The Relationship Between Aberrant Neuronal Activation in the Pregenual Anterior Cingulate, Altered Glutamatergic Metabolism, and Anhedonia in Major Depression

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eTable. Group Comparisons of Metabolite Levels

<table>
<thead>
<tr>
<th>Measure</th>
<th>Controls</th>
<th>Patients With MDD</th>
<th>Patients With MDDhA</th>
<th>Patients With MDDIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala/Cr&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10 (0.02)</td>
<td>0.12 (0.04)</td>
<td>0.10 (0.03)</td>
<td>0.11 (0.02)</td>
</tr>
<tr>
<td>Asc/Cr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.68 (0.18)</td>
<td>0.59 (0.14)</td>
<td>0.59 (0.08)</td>
<td>0.72 (0.30)</td>
</tr>
<tr>
<td>Asp/Cr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.38 (0.10)</td>
<td>0.46 (0.17)</td>
<td>0.43 (0.12)</td>
<td>0.45 (0.13)</td>
</tr>
<tr>
<td>Cho/Cr&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.30 (0.03)</td>
<td>0.30 (0.04)</td>
<td>0.29 (0.04)</td>
<td>0.30 (0.04)</td>
</tr>
<tr>
<td>GSH/Cr&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.35 (0.08)</td>
<td>0.32 (0.07)</td>
<td>0.33 (0.07)</td>
<td>0.30 (0.02)</td>
</tr>
<tr>
<td>Lac/Cr&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.14 (0.04)</td>
<td>0.12 (0.02)</td>
<td>0.11 (0.02)</td>
<td>0.12 (0.03)</td>
</tr>
<tr>
<td>mI/Cr&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.16 (0.30)</td>
<td>1.18 (0.18)</td>
<td>1.15 (0.13)</td>
<td>1.22 (0.25)</td>
</tr>
</tbody>
</table>

Abbreviations: Ala, alanine; Asc, ascorbic acid; Asp, aspartate; Cho, choline; Cr, creatine; GSH, glutathione; Lac, lactate; MDD, major depressive disorder; MDDhA, major depressive disorder with high anhedonia; MDDIA, major depressive disorder with low anhedonia; mI, myo-inositol.

<sup>a</sup>For N-acetylaspartylglutamate, phosphorylethanamin, scyllo-inositol, taurine, and glycine, a group analysis was not meaningful owing to the low number of valid (Cramer-Rao lower bounds < 20) data sets.

<sup>b</sup> Fifteen controls; 10 patients with MDD; 4 patients with MDDhA; and 4 patients with MDDIA.

<sup>c</sup> Eighteen controls; 16 patients with MDD; 8 patients with MDDhA; and 6 patients with MDDIA.

<sup>d</sup> Eighteen controls; 16 patients with MDD; 7 patients with MDDhA; and 6 patients with MDDIA.

<sup>e</sup> Twenty-three controls; 17 patients with MDD; 8 patients with MDDhA; and 6 patients with MDDIA.

<sup>f</sup> Twenty-two controls; 16 patients with MDD; 8 patients with MDDhA; and 5 patients with MDDIA.

<sup>g</sup> Nineteen controls; 8 patients with MDD; 4 patients with MDDhA; and 3 patients with MDDIA.
Figure 1. Typical single-voxel point-resolved spectroscopy (A) and 2-dimensional J-resolved point-resolved spectroscopy (B) spectra acquired from the same volume of interest in the pregenual anterior cingulate cortex. The covariance matrix (C) of the ProFit analysis of the depicted J-resolved point-resolved spectroscopy spectrum (B) indicates low covariance coefficients between glutamate (Glu), glutamine (Gln), γ-aminobutyric acid (GABA), glucose (Glc), and N-acetylaspartate (NAA), which means that these metabolites can be quantified separately (diagonal elements were set from 1 to 0 to achieve meaningful color scaling). For the major metabolites of interest, correlation coefficients are the following: Glu and Glc: 4.7%; Gln and Glc: 0.4%; GABA and Glu: 11.49%; GABA and Gln: 0.4%; Glu and Gln: 15.27%; and NAA and Glu: 1.87%. Ala indicates alanine; Asc, ascorbic acid; Asp, aspartate; Cr, creatine; f1, consonant/multiplet splitting due to J-coupling; f2, chemical shift; Gly, glycine; GPC, glycerophosphorylcholine; GSH, glutathione; Lac, lactate; ml, myo-inositol; NAAG, N-acetylaspartylglutamate; PCh, phosphorylcholine; PE, phosphorylethanolamine; Scy, scyllo-inositol; Tau, taurine.
eFigure 2. Relationship of glutamine (Gln) and γ-aminobutyric acid (GABA) to glucose (Glc) in major depressive disorder (MDD). A, In healthy controls, glutamate (Glu)/Gln ratios positively correlate with Glc levels, whereas in patients with MDD, Glu/Gln and Glc levels are uncorrelated. B, Bar diagram showing the mean Glc/Gln ratios±standard error of the mean measured in the anterior cingulate cortex of MDD patients with high anhedonia (MDDhA) (n=5) and low anhedonia (MDDIA) (n=5) and healthy controls (n=13). A significant increase in Glc/Gln ratios was found in patients with MDDhA compared with healthy controls. In addition, the Glc/Gln ratio in patients with MDDIA is decreased (P<.1) at a trend level of significance compared with patients with MDDhA. C, In healthy controls, GABA and Glc levels are correlated, whereas this correlation is absent in patients with MDD. D, In contrast, GABA/Gln ratios correlate with Glc levels exclusively in patients with MDD. Cr indicates creatine.
eFigure 3. Anhedonia dependence of negative blood oxygenation–dependent (BOLD) response and N-acetylaspartate (NAA) in major depressive disorder (MDD).

A, Bar diagram showing the mean negative BOLD response ± standard error of the mean measured in functional magnetic resonance imaging based on emotional stimulation in the anterior cingulate cortex of MDD patients with high anhedonia (MDDhA) (n = 9) and low anhedonia (MDDlA) (n = 7) and healthy controls (n = 22). A specific and significant decrease of negative BOLD response was found in patients with MDDhA compared with controls. N-acetylaspartate specifically correlates with negative BOLD response (n = 16; r = 0.498, P < .05) (B), glutamate (Glu) (n = 17; r = 0.751, P < .001) (C), and emotional intensity (n = 12; r = 0.638, P < .03) (D) in patients with MDD. In healthy controls, the NAA–negative BOLD response and the NAA–emotional intensity correlations are absent and the NAA-Glu correlation is substantially weaker (n = 23; r = 0.445, P < .03). Cr indicates creatine.
Mean emotional intensity ratings specifically correlate with anhedonia (n=12; r = −0.797, P < .002) (A), glutamate (Glu) (n=10; r = 0.820, P < .002) (C), and negative blood oxygenation-dependent (BOLD) response (n=10; r = 0.633, P < .02) (D) in patients with major depressive disorder (MDD), while none of these correlations were found in healthy controls. B, Bar diagram showing the mean emotional intensity rating scores ± standard error of the mean for MDD patients with high anhedonia (MDDhA) (n=7) and low anhedonia (MDDlA) (n=5) and healthy controls (n=23). A specific and significant increase of the mean emotional intensity score was found in patients with MDDhA compared with patients with MDDlA. The emotional intensity in patients with MDDhA is decreased at a trend level of significance (P < .1) compared with controls. Cr indicates creatine; NS nonsignificant.