No change in N-acetyl aspartate in first episode of moderate depression after antidepressant treatment: (1)H magnetic spectroscopy study of left amygdala and left dorsolateral prefrontal cortex

Bajs Janović, Maja; Kalember, Petra; Janović, Špiro; Hrabač, Pero; Folnegović Grošić, Petra; Grošić, Vladimir; Radoš, Marko; Henigsberg, Neven

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ORIGINAL RESEARCH

No change in N-acetyl aspartate in first episode of moderate depression after antidepressant treatment: ^{1}H magnetic spectroscopy study of left amygdala and left dorsolateral prefrontal cortex

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Maja Bajs Janović[1,3]
Petra Kalember[2]
Špiro Janović[1,3]
Pero Hrabač[2]
Petra Folnegović Grošić[1]
Vladimir Grošić[4]
Marko Radoš[5]
Neven Henigsberg[2,6]

[1]University Department of Psychiatry, Clinical Hospital Center Zagreb, Zagreb, [2]Polyclinic Neuron, Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, [3]University North, Varaždin, [4]Psychiatric Hospital Sveti Ivan, Zagreb, [5]University Department of Radiology, Clinical Hospital Center Zagreb, Zagreb, [6]Psychiatric Clinic Vrapče, Zagreb, Croatia

Correspondence: Špiro Janović
University Department of Psychiatry, Clinical Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia
Tel +38 59 1377 7476
Fax +38 5 1456 6858
Email sjanovic@gmail.com

Background: The role of brain metabolites as biological correlates of the intensity, symptoms, and course of major depression has not been determined. It has also been inconclusive whether the change in brain metabolites, measured with proton magnetic spectroscopy, could be correlated with the treatment outcome.

Methods: Proton magnetic spectroscopy was performed in 29 participants with a first episode of moderate depression occurring in the left dorsolateral prefrontal cortex and left amygdala at baseline and after 8 weeks of antidepressant treatment with escitalopram. The Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Depression, and the Beck Depression Inventory were used to assess the intensity of depression at baseline and at the endpoint of the study. At endpoint, the participants were identified as responders (n=17) or nonresponders (n=12) to the antidepressant therapy.

Results: There was no significant change in the N-acetyl aspartate/creatine ratio (NAA/Cr) after treatment with antidepressant medication. The baseline and endpoint NAA/Cr ratios were not significantly different between the responder and nonresponder groups. The correlation between NAA/Cr and changes in the scores of clinical scales were not significant in either group.

Conclusion: This study could not confirm any significant changes in NAA after antidepressant treatment in the first episode of moderate depression, or in regard to therapy response in the left dorsolateral prefrontal cortex or left amygdala. Further research is necessary to conclude whether NAA alterations in the first episode of depression could possibly be different from chronic or late-onset depression, and whether NAA alterations in stress-induced (reactive) depression are different from endogenous depression. The potential role of NAA as a biomarker of a treatment effect has yet to be established.

Keywords: depression, spectroscopy, antidepressant, N-acetyl-aspartate

Introduction

The neurobiological findings regarding major depressive disorder (MDD) indicate structural, functional, and neurochemical changes in the brain. The most prominent results of MDD, in comparison with healthy persons, are changes in brain volume in the prefrontal and limbic structures, damage to neurons and glia, and alterations in brain metabolism.[1] Depression could take various courses, graduating from single to numerous episodes, and the symptoms could vary from mild to very severe, with different responses to therapy and recovery. Therefore, the significance of determining the correlation of neurobiological findings in MDD with the clinical symptoms,

intensity, treatment response, and course of illness is increasing in many contemporary studies of MDD.

The prefrontal cortex and limbic structures have been suggested to play a key role in the emotional and cognitive processing of patients with MDD.[2,3] The amygdala is implicated in regulation of emotion, and is strongly connected with the prefrontal cortex.[4] Studies have found alterations in the structure and function of the amygdala in patients with MDD, including changes in its volume and an increase in cerebral blood flow and glucose metabolism.[5,6] The left amygdala is considered to be more responsive to emotional stimuli, particularly negative stimuli.[7] Differences related to depression have been reported in the left hemispheric white matter connections between the frontal and limbic regions.[8,9]

The dorsolateral prefrontal cortex (DLPFC) is involved with integrating sensory and mnemonic information, and regulating intellectual function and action.[10] Compared with healthy persons, there have been alterations in the volume and metabolic activity of the DLPFC in patients with MDD.[11,12]

