Prefrontal Cortex Neurochemical Metabolite Levels in Major Depression and the Effects of Treatment: An ^{1}HMRS Study

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SUMMARY

Objective: Neuronal degeneration in the prefrontal cortex during depression results in altered production of neurochemical metabolites. The aim of the present study is to examine changes in neurochemical metabolites in the prefrontal cortex and evaluate the effects of psychodrama group therapy and pharmacotherapy on neurochemical metabolism in the first episode depression using 1HMRS methodology.

Method: Eighteen drug-free female patients with diagnosed first-episode major depression according to DSM-IV criteria and 10 healthy female subjects were enrolled in the study. The Hamilton Rating of Depression Scale (HAM-D) was used to asses the severity of depression in each of the study participants. Proton magnetic resonance spectroscopy (1HMRS) was applied to the right prefrontal cortex both before and after treatment and the concentration of N-Asetil Aspartate (NAA), choline (Cho), and creatine (Cr) were measured. All patients were prescribed ant-depressant medication at the time of the evaluation (essitalopram 10-20 mg/g). In addition, a psychodrama group therapy session was conducted in which 10 patients participated in one 3-hour session each week. HAM-D and 1HMRS were repeated after 16 weeks.

Result: Prior to treatment, the HAM-D score in the patient group was 14.55±4.55 while the HAM-D score was 3.88±2.47 after 16 weeks of treatment. The severity of symptoms among the patient group was determined to be mild/moderate. No neurochemical abnormalities were identified in the right prefrontal cortex of depressed patients compared to the healthy subjects in the baseline measurements and no significant change was observed in neurochemical metabolites following treatment with pharmacotherapy or pharmacotherapy with group psychotherapy.

Conclusion: Our results identified no neurodegeneration, cell membrane dysfunction, alterations in energy metabolism, or altered neurochemical metabolite levels in patients undergoing a first episode of mild/moderate depression. Further studies will be needed to evaluate the effects of alternate treatments and the presence or absence of neuronal damage during follow-up of patients with depression.

Keywords: Major depression, prefrontal cortex, magnetic resonance spectroscopy (HMRS), antidepressant, group psychotherapy

INTRODUCTION

Imaging studies of the brain in patients with major depression suggest the presence of functional irregularities in the portions of the frontal cortex regulating emotion (especially orbitofrontal, ventromedial prefrontal, dorsolateral prefrontal cortex) and the cortical-subcortical loops, including the amygdala, hippocampus, basal ganglion, and anterior and subgenual singulate (Drevetes et al. 2008, Phillips et al. 2008, Grimm et al. 2008, Costafreda et al. 2009, Lorenzetti et al. 2009, Malykhin et al. 2012).

The prefrontal cortex (PFC) is though to play a key role in the cognitive control of emotion, particularly cognitive processing and the suppression of negative emotions; irregular function of these structures contributes to depression (Koenigs et al. 2008, Koenigs and Grafman, 2009). Hypoactivity, hypometabolism, decreased grey matter, and decreased number and size of dorsolateral prefrontal cortex (DLPFC) glial cells

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have also been reported in depressive patients (Galynker et al. 1998, Rajkowska et al. 1999, Narita et al. 2004, Siegle et al. 2007, Vasic et al. 2008)

Proton magnetic resonance spectroscopy (1H-MRS) techniques are capable of measuring the levels of neuronal metabolites such as N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho), in which play a critical role in neuronal functions, cell membranes, and energy metabolism suggest the alteration of the right caudal putamen (Vythilingam et al. 2003) and metabolic changes in the hippocampus major in major depression (Milne et al. 2009, De Diego-Adelino et al. 2013). H-MRS measurements indicate a stable reduction of NAA/Cr and high Cho/Cr levels in the subcortical hippocampus (Yıldız-Yeşiloğlu and Ankerst 2006), although different results have been reported in studies of functional irregularities of the prefrontal/dorsolateral cortex. Postmortem examinations indicate that increased glutaminergic activity results in excitotoxic damage to the dorsolateral prefrontal cortex neurons and glial cells (Oh et al. 2012). In addition to the prominent metabolic changes to the left prefrontal cortex, neurochemical changes in the right cortical regions associated with emotion have also been reported (Grachev et al. 2003, Olvera et al. 2010, Carballedo et al. 2011).

While several researchers have reported decreased NAA, Cho and Cr levels in the prefrontal/dorsolateral prefrontal cortex of depressive patients (Gruber 2003, Wang et al. 2012), other studies were unable to detect altered metabolism in these regions of the brain (Coupland et al. 2005, Nery et al. 2009, Henigsberg et al. 2011).

