Multivoxel proton magnetic resonance spectroscopy detects thalamic neurochemical metabolic changes in patients with major depressive disorder

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Aims and objectives

Background and aim of the work:

Major depressive disorder (MDD), also known as unipolar depression, is a severe, prevalent and debilitating mental disorder which negatively affects a person’s life and functionality (1). It is considered as a major illness in primary care settings because of its devastating impact not only on symptomatic individuals but also on society as a whole, through high medical costs and loss of productivity (2).

Currently, MDD is considered to be the consequence of a malfunction of multiple circuits that connect the limbic system with the prefrontal cortex, the brainstem, the hypothalamus and thalamus (3). The thalamus, which is a key structure in brain anatomic circuits potentially involved in the pathophysiology of mood disorders, is generally believed to have a role in the pathophysiology of depression (4). More precisely, altered function in the limbic-cortical-striatal-pallidal-thalamic circuit has been implicated in the pathophysiology of MDD (5).

The severity of depression may be a factor that affects the changes in the neurochemical metabolite levels that are observed in MDD. The advances that have been made in neuroimaging led to understanding of alterations in certain brain regions in patients with MDD and offered clues about the mechanisms that possibly underlie the response to therapy, in particular proton magnetic resonance spectroscopy (1H-MRS) which measures in vivo the levels of brain metabolites (3). The mediodorsal and anteroventral/anteromedial nuclei of the thalamus are brain regions of interest in the study of mood disorders including MDD because they connect subcortical limbic system structures such as the amygdala with the prefrontal, cingulate, and temporal cortices (6).

The aim of this work was to observe the thalamic neurochemical metabolic changes in patients with MDD by multivoxel 1H-MRS.
Methods and materials

Study participants:

The study participants included a total of 43 patients with MDD; 20 patients with mild MDD (14 females and 6 males; age ranged from 28 to 61 years; mean ± standard deviation = 42.3 ± 9.7 years), 16 patients with moderate MDD (11 females and 5 males; age ranged from 32 to 65 years; mean ± standard deviation = 48.7 ± 8.2 years), and 7 patients with severe MDD (5 females and 2 males; age ranged from 29 to 63 years; mean ± standard deviation = 42.7 ± 6.2 years), in addition to 15 age and sex matched normal healthy control subjects (10 females, 5 males; age ranged from 31 to 63 years; mean ± standard deviation = 45.2 ± 4.7 years). This study was performed from March 2013 to September 2014. All patients were in their first episode depression, which was diagnosed following the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (7). Neither patients nor controls were taking any medications at the time of examinations. An informed consent from subjects enrolled in the study was obtained. An official permission to carry out the study was also obtained from the responsible authorities.

Patients were categorized according to the Hamilton Depression Rating Scale (HDRS) into mild, moderate and severe depression (8). Patients with bipolar disorders, schizophrenia, anxiety, substance abuse and patients with any metabolic illness that might affect the cerebral metabolite concentration ratios, such as diabetes mellitus, were excluded from the study. Patients with comorbid neurologic disorder, psychiatric illness or mental retardation were also excluded from the study.

The HDRS is a 17-item questionnaire scale that is commonly used to rate the severity of depression in adults. The original version, first published in 1960, contains 17 items to be rated (HDRS-17), but 4 other questions are not added to the total score and are used to provide additional clinical information. Each item on the questionnaire is scored on a 3 or 5 point scale, depending on the item. Assessment time is estimated at 20 minutes. Total scores between 0 and 7 indicate no depression, between 8 and 15 indicate mild depression, between 16 and 28 indicate moderate depression, and scores above 29 indicate severe depression. The highest possible score is 53 (8).

Imaging procedures:

Within three to eight days of the neuropsychiatric assessment, the study participants were initially examined with MRI and then with multivoxel 1H-MRS by using 1.5-Tesla MR unit, which had a spectroscopy capability (Signa Horizon SR 120; General Electric Medical Systems, Milwaukee, WI, USA) using a standard quadrature head coil (28 cm quadrature birdcage resonator). The MRI studies comprised the following sequences: multiplanar axial T1-weighted fast spin-echo (T1WFSE) with repetition time/echo time/number of excitations (TR/TE/NEX) of 500/14/2, multiplanar axial T2-weighted
fast spin-echo (T2WFSE) with TR/TE/NEX of 4000/126/2, and axial fluid-attenuated inversion recovery (FLAIR) with TR/TE/NEX of 8000/142/1 and inversion time (TI) of 2200 milliseconds (ms).

**1H-MRS protocol:**

The 1H-MRS was performed via using two-dimensional multivoxel long-echo (TE of 144 ms) point-resolved spatially localized spectroscopy (PRESS) to assess the relative concentrations of metabolites with biological importance including: N-acetylaspartate (NAA), choline (Cho), creatine (Cr) and myo-inositol (MI).