Of particular interest in the frontal cortex and amygdala are their interconnections and involvement in mood regulation, supporting the theory of frontolimbic dysregulation in depression.[13] In post mortem studies, depressive patients showed neuronal and glial alterations in these regions, which underlie brain metabolite chemistry.[14] Neuronal and glial alterations are considered to be related to brain metabolite changes, such as in N-acetyl aspartate (NAA), choline, myo-inositol, and creatine (Cr), and may affect glutamate regulation.[15] Neurobiological alterations, particularly on the left side of the amygdala and DLPFC, are considered to be related to the pathophysiology of depression.[16]

The development of magnetic resonance spectroscopy (MRS) has allowed the quantification of brain metabolites in real time, as well as follow-up of the changes in brain metabolites in different disorders and clinical states. It is expected that MRS would provide valid biological markers of brain disorders, including mental disorders and biological correlates of symptoms and treatment response. Proton magnetic resonance spectroscopy (^{1}H-MRS) studies regarding MDD have reported different alterations in brain metabolites, such as in NAA, glutamate, gamma-aminobutyric acid, choline, and myo-inositol, in different brain regions.[17] Studies using MRS have shown abnormalities in brain metabolism in the prefrontal cortex and limbic structures in patients with depression.[18] So far, MRS studies of the amygdala have shown alterations in choline, myo-inositol, and glutamate in patients with MDD.[19] MRS studies of the prefrontal cortex have shown glutamate changes in patients with depression.[19]

NAA is the second most abundant amino acid in the human brain. It is localized mostly in neurons, oligodendrocyte precursors, and mature oligodendrocytes. NAA is considered a neuron-specific metabolite and a marker of neuronal viability. Its biological function is not fully understood, but it is considered a marker of neuronal loss.[20] Previous MRS studies have found no differences in NAA in depressive patients and healthy subjects in the basal ganglia and frontal lobes.[19,21,22] In contrast, some studies have reported a reduction of NAA in different brain regions during late-onset depression.[23–26]

Cr is distributed in gray and white matter, and serves as a measure of the amount of brain tissue contained within an analyzed voxel.[27] In the absence of major brain pathology, Cr levels are stable over time.[16] Many studies have confirmed unaltered Cr levels in patients with MDD, and Cr levels have been widely used as an internal standard for comparison.[3,19,28]

Antidepressant medication is widely used for the treatment of MDD, as its efficacy has been linked to clinical improvement. Still, fewer than 50% of patients with MDD show full treatment responses.[29] Finding biological markers that would predict the response to therapy and outcome of treatment would be valuable in clinical practice; much effort has been put into achieving this goal.

Many studies report that antidepressants have specific effects on brain regions.[29] Selective serotonin reuptake inhibitors have been found to affect the volumes, activation, and biochemistry of brain regions, including the prefrontal cortex and amygdala.[30–34] It is thought that treatment with antidepressant medication could normalize abnormalities in corticolimbic function.[35,36]

Potentially, the findings of neuroimaging may be used for monitoring the response to treatment and predicting the clinical outcome for MDD patients after treatment.[29] Recent MRS studies have evaluated the effects of antidepressants on brain metabolites in healthy individuals and MDD patients. Some studies have reported a significant increase in NAA after antidepressant medication or electroconvulsive therapy in depressive patients.[37–41] However, other studies have found no significant changes in brain metabolites after antidepressant treatment in different groups of depressive patients.[42–44] Increases in NAA after antidepressant treatment would mean that the treatment had a neurotropic effect, which could account for the rise in neuroprotection and in the viability of neurons. Based on current knowledge, the correlation between

brain metabolite changes and changes in clinical symptoms and intensity of MDD during treatment is still not clear.

The aim of this study was to investigate whether there would be any changes in NAA/Cr, measured with ^{1}H-MRS in two brain regions, ie, the left DLPFC and left amygdala, corresponding to clinical changes in the intensity of MDD in depressive patients with regard to therapy response.