Antidepressant medications may have a reparative effect on neuronal damage caused by increased NAA, NAA/Cr, and myoinositol (myo-I) levels (Sonawalla et al. 1999, Block et al. 2009, Herman-Sucharska et al. 2010). Ulusoy-Kaymak et al. (2009) have reported no significant change in NAA/Cr and Cho/Cr levels, while myo-inositol/Cr ratios are decreased in major depression following treatment. H-MRS studies suggest that current understanding of these phenomena is incomplete. Alterations in metabolite levels in the prefrontal cortex of depression patients and the specific regions of the brain where these differences are manifest and the effect of antidepressant therapy remains to be completely evaluated.

The application of psychotherapy (cognitive-behavioral therapies, interpersonal psychotherapy and short psychodynamic psychotherapies) in depressive patients results in functional changes to the prefrontal cortex, various regions of the singular cortex and the hippocampus . While Goldapple et al. (2004) states that cognitive behavioral therapy (CBT) normalizes the subcortical and PFK metabolism of depressive patients, Sanacora et al. (2006) has proposed that this form of treatment has a corrective effect on gamma-aminobutiric acid levels that is, however, inferior to medical therapies. Interpersonal psychotherapy applied in major depression is associated with improvement in right prefrontal cortex and left temporal metabolism (Brody et al. 2001). A relationship between recovery from depression via psychodynamic psychotherapy and the associated neurobiological changes in the limbic area and medial prefrontal cortex has recently been proposed (Buchheim et al. 2012). Psychodrama (Özbek and Leutz 2003), a group therapy method of encouraging interpersonal learning and behavioral changes and the activation of spontaneity and creative resources through spontaneous theatrical exercises, has been found to be helpful in mild-moderate depressive patients (Uysal, 2007, Costa et al. 2006). No data has been reported regarding the effect of psychodramatic group therapy on the presence and regulation of brain metabolites.

The primary objective of this study is to examine the neurochemical metabolite levels in the right prefrontal area of patients with mild/moderate major depression relative to healthy control subjects. Secondly, this study will examine whether pharmacotherapy with psychodrama group psychotherapy results in significant alteration of metabolite levels in the right prefrontal cortex and will evaluate the contribution of each treatment method to clinical recovery.

MATERIALS and METHOD

Study Population

The study was conducted between May 2010 and May 2011 at the Pamukkale University Faculty of Medicine Psychiatry polyclinic in volunteer patients who were diagnosed with a first episode of major depressive disorder according to the DSM-IV TR (APA) diagnostic criteria. Patients with severe clinical conditions, active suicidal or psychotic thoughts, or advanced age were excluded from the study group.

Specific exclusion criteria include: 1) presence of other psychiatric disorders such as schizophrenia, bipolar mood and anxiety disorder or alcohol-substance addiction; 2) mental retardation; 3) neurological diseases; 4) existence of a physical or cognitive problem that hinders communication. A staff psychiatrist carried out a full psychological evaluation of the healthy volunteer group, which consisted of relatives of hospital employees. Subjects who did not have any psychiatric disease according to DSM-IV diagnosis criteria, who did not have a first degree relative with a history of psychiatric disorder, and who did not have an ongoing medical problem were included in the healthy control group. All patients and healthy control subjects were right handed.

The Pamukkale University Ethics Committee granted approval for all aspects of this study

Clinical and Psychological Evaluation

Patients without severe clinical conditions who met the DSM-IV TR major depressive disorder diagnosis criteria and who were experiencing a first depressive episode were informed

about the nature of the investigation and were enrolled in the study at the polyclinic. The Hamilton Depression Rating Scale (HAM-D, Hamilton, 1967) was applied to determine the intensity of in patients who consented to participation in the study. Ten volunteers with similar age and education levels of the patients selected from among hospital staff relatives comprised the healthy control group. Proton magnetic resonance spectroscopy (1H-MRS) measurements of the patients and the healthy control subjects were completed within one week of study enrollment. Drug therapy (essitalopram 10-20 mg/d) was initiated in all depression patients following the 1H-MRS study. All patients reported to the polyclinic for monitoring once monthly and drug doses were adjusted as necessary. A total of 8 patients out of the 24 who gave consent to enter the drug treatment group completed the treatment regimen, excluding 10 subjects who did not attend regular control appointments or the final 1H-MRS scan, 2 who refused the final scan and 4 who were excluded due to medical problems (n= 16, 66.6%). Among the 16 who gave consent to participate in psychodrama group psychotherapy once every week in addition to the use of anti-depressant medication, 10 patients completed the protocol, excluding 3 who moved out of the city, 2 individuals who discontinued participation after a few sessions, and 1 subject in whom metabolite evaluation could not be carried out due to a technical issue (n= 6, 37.5%). HAM-D was conducted in 18 patients who completed the study protocol including all 1HMRS scans following the 16th week of treatment.