The thalamus was examined bilaterally in both patients and control groups by using a spin-echo (SE) mode sequence with the localized voxels of interest (VOIs) were located and distributed within different parts of both thalami as regions of interest (ROIs). In all patients, the obtained spectra were displayed as grids of localized voxels with nominal size of 10 x 10 x 10 mm, which were overlaid on the conventional MR images (either axial T2-weighted images or axial FLAIR images). Water resonance suppression was optimally achieved by using the chemical shift selective water suppression (CHESS) technique. In all patients, the used parameters were [TR 1000 ms, TE 144 ms and 35 ms, FOV 24 cm, 18 x 18 phase encoding matrices, 1.0 cm section thickness, 2500 Hz spectral width and 2048 data points]. The MRS scan was initiated if the line width reported by the pre-scan process was less than 8 Hz. The MR spectra were obtained with a long TE of 144 ms and additional short TE of 35 ms was utilized to confirm the phase inversion associated with J-coupled metabolites of lactate, and amino acids, but not of lipids, which may be helpful to discriminate lactate or amino acid signals from lipid signals. The acquisition time for each sequence was 5 minutes and 54 seconds. The Off-line spectral post-processing was carried out by using semi-automated software (Functool, Version 2.33, GE Medical Systems, Milwaukee, WI, USA).

The main metabolites resonances were limited to 2.02 parts per million (ppm) for NAA, 3.02 ppm for Cr, 3.20 ppm for Cho and 3.56 ppm for MI. As a result of difficulties in calculation of the absolute metabolite concentrations, their relative concentration ratios were assessed by using the method of relative quantification with calculation of peak ratios of the NAA/Cr, NAA/Cho, Cho/Cr, MI/NAA and MI/Cr in each thalamus separately in all study participants. The means of these peak ratios were then calculated in each of the 3 subgroups of patients and compared with those of the control group.

**Statistical Analysis:**

The SPSS for Windows version 18.0 software package (SPSS Inc, Chicago, IL) was used for statistical data analysis. The data were collected and revised. Quantitative data were expressed as mean ± standard deviation (SD). The student *t*-test and *chi*-square test were used for comparison between two groups and the analysis of variance (ANOVA) test was used for correlation of the data. The post-hoc test (Tukey's test) was used to
determine which groups in the compared samples were significantly differ. $P$-value $< 0.05$ was considered statistically significant.
Results

This study included 43 patients with MDD and 15 age- and sex- matched normal controls. The scores of the HDRS, in all patients with MDD, ranged from 8 to 51 with a mean of 17.32 ± 4.98; (Table 1).

The peak metabolites concentration ratios were bilaterally measured in both thalami of all study participants. When compared to normal controls, patients with MDD showed significant decrease in both NAA/Cho and NAA/Cr peak metabolites concentration ratios ($P = 0.008$ and $P < 0.001$, respectively). Also, there was a non-significant increase in the Cho/Cr, MI/NAA and MI/Cr ($P = 0.165$, $P = 0.810$ and $P = 0.770$, respectively) peak metabolites concentration ratios in both thalami of patients when compared to normal controls; (Table 2).

The relationship between the means of the peak metabolites concentration ratios in both thalami and the degree of severity of depression in patients with MDD evaluated by the HDRS-17 points was assessed. Increased severity of depression was significantly associated with decreased NAA/Cho and NAA/Cr ($P < 0.001$ for each) peak metabolites concentration ratios. On the other hand, the severity of depression was significantly associated with increased MI/NAA and MI/Cr ($P < 0.001$ for each) peak metabolites concentration ratios. However, a non-significant increase in the mean Cho/Cr peak metabolites concentration ratio was observed in relation to increased severity of depression ($P = 0.424$); (Table 3).

Additionally, no significant difference was found in all studied ratios when compared in patients with mild MDD versus normal controls ($P > 0.05$). On comparing moderate MDD to normal controls; the NAA/Cho and the NAA/Cr mean peak metabolites concentration ratios showed significant decrease ($P = 0.011$ and $P = 0.018$, respectively), while the MI/NAA and the MI/Cr peak metabolites concentration ratios were significantly increased ($P = 0.008$ and $P = 0.017$, respectively). Additionally, the Cho/Cr peak metabolites concentration ratio showed a non-significant difference ($P = 0.611$). Moreover, on comparing severe MDD to normal controls; the NAA/Cho and the NAA/Cr peak metabolites concentration ratios were highly significantly decreased ($P < 0.001$ for each), while the MI/NAA and the MI/Cr peak metabolites concentration ratios were highly significantly increased ($P < 0.001$ for each). Also, the Cho/Cr peak metabolites concentration ratio showed a non-significant difference ($P = 0.430$) between patients and controls.