Materials and methods

Participants

Twenty-nine patients who had never been treated for mental illness were recruited from an outpatient polyclinic. A diagnosis of MDD was made according to the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[45] A comorbid diagnosis, mental or somatic, was the exclusion criterion. Participants were assigned to take 10 mg/day of escitalopram, an antidepressant medication. ^{1}H-MRS was performed before starting medication (baseline) and after 8 weeks of therapy (endpoint). The Montgomery-Asberg Depression Rating Scale (MADRS),[46] the Hamilton Rating Scale for Depression (HAMD, 21-item),[47] and the Beck Depression Inventory (BDI)[48] were used to assess patients at baseline and at week 8 of antidepressant therapy. At endpoint, participants were identified as responders (n=17) or nonresponders (n=12) to the antidepressant treatment, based on the change in total results according to the scales. Treatment response was defined as having a minimum of 50% improvement in the total score on the HAMD, MADRS, and BDI from baseline to endpoint.[49] For the purpose of this study, only patients who fulfilled this criterion in all three instruments were defined as treatment "responders". All participants signed informed consent forms before participating in the study. The study was approved by the institutional ethics committee.

^{1}H-MRS analyses

A ^{1}H-MRS examination was performed using a clinical 2.0 T system (Gyrex 2T-Prestige, GEMS/Elscint, Haifa, Israel) with a quadrate head coil. The subject lay in the supine position, with the intersection of the frontal bone and two nasal bones (nasion) serving as a landmark. Foam pads were used to minimize head motion. Voxels were placed for spectroscopy, and all data analyses were performed by a trained radiologist who was blind to each subject's diagnosis. The voxels were repositioned in predefined brain areas, which were localized in both the left DLPFC and left amygdala. The routine imaging studies included a multilane T1-weighted spin-echo (650/12/2 [TR/TE/NEX]), a T2-weighted fast spin-echo (6000/90/2) with an echo train length of 10, and fast fluid attenuated inversion recovery (9100/126/1; inversion time, 2,200 msec) sequences. Axial T2 fast spin-echo images (8500/2200/126) were obtained, followed by placement of a single 8 cm^{3} voxel (15×15×15 mm) over the left DLPFC and left amygdala (Figures 1 and 2). ^{1}H-MRS was performed

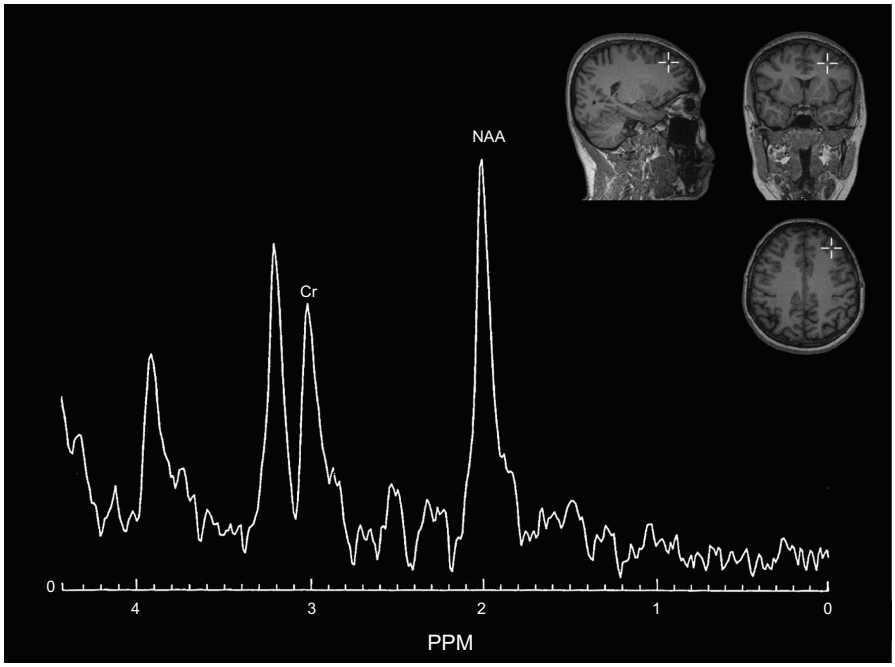

Figure 1 Left dorsolateral prefrontal cortex.
Abbreviations: NAA, N-acetyl aspartate; Cr, creatine.

