymic states in patients with unipolar depression were assessed in a single study. Remitted patients (remission defined as Montgomery–Åsberg Depression Rating Scale [MADRS] score $< 3$) and healthy controls had similar plasma GABA levels ($0.99$ and $1.15$, respectively).

Fig. 1: Study selection process. *The studies by Petty and Schlesser and Petty and colleagues were included in analyses of unipolar and bipolar disorders. **Studies by Gerner and colleagues, Kasa and colleagues, Mann and colleagues and Post and colleagues were included in analyses of unipolar and bipolar disorders. †The study by Bhagwagar and colleagues was included in analyses of unipolar and bipolar disorders. CSF = cerebrospinal fluid; GABA = $\gamma$-aminobutyric acid; MDE = major depressive episode; MRS = magnetic resonance spectroscopy.
Treatment-related plasma GABA changes in patients with unipolar depression with current MDE were assessed in 2 studies. In the study by Palmio and colleagues, MADRS scores improved from 29 at baseline to 9 at the end of the study. The SMD showed no difference in GABA levels before versus after treatment (2 studies including a total of 18 patients and 18 healthy controls; test for overall effect: SMD $-0.07$, 95% CI $-0.73$ to $0.58$, $p = 0.83$; test for heterogeneity: $\chi^2 = 0.04$, $p = 0.85$).

**Cerebrospinal fluid GABA levels**

The CSF GABA levels were diminished in individuals with current unipolar MDE compared with healthy controls (3 studies including a total of 159 patients and 91 healthy controls; test for overall effect: SMD $-0.56$, 95% CI $-0.96$ to $-0.17$, $p = 0.005$; test for heterogeneity: $\chi^2 = 3.10$, $p = 0.21$). No study assessed CSF GABA changes in patients with unipolar depression in euthymic states or before versus after treatment.

**Magnetic resonance spectroscopy GABA levels**

The MRS GABA levels were diminished in patients with unipolar depression compared with healthy controls; however, there was a great heterogeneity across studies (10 studies including a total of 208 patients and 203 healthy controls; test for overall effect: SMD $-0.57$, 95% CI $-0.99$ to $-0.15$, $p = 0.007$; test for heterogeneity: $\chi^2 = 35.79$, $p < 0.001$, $I^2 = 75$%). This heterogeneity was not explained by medication status, as all studies included unmedicated patients. There was a great heterogeneity among defined ROIs across studies, but subanalyses showed similar findings without changing the level of heterogeneity (e.g., occipital cortex: $\chi^2 = 30.07$, $p < 0.001$, $F = 80$%; prefrontal cortex: $\chi^2 = 6.08$, $p = 0.05$, $F = 51$%). Regarding the heterogeneity among ROIs, results from subanalyses are included in Appendix 1 and should be interpreted cautiously.

**Patients with bipolar depression versus healthy controls**

**Plasma GABA levels**

Patients with bipolar depression with current MDE had diminished plasma GABA levels compared with healthy controls (3 studies including a total of 62 patients and 121 healthy controls; test for overall effect: SMD $-0.42$, 95% CI $-0.74$ to $-0.10$, $p = 0.001$; test for heterogeneity: $\chi^2 = 0.42$, $p = 0.81$).

Patients with bipolar disorder in euthymic states had diminished plasma GABA levels compared with healthy controls (3 studies including a total of 65 patients and 93 healthy controls; test for overall effect: SMD $-0.46$, 95% CI $-0.83$ to $-0.09$, $p = 0.01$).