Cases:

The figures (from 1 to 4) demonstrate a sample of selected cases of our study, each figure outlines one case.
Fig. 1: A thirty year old healthy control female subject with HDRS score of 2 (no depression). Brain axial non-contrast T1WI (A) and axial T2WI (B) are unremarkable with normal signal intensity of the brain parenchyma and well-differentiated grey/white matter. The 1H-MRS multivoxel picture (C) and MRS spectrum of the right (D) and left (E) thalami at a long TE of 144 ms, in addition to 1H-MRS multivoxel picture (F) and MRS spectrum of the right (G) and left (H) thalami at a short TE of 35 ms demonstrate normally average NAA/Cho, NAA/Cr, Cho/Cr, MI/NAA and MI/Cr peak metabolites concentration ratios of both thalami. In the right thalamus (D and G), the NAA/Cho is 1.50, NAA/Cr is 1.75, Cho/Cr is 1.17, MI/NAA is 0.35 and MI/Cr is 0.57. In the left thalamus (E and H), the NAA/Cho is 1.46, NAA/Cr is 1.73, Cho/Cr is 1.26, MI/NAA is 0.38 and MI/Cr is 0.56.
Fig. 2: A thirty five year old male patient with HDRS score of 12 (mild MDD). Brain axial non-contrast T1WI (A) and axial T2WI (B) are unremarkable with normal signal intensity of the brain parenchyma and well-differentiated grey/white matter. The 1H-MRS multivoxel picture (C) and MRS spectrum of the right (D) and left (E) thalami at a long TE of 144 ms, in addition to 1H-MRS multivoxel picture (F) and MRS spectrum of the right (G) and left (H) thalami at a short TE of 35 ms demonstrate significant reduction in the NAA/Cr and NAA/Cho peak metabolite concentration ratios of both thalami. On the other hand, there is significant increase in the MI/NAA and MI/Cr peak metabolites concentration ratios, as well as non-significant increase in the Cho/Cr peak metabolites concentration ratio of both thalami. These ratios are (NAA/Cr = 1.40, NAA/Cho = 0.91, Cho/Cr = 1.53, MI/NAA = 0.67 and MI/Cr = 0.70) in the right thalamus (D and G) and they are (NAA/Cr = 1.47, NAA/Cho = 0.90, Cho/Cr = 1.63, MI/NAA = 0.69 and MI/Cr = 0.80) in the left thalamus (E and H).

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Fig. 3: A forty two year old female patient with HDRS score of 20 (moderate MDD). Brain axial non-contrast T1WI (A) and axial T2WI (B) are unremarkable with normal signal intensity of the brain parenchyma and well-differentiated grey/white matter. The 1H-MRS multivoxel picture (C) and MRS spectrum of the right (D) and left (E) thalami at a long TE of 144 ms, in addition to 1H-MRS multivoxel picture (F) and MRS spectrum of the right (G) and left (H) thalami at a short TE of 35 ms demonstrate significant reduction in the NAA/Cr and NAA/Cho peak metabolite concentration ratios of both thalami. On the other hand, there is significant increase in the MI/NAA and MI/Cr peak metabolites concentration ratios, as well as non-significant increase in the Cho/Cr peak metabolites concentration ratio of both thalami. These ratios are (NAA/Cr = 1.08, NAA/Cho = 0.80, Cho/Cr = 1.45, MI/NAA = 0.63 and MI/Cr = 0.84) in the right thalamus (D and G), and they are (NAA/Cr = 1.15, NAA/Cho = 0.75 and Cho/Cr = 1.58, MI/NAA = 0.60 and MI/Cr = 0.86) in the left thalamus (E and H).
**Fig. 4:** A forty nine year old male patient with HDRS score of 34 (severe MDD). Brain axial non-contrast T1WI (A) and axial T2WI (B) are unremarkable with normal signal intensity of the brain parenchyma and well-differentiated grey/white matter. The 1H-MRS multivoxel picture (C) and MRS spectrum of the right (D) and left (E) thalami at a long TE of 144 ms, in addition to 1H-MRS multivoxel picture (F) and MRS spectrum of the right (G) and left (H) thalami at a short TE of 35 ms demonstrate significant reduction in the NAA/Cr and NAA/Cho peak metabolite concentration ratios of both thalami. On the other hand, there is significant increase in the MI/NAA and MI/Cr peak metabolites concentration ratios, as well as non-significant increase in the Cho/Cr peak metabolites concentration ratio of both thalami. These ratios are (NAA/Cr = 0.92, NAA/Cho = 0.61, Cho/Cr = 1.50, MI/NAA = 0.74 and MI/Cr = 1.03) in the right thalamus (D and G), and they are (NAA/Cr = 0.92, NAA/Cho = 0.51 and Cho/Cr = 1.83, MI/NAA = 0.77 and MI/Cr = 1.04) in the left thalamus (E and H).