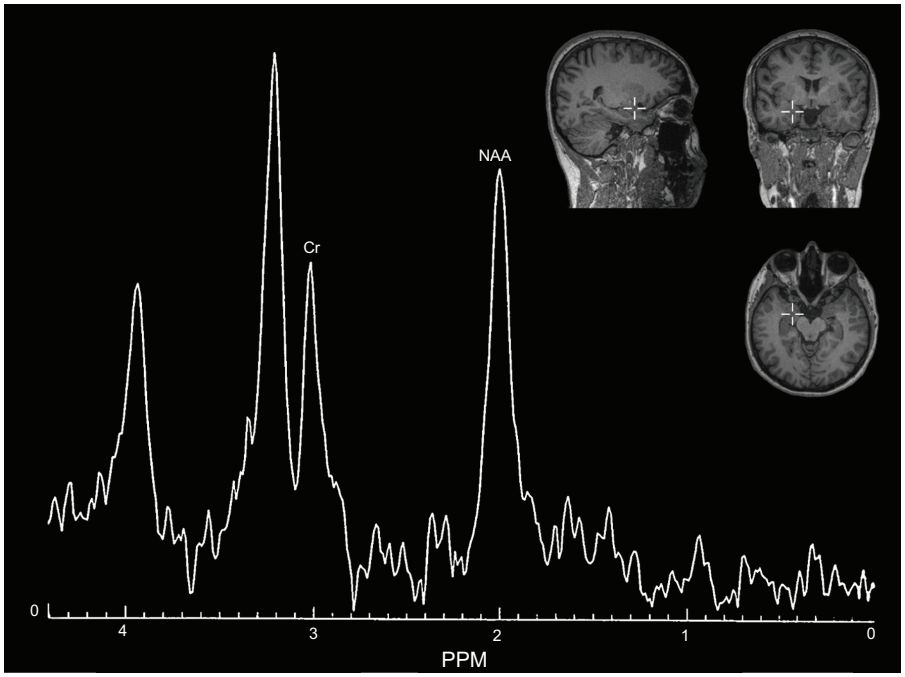

Figure 2 Left amygdala.
Abbreviations: NAA, N-acetyl aspartate; Cr, creatine.

using a point-resolved spectroscopy sequence (1500/54 [TR/TE]), with 100 averages. Each spectrum was evaluated for peak Cr (at 3.03 ppm) and NAA (at 2.02 ppm). The values of NAA/Cr ratios were used for the analyses. Analyses of the spectral dataset were performed using the software package program supplied by the manufacturer of the magnetic resonance system (Gyrex 2T-Prestige, GEMS/Elscint).

Statistical analysis

The statistical analysis was done using Statistica version 10 software (StatSoft Inc, Tulsa, OK, USA). Data for continuous variables are shown as the mean ± standard deviation, while data for categorical variables are laid out as frequencies and/or percentages. Due to the group size, normality testing was performed using a Shapiro–Wilk test rather than a Kolmogorov–Smirnov test. A between-group analysis was done using appropriate parametric or nonparametric tests (continuous variables), or chi-square test (categorical variables). Correlations between variables measured on an interval scale were explored by means of a Pearson or Spearman correlation. The statistical significance (type I error level) cut-off point was 0.05.

Results

Participants

Of the 29 patients who completed the study, 17 were identified as responders and 12 as nonresponders at endpoint. There were no differences in age, gender, or MADRS baseline scores between the responder and nonresponder groups. Differences between the groups were significant for baseline HAMD and BDI scores, as well as in endpoint scores for all three scales (Table 1).

MRS results

For all participants, there were no significant differences in NAA/Cr ratios between baseline and endpoint MRS in the DLPFC (P=0.950) and amygdala (P=0.649; Figure 3).

After separately analyzing the responder and nonresponder groups, no significant differences were found in either region for either group (Figure 4). There were no significant differences between the responder and nonresponder groups in the baseline NAA/Cr ratio, with P=0.795 for the DLPFC and P=0.718 for the amygdala. Neither the responder group nor the nonresponder group showed significant differences in endpoint NAA/Cr ratios. For the responder group, NAA/Cr in the DLPFC was P=0.805 and P=0.552 in the amygdala. For the nonresponder group, NAA/Cr in the DLPFC was P=0.862 and P=0.977 in the amygdala.