**Table 1: Studies included in analyses of plasma GABA level**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic status</th>
<th>Disorder state</th>
<th>n</th>
<th>Female sex, %</th>
<th>Mean age, yr</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty et al.39</td>
<td>Unipolar and bipolar</td>
<td>Current MDE</td>
<td>29</td>
<td>NA</td>
<td>NA</td>
<td>Diminished GABA in unipolar disorder, no change in bipolar disorder</td>
</tr>
<tr>
<td>Petty et al.40</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>16</td>
<td>NA</td>
<td>NA</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Petty et al.41</td>
<td>Unipolar and bipolar</td>
<td>Current MDE</td>
<td>113</td>
<td>NA</td>
<td>NA</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Petty et al.42</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>77</td>
<td>0</td>
<td>44.7</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Petty et al.43</td>
<td>Bipolar</td>
<td>Current MDE</td>
<td>33</td>
<td>NA</td>
<td>41.2</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Paige et al.34</td>
<td>Older adults with unipolar MDE</td>
<td>Current MDE</td>
<td>9</td>
<td>44</td>
<td>67.4</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Lu et al35</td>
<td>Melancholic unipolar MDE</td>
<td>Current MDE</td>
<td>27</td>
<td>48</td>
<td>NA</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Berrettini et al.51</td>
<td>Bipolar</td>
<td>Euthymic</td>
<td>10</td>
<td>NA</td>
<td>35</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Berrettini et al.52</td>
<td>Bipolar</td>
<td>Euthymic</td>
<td>49</td>
<td>44</td>
<td>35–39</td>
<td>Diminished GABA in bipolar patients without lithium</td>
</tr>
<tr>
<td>Palmio et al.49</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>10</td>
<td>70</td>
<td>56</td>
<td>No GABA level change after ECT</td>
</tr>
</tbody>
</table>

ECT = electroconvulsive therapy; GABA = $\gamma$-aminobutyric acid; MDE = major depressive episode; NA = not available.

**Table 2: Studies included in analyses of cerebrospinal fluid GABA level**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic status</th>
<th>Disorder state</th>
<th>n</th>
<th>Female sex, %</th>
<th>Mean age, yr</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerner et al.33</td>
<td>Unipolar and bipolar</td>
<td>Current MDE</td>
<td>24</td>
<td>54</td>
<td>42.6</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Kasa et al.36</td>
<td>Unipolar and bipolar</td>
<td>Current MDE</td>
<td>13</td>
<td>15</td>
<td>42</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Mann et al.37</td>
<td>Unipolar and bipolar</td>
<td>Current MDE</td>
<td>167</td>
<td>51</td>
<td>36.3</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Berrettini et al.52</td>
<td>Bipolar</td>
<td>Euthymic</td>
<td>25</td>
<td>60</td>
<td>35</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Post et al.55</td>
<td>Unipolar and bipolar</td>
<td>Before/after treatment</td>
<td>7</td>
<td>29</td>
<td>41</td>
<td>No GABA level change after carbamazepine</td>
</tr>
</tbody>
</table>

GABA = $\gamma$-aminobutyric acid; MDE = major depressive episode.
87 healthy controls; test for overall effect: SMD $-0.64$, 95% CI $-1.17$ to $-0.11$, $p = 0.020$; test for heterogeneity: $\chi^2 = 3.54$, $p = 0.17$). No study assessed plasma GABA changes before and after treatment in patients with bipolar depression.

Cerebrospinal fluid GABA levels

No changes in CSF GABA levels were observed between patients with bipolar disorder and healthy controls (3 studies including a total of 45 patients and 91 healthy controls; test