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (n=43)</th>
<th>Controls (n=15)</th>
<th>Statistical test value</th>
<th>P-value</th>
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<td></td>
<td></td>
<td></td>
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<td>28 - 65</td>
<td>31 - 63</td>
<td>t = 1.141</td>
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<td>42.3 ± 9.4</td>
<td>45.2 ± 4.7</td>
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<td></td>
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<tr>
<td><strong>Sex</strong></td>
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</tr>
<tr>
<td>Female; n</td>
<td>30</td>
<td>10</td>
<td>χ² = 0.010</td>
<td>0.919</td>
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<tr>
<td>Male; n</td>
<td>13</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td><strong>HDRS scores</strong></td>
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<td></td>
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<tr>
<td>Range</td>
<td>8 - 51</td>
<td>0 - 7</td>
<td>t = 18.036</td>
<td>&lt;0.001*</td>
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<tr>
<td>Mean ± SD</td>
<td>28.7 ± 5.4</td>
<td>3.2 ± 1.2</td>
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</table>

**Table 1:** Table (1): Age, sex and HDRS scores in patients versus controls. HDRS: Hamilton depression rating scale, n: number, *: significant.

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<table>
<thead>
<tr>
<th>Metabolite ratio</th>
<th>Patients (n=43)</th>
<th>Controls (n=15)</th>
<th>Student #t test</th>
<th>P-value</th>
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</thead>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>1.19 ± 0.45</td>
<td>1.52 ± 0.19</td>
<td>2.743</td>
<td>0.008*</td>
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<tr>
<td>NAA/Cr</td>
<td>1.28 ± 0.26</td>
<td>1.92 ± 0.03</td>
<td>9.458</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>1.37 ± 0.20</td>
<td>1.28 ± 0.25</td>
<td>1.405</td>
<td>0.165</td>
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<tr>
<td>MI/NAA</td>
<td>0.50 ± 0.31</td>
<td>0.48 ± 0.14</td>
<td>0.240</td>
<td>0.810</td>
</tr>
<tr>
<td>MI/Cr</td>
<td>0.54 ± 0.16</td>
<td>0.52 ± 0.36</td>
<td>0.294</td>
<td>0.770</td>
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**Table 2:** Table (2): The mean metabolite concentration ratios in patients versus control.

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Table 3: Table (3): Relationship between the mean metabolite concentration ratios and the severity of depression in patients with MDD (n=43). Note: on comparing individual groups; similar adjacent letters (between brackets) indicate a non-significant difference (P ≥ 0.05), while different letters indicate a significant difference (P ≤ 0.05) from Tukey’s test.

<table>
<thead>
<tr>
<th>Metabolite ratio</th>
<th>Controls (n=15)</th>
<th>Mild MDD (n=20)</th>
<th>Moderate MDD (n=16)</th>
<th>Severe MDD (n=7)</th>
<th>F</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>NAA:Cho</td>
<td>1.52 ± 0.19 (a)</td>
<td>1.26 ± 0.07 (b)</td>
<td>1.06 ± 0.13 (b)</td>
<td>0.79 ± 0.15 (c)</td>
<td>68.342</td>
<td>&lt;0.001**</td>
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<tr>
<td>NAA:Cr</td>
<td>1.92 ± 0.03 (a)</td>
<td>1.29 ± 0.13 (a)</td>
<td>1.07 ± 0.19 (b)</td>
<td>0.75 ± 0.17 (c)</td>
<td>152.002</td>
<td>&lt;0.001**</td>
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<td>Cho:Cr</td>
<td>1.28 ± 0.25 (a)</td>
<td>1.26 ± 0.12 (a)</td>
<td>1.26 ± 0.18 (a)</td>
<td>1.36 ± 0.41 (a)</td>
<td>0.047</td>
<td>0.424</td>
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<td>M-NAAG</td>
<td>0.48 ± 0.14 (a)</td>
<td>0.70 ± 0.17 (a)</td>
<td>0.74 ± 0.14 (b)</td>
<td>1.14 ± 0.18 (c)</td>
<td>26.946</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>M:Cr</td>
<td>0.52 ± 0.36 (a)</td>
<td>0.72 ± 0.05 (a)</td>
<td>1.05 ± 0.09 (a)</td>
<td>1.23 ± 0.21 (a)</td>
<td>38.541</td>
<td>&lt;0.001**</td>
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</table>
Conclusion

The multi-voxel 1H-MRS has the potential to provide insights into the in-vivo neurochemical metabolic changes occurring in both thalami in patients with MDD. Increased severity of depression is significantly related to these thalamic neurochemical changes. Therefore, such changes can be considered as useful markers for assessment of the severity of depression in patients with MDD.
References