Psychodrama group psychotherapy application

In addition to the use of anti-depressant medication, group psychotherapy sessions were conducted weekly for 16 weeks, between 14:00 and17:00 at a location suited for group work. The sessions were managed by a psychodramatist and her associate therapist (certified from the Abdülkadir Özbek Psychodrama Institute). Supervision regarding group studies was carried out after each session by a different psychodrama therapist who was also trained at Abdülkadir Özbek Psychodrama Institute. Feedback regarding the previous week was encouraged at the start of each session. The objective of the session was to use basic methods of psychodrama including role-playing and role reversal, doubling, and mirroring. The sessions followed a loose structure:

First four weeks

Meeting, warming up, group decision making,

Structured warm up studies and basic performance studies with known group games,

Last 12 weeks

Emotion-symptom control that revives the status of group members based on the individual (awareness from emotion to symptom), protagonist games,

Group games for identification of depression and how to cope with depressive symptoms.

Hamilton Depression Rating Scale (HAM-D)

The Hamilton Depression Rating Scale (HAM-D) is used to measure the severity of depression (Hamilton 1967) and reliability and validity studies in Turkish have been previously conducted (Akdemir et al. 2001). It consists of 17 items evaluating depressive symptoms occurring in the previous week. Since HAM-D was initially developed for patients who had been admitted to the clinic, the melancholic and physical symptoms of depression are emphasized. The HAM-D scale evaluated difficulty falling asleep, waking during the night, waking in early hours of the morning, somatic symptoms, genital symptoms, loss of weight and insight; these criteria are assigned a rating between 0-2, whereas other items are rated between 0-4. The maximum score is 53. Scores between 0-7 indicate no depression, 8-15 indicates mild depression, 16-28 indicates moderate depression and scores of 29 and above indicate severe depression.

Proton magnetic resonance spectroscopy (1H-MRS)

Proton Magnetic Resonance Spectroscopy (1H-MRS) was conducted using the 1.5 tesla magnetic resonance device (GE Medical System, Milwaukee, WI, USA) with a standard head coil. Initially, a whole brain guide image was taken in the sagittal plan for the purposes of orientation and to determine the position of the consecutive sequences. Afterwards, a magnetic resonance protocol was conducted in the coronal plane with a T2-weighted fast spin eco (FSE) scan taken according to the following parameters: 10 mm thickness,Time of Repetition/Time of Echo =3000/85, Field of View= 14, matrix= 352X352, Number of Excitation= 1. MR spectroscopy was carried out using the single voxel (^{1}H-voksel) method applied to the frontal cortex region. The volume of interest (VOI) was determined as 20 x 20 x 20 mm^3 for each voxel and was placed so as to cover the relevant brain tissue in the frontal lobe. The chemical shift selective pulse (CHESS) method was used to suppress water-based signals (Kienlin 1998). Afterwards, the point-resolved spectroscopy (PRESS) (Klose 2008) method to localize spectroscopy volume (TR/TE: 3000- 144, and 35) was applied. At the conclusion of the procedure, short and medium TE timed spectrums from the VOI in the right prefrontal cortex region were obtained (Figure I). Regular spectroscopies were collected for quality control purposes in the same device phantom where all the metabolites were located to observe the obtained spectrum quality. In addition, the signal-to-noise ratio of resonances obtained from patients were recorded using the device software; images with signal-to-noise ratios <3 were removed from the spectrum measurements. Measurements of semi-amplitude of the peak values (FWHM) during the spectroscopy sequence

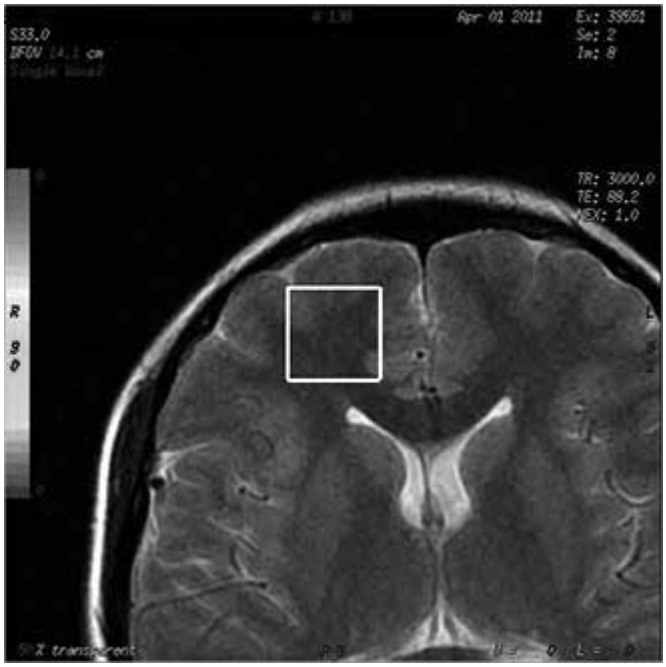

Figure 1. Proton magnetic resonance spectroscopy (1H-MRS) scan region in right prefrontal cortex of a patient with major depressive disorder-first episode.