Correlation of change in metabolite measures and depression scale scores between baseline and endpoint

There was a significant difference in the mean decrease in scores on the depression scales between the responder and

Table 1 Group characteristics

	Participants (n=29)	Responders (n=17)	Nonresponders (n=12)	*P*-value
Age, mean (SD)	46.6±7.5	47.0±5.7	46.0±9.7	0.729*
Sex				
Male	17	8	9	0.132†
Female	12	9	3	
MADRS baseline, mean ± SD		31.4±5.01	32.3±4.09	0.637*
MADRS endpoint, mean ± SD		8.9±3.35	23.7±3.85	0.000*
HAMD baseline, mean ± SD		25.7±4.09	31.1±4.06	0.002*
HAMD endpoint, mean ± SD		8.2±2.94	22.3±2.84	0.000*
BDI baseline, mean ± SD		24.1±8.82	31.1±4.78	0.020*
BDI endpoint, mean ± SD		7.8±3.60	24.9±4.14	0.000*
NAA/Cr DLPFC, mean ± SD, baseline	1.30±0.22	1.31±0.20	1.29±0.24	0.795*
NAA/Cr amygdala, mean ± SD, baseline	1.23±0.22	1.24±0.21	1.21±0.25	0.718*
NAA/Cr DLPFC, mean ± SD, endpoint	1.33±0.20	1.32±0.20	1.34±0.20	0.757*
NAA/Cr amygdala, mean ± SD, endpoint	1.21±0.23	1.18±0.23	1.25±0.21	0.471*

Notes: *Student's *t*-test; †chi-square test.
Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; HAMD, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; SD, standard deviation; NAA/Cr, N-acetyl aspartate/creatine ratio; DLPFC, dorsolateral prefrontal cortex.

nonresponder groups (Table 2). However, the decrease in NAA/Cr ratios in the DLPFC and amygdala was not significantly different between the groups. For all three scales, there was no significant correlation between the difference in the endpoint and baseline scores of the scales, or the difference in the endpoint and baseline NAA/Cr ratios, in both regions (Table 3) and groups (Table 4).

Discussion

In this study, no significant change in NAA/Cr, measured with ^{1}H-MRS, was found after antidepressant treatment in participants experiencing their first episode of moderate depression. There was also no difference in the change in NAA/Cr between the responder and nonresponder groups. These findings suggest there were no effects of antidepressant treatment on NAA/Cr that could be observed by ^{1}H-MRS in either the frontal or limbic region.

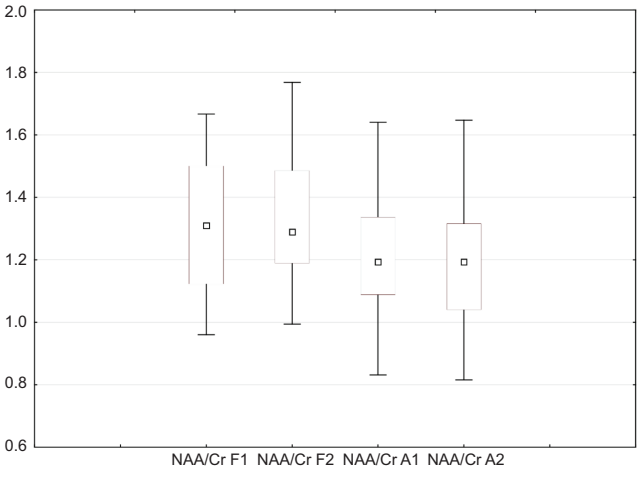

Figure 3 Box plots of NAA/Cr, showing baseline and endpoint in DLPFC and amygdala for all subjects. Shown are medians (squares), interquartile ranges (boxes), and nonoutlier range (whiskers).
Abbreviations: NAA/Cr, N-acetyl aspartate/creatine ratio; DLPFC, dorsolateral prefrontal cortex; F1, baseline in DLPFC; F2, endpoint in DLPFC; A1, baseline in amygdala; A2, endpoint in amygdala.

These results support those of the MRS study reported by Kaymak et al in drug-naïve female patients experiencing their first episode of MDD, as no significant metabolic alterations to NAA/Cr were found in the left DLPFC after 8 weeks of antidepressant treatment.[43] In our previous report, even in a higher magnetic field, we did not observe significant changes in NAA/Cr in the left DLPFC after 6 weeks of antidepressant treatment; the patients were diagnosed with comorbid MDD and posttraumatic stress disorder, and there was a significant posttreatment increase in choline.[44]