### Table 3: Studies included in analyses of magnetic resonance spectroscopy GABA level

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic status</th>
<th>Disorder state</th>
<th>n</th>
<th>Female sex, %</th>
<th>Mean age, yr</th>
<th>ROI</th>
<th>Voxels size, mL</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanacora et al.\textsuperscript{10}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>14</td>
<td>43</td>
<td>42.9</td>
<td>OCC</td>
<td>13.5</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Kugaya et al.\textsuperscript{8}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>6</td>
<td>0</td>
<td>36.2</td>
<td>OCC</td>
<td>11.1</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Sanacora et al.\textsuperscript{8}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>33</td>
<td>NA</td>
<td>41.9</td>
<td>OCC</td>
<td>13.5</td>
<td>Diminished GABA</td>
</tr>
<tr>
<td>Epperson et al.\textsuperscript{14}</td>
<td>Postpartum</td>
<td>Unipolar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trend for enhanced GABA</td>
</tr>
<tr>
<td>Hasler et al.\textsuperscript{20}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>20</td>
<td>65</td>
<td>34</td>
<td>VMPFC &amp; DA/dmPFC</td>
<td>18 and 30</td>
<td>Diminished GABA in DA/dmPFC, no change in vmPFC</td>
</tr>
<tr>
<td>Price et al.\textsuperscript{15}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>33</td>
<td>39</td>
<td>42.2</td>
<td>OCC &amp; ACC</td>
<td>18 and 18.75</td>
<td>Diminished GABA in resistant MDE, no change in nonresistant MDE</td>
</tr>
<tr>
<td>Walter et al.\textsuperscript{19}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>17</td>
<td>58</td>
<td>40</td>
<td>ACC</td>
<td>17.5</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Murrough et al.\textsuperscript{17}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>31</td>
<td>47.6</td>
<td>39.1</td>
<td>OCC &amp; ACC</td>
<td>18 and 18.75</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Gabbay et al.\textsuperscript{16}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>20</td>
<td>60</td>
<td>16.7</td>
<td>ACC</td>
<td>18.75</td>
<td>Diminished GABA in anhedonic MDE, no change in nonanhedonic MDE</td>
</tr>
<tr>
<td>Abdallah et al.\textsuperscript{11}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>23</td>
<td>70</td>
<td>43</td>
<td>OCC</td>
<td>13.5</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Godlewska et al.\textsuperscript{12}</td>
<td>Unipolar</td>
<td>Current MDE</td>
<td>33</td>
<td>42</td>
<td>29.9</td>
<td>OCC</td>
<td>10</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Wang et al.\textsuperscript{18}</td>
<td>Bipolar</td>
<td>Current MDE &amp; Euthymic</td>
<td>29</td>
<td>52</td>
<td>34.4</td>
<td>OCC &amp; mPFC</td>
<td>18 and 12.5</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Hasler et al.\textsuperscript{20}</td>
<td>Unipolar</td>
<td>Euthymic</td>
<td>16</td>
<td>75</td>
<td>41</td>
<td>VMPFC &amp; DA/dmPFC</td>
<td>18 and 30</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Shaw et al.\textsuperscript{27}</td>
<td>Unipolar</td>
<td>Euthymic</td>
<td>19</td>
<td>100</td>
<td>21</td>
<td>OCC</td>
<td>27</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Kaufman et al.\textsuperscript{54}</td>
<td>Bipolar</td>
<td>Euthymic</td>
<td>13</td>
<td>38</td>
<td>40</td>
<td>Basal ganglia</td>
<td>NA</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Brady et al.\textsuperscript{22}</td>
<td>Bipolar</td>
<td>Euthymic</td>
<td>14</td>
<td>43</td>
<td>33</td>
<td>POC &amp; ACC</td>
<td>16.7 and 16.7</td>
<td>Enhanced GABA level</td>
</tr>
<tr>
<td>Godlewska et al.\textsuperscript{23}</td>
<td>Bipolar</td>
<td>Euthymic</td>
<td>13</td>
<td>54</td>
<td>24</td>
<td>OCC &amp; mPFC</td>
<td>10 and 6.75</td>
<td>No GABA level change</td>
</tr>
<tr>
<td>Sanacora et al.\textsuperscript{25}</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>11</td>
<td>36</td>
<td>39</td>
<td>OCC</td>
<td>13.5</td>
<td>Enhanced GABA after SSRI</td>
</tr>
<tr>
<td>Sanacora et al.\textsuperscript{26}</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>8</td>
<td>38</td>
<td>46</td>
<td>OCC</td>
<td>13.5</td>
<td>Enhanced GABA after ECT</td>
</tr>
<tr>
<td>Sanacora et al.\textsuperscript{26}</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>OCC</td>
<td>20.5</td>
<td>No GABA level change after CBT</td>
</tr>
<tr>
<td>Valentine et al.\textsuperscript{28}</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>10</td>
<td>60</td>
<td>42</td>
<td>OCC</td>
<td>13.5</td>
<td>No GABA level change after ketamine</td>
</tr>
<tr>
<td>Abdallah et al.\textsuperscript{20}</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>28</td>
<td>63</td>
<td>42</td>
<td>OCC</td>
<td>13.5</td>
<td>No GABA level change after CBT</td>
</tr>
<tr>
<td>Godlewska et al.\textsuperscript{12}</td>
<td>Unipolar</td>
<td>Before/after treatment</td>
<td>27</td>
<td>42</td>
<td>30</td>
<td>OCC</td>
<td>10</td>
<td>No GABA level change after SSRI</td>
</tr>
</tbody>
</table>