In contrast with these findings, several MRS studies on the medial frontal cortex and the hippocampus found an increase in NAA/Cr in depressive patients after antidepressant treatment.[37,38,50] Taylor et al found an increase of NAA/Cr in the medial frontal cortex after only 7 days of antidepressant treatment in depressive patients treated with escitalopram, compared with a healthy group given a placebo.[9] An increase in NAA after treatment would indicate the neurotrophic effect of antidepressant medication on the medial frontal cortex and the hippocampus. Two studies found a significant increase in NAA/Cr in the amygdala and the anterior cingulum after electroconvulsive therapy in depressive patients, and reached similar conclusions about the neurotrophic effect of antidepressant medicine,[40,41] while one study did not.[42]

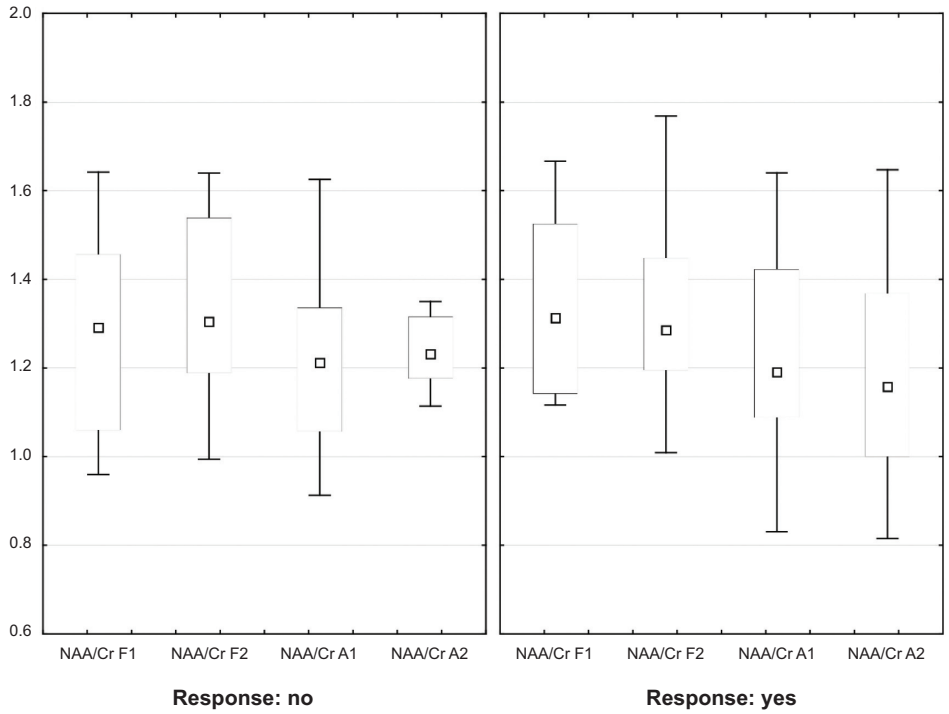

Figure 4 Box plots of NAA/Cr in responders and nonresponders to antidepressant treatment showing baseline and endpoint in DLPFC and amygdala. Shown are medians (squares), interquartile ranges (boxes), and nonoutlier range (whiskers).
Abbreviations: NAA/Cr, N-acetyl aspartate/creatine ratio; DLPFC, dorsolateral prefrontal cortex; F1, baseline in DLPFC; F2, endpoint in DLPFC; A1, baseline in amygdala; A2, endpoint in amygdala.

NAA is considered to be a marker of neuronal density. Unaltered NAA in MDD could be explained by the absence of cellular loss in some groups of depressive patients.[19] According to previous reports, the neuronal cell number in patients with MDD is normal.[40] Some studies of unmedicated MDD patients found no differences in NAA in the left frontal cortex, compared with healthy controls and medicated patients.[19] Portella et al reported significantly lower NAA levels, which were associated with the onset of illness at earlier ages, in the ventromedial prefrontal cortex in remitted recurrent and chronic patients with MDD.[51] Wang et al found significantly lower NAA levels in the bilateral DLPFC white matter during first-episode treatment of naïve patients with MDD, compared with healthy controls.[39] In contrast with these studies, Milne et al found no significant decrease in NAA in either the first-episode or multiple-episode groups.[22] Low NAA levels imply neurodegenerative changes, and could be related to age, duration of illness, and number of depressive episodes.[18,52] In the study by de Diego-Adelino et al it was found that metabolic alterations were more pronounced in patients with recurrent or chronic depression.[53] Further research is necessary to conclude whether NAA alterations in the first episode of depression could be different from chronic or late-onset depression, or whether stress-induced (reactive) depression could be different from endogenous depression.

There have been high expectations of a correlation between biological changes in the brain and the clinical

Table 2 Changes in scales and NAA/Cr ratios from baseline to endpoint

	n	All subjects	Responders	Nonresponders	*P*-value
MADRS	29	−16.75 (8.16)	−22.53 (4.62)	−8.58 (3.77)	<0.001
HAMD	29	−13.89 (5.88)	−17.53 (4.15)	−8.75 (3.69)	<0.001
BDI	29	−12.13 (8.30)	−16.35 (7.81)	−6.17 (4.54)	<0.001
NAA/Cr A	29	−0.026 (0.260)	−0.036 (0.25)	−0.003 (0.29)	0.791
NAA/Cr F	29	−0.003 (0.241)	−0.016 (0.23)	0.016 (0.27)	0.767

Note: Values are shown as the mean (standard deviation).
Abbreviations: A, amygdala; F, dorsolateral prefrontal cortex; MADRS, Montgomery-Asberg Depression Rating Scale; HAMD, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; NAA/Cr, N-acetyl aspartate/creatine ratio.

Table 3 Correlations of changes in scale scores with changes in NAA/Cr ratios from baseline to endpoint

		Difference endpoint – baseline	
		NAA/Cr F	**NAA/Cr A**
Difference endpoint – baseline	MADRS	0.1442	0.0530
		P=0.556	*P*=0.829
	HAMD	–0.0737	0.1338
		P=0.764	*P*=0.585
	BDI	0.3044	0.1521
		P=0.205	*P*=0.534

Abbreviations: A, amygdala; F, dorsolateral prefrontal cortex; MADRS, Montgomery-Asberg Depression Rating Scale; HAMD, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; NAA/Cr, N-acetyl aspartate/creatine ratio.

changes in the course of MDD, especially with the treatment response. In this study, we found no significant differences between the responder and nonresponder groups with regard to measures of NAA/Cr at baseline and endpoint. Block et al found that low baseline NAA and choline levels in the hippocampus were associated with a positive treatment response, which was considered to be evidence of neuronal restoration in the hippocampus.[38] Kado et al reported that high baseline NAA/Cr levels in the frontal lobes were associated with clinical responses in depression in the elderly.[52] In addition, a group of patients with depressive psychosis, who had decreased NAA/Cr in their frontal lobes, showed resistance to antidepressant medication. Therefore, metabolic reactivity to antidepressant treatment could be more pronounced in patients with low baseline NAA levels as an effect of age, duration of MDD, and number of episodes. After electroconvulsive therapy in refractory depressive patients, increased NAA levels were observed only in the responder group.[41]

In this study, an association could not be established between changes in depression intensity and changes in metabolites as effects of antidepressant therapy. Neither baseline nor after-treatment NAA/Cr levels showed a correlation with the changes in depression intensity observed from baseline to the endpoint of the study. As expected, the responder group showed significantly more improvement in scores on the clinical scales than the nonresponder group. Nevertheless, changes measured by the scales were not correlated with changes in metabolites, meaning that changes in the clinical course and intensity of depression were not followed by changes in the level of NAA/Cr, which could be measured by MRS.

Kaymak et al also did not find a correlation between NAA and HAMD scores before or after treatment.[43] The same studies that reported a significant increase in NAA after antidepressant treatment did not find a significant correlation between NAA and scores on clinical scales.[37,39,50] Block et al found a negative correlation between changes measured by BDI and changes in NAA after antidepressant treatment in their responder group, suggesting the importance of following changes in NAA with regard to treatment response.[38] Sozeri-Varma et al did not find a correlation between metabolite levels and HAMD scores in patients experiencing their first episode of mild-to-moderate depression.[54]

In our group of participants, the severity of depression, assessed by scores on the three clinical scales, was moderate, thus excluding the possibility of an overall conclusion for patients with more severe depression. Since the severity of illness has been associated with the degree of volumetric loss in the prefrontal lobes,[55] a more pronounced change in neuronal viability markers could be better observed in more

Table 4 Correlations of changes in scale scores with changes in NAA/Cr ratios from baseline to endpoint in responders and nonresponders