ACC = anterior cingulate cortex; CBT = cognitive behavioural therapy; DA/dmPFC = dorsoantero/dorsomedial prefrontal cortex; ECT = electroconvulsive therapy; GABA = $\gamma$-aminobutyric acid; MDE = major depressive episode; MRS = magnetic resonance spectroscopy; mPFC = medial prefrontal cortex; NA = not available; OCC = occipital cortex; POC = parieto-occipital cortex; ROI = region of interest; SSRI = selective serotonin reuptake inhibitor; vmPFC = ventromedial prefrontal cortex.
for overall effect: SMD $-0.35$, $95\%$ CI $-1.06$ to $0.36$, $p = 0.34$; test for heterogeneity: $\chi^2 = 4.29$, $p = 0.12$).\textsuperscript{33,35,37}

**Magnetic resonance spectroscopy GABA levels**

Only 2 comparisons between medicated patients with current bipolar depression and healthy controls were identified, and no difference was observed (2 studies including a total of 10 patients and 12 healthy controls; test for overall effect: SMD $0.36$, $95\%$ CI $-0.51$ to $1.23$, $p = 0.42$; test for heterogeneity: $\chi^2 = 0.01$, $p = 0.93$).\textsuperscript{18}

During euthymic states, bipolar disorder was not associated with change in MRS GABA levels (6 studies including a total of 74 patients and 66 healthy controls; test for overall effect: SMD $0.14$, $95\%$ CI $-0.42$ to $0.71$, $p = 0.62$; test for heterogeneity: $\chi^2 = 13.13$, $p = 0.020$, $I^2 = 62\%$).\textsuperscript{18,21–23,54}

No study assessing GABA changes before and after treatment was identified.

**Patients with unipolar depression versus bipolar depression**

**Plasma GABA levels**

Two studies compared plasma GABA levels between patients with current MDE with unipolar and bipolar disorders.\textsuperscript{36,41} There was no difference in SMD (2 studies including a total of 112 patients with unipolar depression and 32 with bipolar depression; test for overall effect: SMD $-2.17$, $95\%$ CI $-5.85$ to $1.51$, $p = 0.25$), but there was a great heterogeneity across those studies (test for heterogeneity: $\chi^2 = 25.71$, $p < 0.001$, $I^2 = 96\%$).

**Cerebrospinal fluid GABA levels**

The CSF GABA levels were diminished in patients with unipolar depression versus those with bipolar depression (3 studies including a total of 159 patients with unipolar depression and 45 patients with bipolar depression; test for overall effect: SMD $-0.34$, $95\%$ CI $-0.67$ to $-0.01$, $p = 0.05$; test for heterogeneity: $\chi^2 = 1.53$, $p = 0.47$).\textsuperscript{33,35,37}

**Magnetic resonance spectroscopy GABA levels**

We did not identify a study comparing MRS GABA levels between patients with unipolar depression and patients with bipolar depression.

**Meta-regression**

Meta-regression analyses were not significant and did not explain significant SMDs or heterogeneity.

**Discussion**

The aim of the present meta-analysis was to assess peripheral and brain GABA concentrations in patients with unipolar and bipolar depression and to associate them with patients’ clinical characteristics. The results of our meta-analysis show that central and peripheral GABA levels are diminished in patients with unipolar depression, but tend to reach comparable levels to those of healthy controls in euthymic patients. In patients with bipolar disorder, results were more difficult to synthesize; reduced plasma GABA levels in depressed patients normalized with medication use. Central GABA levels were normal in patients with bipolar depression or during euthymic states. Together, our results suggest that GABA concentration may be associated with clinical states in patients with unipolar disorder, whereas GABA levels should be more closely associated with medication use in those with bipolar disorder; however, this interpretation is based on analyses characterized by high levels of heterogeneity and a small number of included studies.

**GABA levels in unipolar depression**

We found decreased central and peripheral GABA concentrations in patients with unipolar depression and normal central and peripheral GABA levels in patients in an euthymic state, suggesting that GABA concentration is a state rather than a trait marker of unipolar depression. Diminished GABA levels in these patients are in accordance with the reduction of the expression of inhibitory interneuron markers described in patients with current MDE.\textsuperscript{7} Indeed, GABAergic interneurons are involved in the regulation of the input and output of excitatory pyramidal neurons. In a recent and coherent model of depression pathophysiology,\textsuperscript{7} it has been proposed that network dysbalance observed in patients with unipolar depression, thus induced by the dysregulation of glutamatergic and GABAergic innervation, may translate trends to shift in focus from external to internal mental contents associated with unipolar depression, which is a central to depressive symptomatology.\textsuperscript{56,57} This decrease of GABAergic interneuron activity may thus contribute to enhanced activity of the perigenual ACC and a decrease of dlPFC activity associated with unipolar depression.

No difference in plasma GABA levels was observed before and after treatment in patients with unipolar depression with current MDE, and the possible effects of treatment on central GABA concentrations could not be assessed because of missing data. The absence of treatment-related difference could appear at odds with other results showing different GABA levels in patients with unipolar depression with current MDE and those in an euthymic state. However, the posttreatment-related improvement in depressive symptoms was not necessarily reported in patients in an euthymic state, and many of them may still experience depressive symptoms. For example, Sanacora and colleagues\textsuperscript{26} reported a mean posttreatment Hamilton Rating Scale for Depression score of 12.3, revealing that patients had clinically significant symptoms. Therefore, this observation supported the idea that plasma GABA levels could mark clinical states and were not affected by antidepressants. Further studies should specifically address this question and assess the time course of GABA levels in parallel with symptomatic evolution.

**GABA levels in bipolar depression**

For bipolar disorder, we found plasma GABA decreases in medication-free patients and normalized plasma GABA levels in medicated patients, whereas no change was observed for
central GABA levels. Antiepileptic drugs, such as valproate, have been shown to enhance GABA levels in preclinical studies, possibly by the inhibition of some enzymes such as GABA transaminase or succinic semialdehyde dehydrogenase. The enhancement of GABA has also been shown with lithium in a human study. This difference further shows the importance of taking into account mood stabilizers, antiepileptic drugs, or lithium when evaluating GABA levels in patients with bipolar disorder. It remains unclear whether the treatment-related normalisation of GABA levels in patients with bipolar disorder has clinical relevance. For example, future studies may assess whether GABA levels can predict therapeutic response in patients with bipolar depression, especially at the individual level. Furthermore, although the absence of differences in central GABA levels must take into account the small number of included studies and, therefore, poor statistical power, the apparent discrepancy between peripheral and central GABA levels remains unexplained. Pathophysiological associations between peripheral and central GABA levels in patients with mood disorders have to be clarified.

GABA differences between unipolar and bipolar depression

Direct comparisons between patients with unipolar and bipolar depression with current MDE appeared contradictory. Indeed, plasma GABA levels were similar between patients with unipolar and bipolar depression, whereas CSF GABA levels were decreased in patients with unipolar depression. However, studies measuring plasma GABA levels were all conducted in medicated patients, and leave-one-out analyses for studies assessing CSF GABA levels suggested that medications tended to abolish GABA differences between patients with unipolar and bipolar depression. Future studies should specifically address whether plasma GABA levels may be a biomarker of clinical states in patients with unipolar depression or of therapeutic responses to mood stabilizers in patients with bipolar disorder. Different imbalances of inhibitory and excitatory systems in patients with unipolar and bipolar depression could explain the observed difference between CSF GABA levels in these patients. This idea was also supported by the difference in network dynamics between patients with unipolar and bipolar depression, with a relative specificity for disrupted networks involving the pregenual ACC, regions of the default mode network, or other regions implicated in emotion processing or regulation in patients with unipolar depression that are not found in those with bipolar disorder.

Limitations

Our meta-analysis had several limitations. First, there was a great heterogeneity across studies, probably because of the substantial variation in clinical characteristics of the included samples. However, we performed many subanalyses taking into account the effects associated with the diagnosis, medications, or the type of measurements of peripheral or central GABA levels. Furthermore, we performed meta-regression to assess the possible associations between SMDs and clinical variables. Second, we were not able to correlate central and peripheral dosages of GABA, which could provide important information regarding methodological issues or clinical practice. Further studies should specifically address this question in samples with depression. Third, GABA changes in ROIs, such as the subgenual ACC, a major actor in depression, could not be assessed specifically because of the limited available data. Finally, many secondary analyses were performed with a small number of studies, which has to be taken into account when interpreting the present results.

Conclusion

This meta-analysis provides evidence of the implication of GABA in depression and emphasizes the importance of imbalance of inhibitory and excitatory systems in patients with mood disorders. The GABA levels evolved differentially between patients with unipolar and bipolar depression. Plasma GABA changes in those with unipolar depression were associated with symptomatic states, whereas plasma GABA changes in those with bipolar disorder seemed to be more closely associated with medication use. It remains to be elucidated whether GABA levels could be useful in clinical practice.

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