	Responders		**Nonresponders**	
	Diff NAA/Cr F	**Diff NAA/Cr A**	**Diff NAA/Cr F**	**Diff NAA/Cr A**
Diff MADRS	0.3563	0.1609	0.0124	–0.6119
	P=0.232	*P*=0.600	*P*=0.981	*P*=0.197
Diff HAMD	–0.1132	0.3163	–0.0579	0.5784
	P=0.713	*P*=0.292	*P*=0.913	*P*=0.229
Diff BDI	0.4029	0.1246	0.2950	0.0479
	P=0.172	*P*=0.685	*P*=0.570	*P*=0.928

Abbreviations: A, amygdala; F, dorsolateral prefrontal cortex; MADRS, Montgomery-Asberg Depression Rating Scale; HAMD, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; NAA/Cr, N-acetyl aspartate/creatine ratio; Diff, difference.

severely depressed patients. So far, changes in the clinical severity of MDD and treatment response have not been conclusively correlated with changes in the NAA levels of depressed patients. At this point in the research, changes in NAA levels, if any, could not be definitely translated to clinical changes during antidepressant treatment. The potential role of NAA as a biomarker of treatment effect or improvement of MDD has yet to be established.

Differences in sample characteristics, acquisition, and post-processing parameters could be responsible for the differences between this study and other MRS studies. Quantifying and interpreting metabolic information from brain MRS is complicated by a number of variables, which can affect determination of the apparent concentration.[56] There were also differences in the selection of participants with regard to multiple depressive episodes, therapy resistance, duration of illness, and comorbidity, as compared with similar studies. The sample of depressive participants in this study was characterized as first-episode patients who had never been treated. However, it is possible that minor depressive episodes had occurred previously, and had gone undiagnosed and untreated. This sample was comprised of middle-aged participants, with no data on previous episodes of depression, traumatic events, or insidious organic brain processes, which could not be detected at the point of inclusion in the study. It would be interesting to study brain metabolites in relation to the subsequent course of illness and aging of participants.

Better selection of MDD patients, which could be done with knowledge of the duration of untreated MDD, number of episodes, impacts of early stress, and specific depressive features, could provide a valid insight into the metabolic changes in the brain after antidepressant treatment. In this study, after differentiating responders from nonresponders, it was observed that the responder group showed significantly lower baseline HAMD and BDI scores, but not MADRS scores, compared with the nonresponder group. It is possible that, in our sample of depressive participants, psychosomatic symptoms were more prominent in the nonresponder group, which would have resulted in score differences between the HAMD and BDI, although there were no differences in the MADRS scores, which are related to the mood and cognition/energy of patients with depression. The cut-off criteria for the scales could explain differences in the severity of MDD. In this sample, the baseline scores of HAMD were indicative of more severe depression. In comparison, the baseline scores of MADRS and BDI indicated moderate depression. Putting all three assessments together, we felt the intensity was better described as moderate, rather than severe, in this sample.

Because of the known differences in clinician-rated scales and self-reported measures,[57] for the purpose of this study, the results of the three clinical scales were set in the correlation with changes in NAA/Cr levels.

A limitation of this study is that the participants had never been treated for depression or other mental illnesses, and were not diagnosed with comorbidity; which would hardly resemble everyday clinical practice. The number of participants in both the responder and nonresponder groups was too small for far-reaching conclusions, so there is a need for larger samples. Further limitations include the lack of a healthy control group and the inclusion of a placebo for further comparative and interpretative purposes.

In conclusion, this study did not find a significant change in the level of NAA/Cr after treatment with antidepressant medication, suggesting a prompt beneficial effect of antidepressant medication on neuronal integrity or restoration in patients experiencing their first episode of MDD. The baseline and endpoint NAA/Cr ratios were not significantly different between the responder and nonresponder groups, and could not serve as biological markers for predicting the response to treatment. Additionally, the correlation between NAA/Cr and changes in severity of MDD was not significant, meaning that the possible role of NAA as a biological correlate of the intensity of MDD and the clinical course could not be confirmed.

Considering the fact that antidepressants have an impact on both the clinical state and the neurochemistry of the brain, it would be expected that some biological changes in brain metabolites would follow clinical changes during treatment. Further studies are needed to determine conclusively whether patients with MDD have a deficit of brain metabolites, and how changes in brain metabolites correlate with symptoms, onset, outcome, and treatment response. It would also be important to determine whether the brain metabolite deficit could be reversible after antidepressant treatment, and how it could be significant for predicting the individual outcomes of treatment and the course of illness.

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Disclosure

The authors report no conflicts of interest in this work.

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