<6 Hz were included in the study data. The data was collected and evaluated using General Electric spectral analysis software. The levels of right cortex N-Acetyl Aspartate (NAA), choline (Cho), and creatine (Cr) containing compounds were determined and the corresponding NAA/Cr, Cho/Cr levels were calculated. The total creatine resonance value consisting of creatine andphosphocreatine, indicating overall energy metabolism was accepted as the reference value according to prior reports that this value is not affected by various pathologies (Monkul et al. 2004).

Statistical analyses

Statistical analysis was carried out using SPSS 10.0 software. The non-parametric Mann-Whitney U test was used to compare the age, education level, HAM-D scores and neurochemical metabolite levels of the two groups since the number of cases in the depression and control groups were low and that the neurochemical metabolite values did not fit a normal distribution according to the results of Kolmogorov-Smirnov analyses. The Kruskal Wallis test was applied in the pairwise comparisons according to treatment methods (anti-depressant medication alone, anti-depressant medication with psychodramatherapy, and the control group). The Wilcoxon signed-rank test was used both prior to and after the treatment to compare the HAM-D scale scores of depression patients. A p-value of $p<0.05$ was established as the threshold of statistical significance.

RESULTS

All 18 patients participating in the study were female with an average age of 35.27±11.60 years and an average educational period of 10.61±3.53 years. The control group consisted of 10 females with an average age of 32.50±5.21 years and an average educational period of 10.55±3.57 years. The depression group and the control group did not differ significantly in terms of age and education level (respectively, z=0.720 p=0.472, z=0.027 p=0.978, Mann Whitney U test).

While 8 of the 18 patients experiencing the first major depressive period used only essitalopram (10-20 mg/daily), the remaining 10 patients participated in psychodrama psychotherapy sessions in addition to anti-depressant use. The appropriate dose of essitalopram was determined following evaluation by the polyclinic doctor. The essitalopram dose did not differ significantly between the group that was only using essitalopram and the group undergoing essitalopram with group psychodramatherapy (respectively 15.00±5.34, 18.00±4.21, z=1.304 p=0.192, Mann-Whitney U test).

The average pre-treatment HAM-D score was 14.55±4.55 (minimum 8, maximum 27) and the post-treatment score was 3.88±2.47 (minimum 0, maximum 6) for the patient group. The HAM-D scores indicated a statistically significant decrease in the intensity of post-treatment depressive symptoms (z=3.519. p<0.001, Wilcoxon test). Imaging analysis revealed no statistically significant difference between the pre-treatment and post-treatment right prefrontal cortex NAA, Cho, Cr, NAA/Cr and Cho/Cr levels between the depression and control group (Mann-Whitney U test, p>0.05, Table I).

Patients taking anti-depressants and participating in the psychodrama therapy sessions demonstrated no significant difference in pre-treatment and post-treatment HAM-D scores of patients (respectively, z=1.250, p=0.211; z=0.828, p=0.408, Mann Whitney U test). No statistically significant difference was determined between the pre- and post treatment NAA, Cho, Cr, NAA/Cr and Cho/Cr ratios in the medication with psychotherapy treatment group and the imaging data in the medication with psychotherapy group did not differ significantly relative to the healthy control group or the medication only group (Kruskal Wallis test, p>0.05 for all of them, Table II).

The initial psychodrama sessions consisted of an introduction to a structured warm up study in the meaning of names along and an orientation to the game. Group rules were agreed upon by the participants that included conforming to the group hours, confidentiality, equality of participants, and reservation of judgment or blame. Basic psychodrama methods such as role playing, role reversal, doubling and mirroring were used during the sessions. Each session began with a discussion of the previous week, after which simple

Table 1. Pre-treatment and post-treatment neurochemical metabolite levels for the depression and control group.

Metabolites	Depressive group (n:18)	Control group (n:10)	z*	p
pre-treatment				
NAA	67.88±19.23	65.33±10.95	0.216	0.829
Cho	34.10±8.13	36.60±5.25	1.207	0.227
Cr	37.81±6.59	39.60±8.00	0.503	0.615
NAA/Cr	1.87±0.50	1.71±0.18	0.026	0.979
Cho/Cr	0.91±0.22	0.96±0.13	1.128	0.259
post-treatment				
NAA	61.06±13.97	65.33±10.95	0.624	0.533
Cho	35.56±9.91	36.60±5.25	0.370	0.711
Cr	38.12±8.84	39.60±8.00	0.370	0.711
NAA/Cr	1.77±0.49	1.71±0.18	0.566	0.571
Cho/Cr	0.97±0.23	0.96±0.13	0.408	0.683

NAA: N-acetyl aspartate, Cho:choline, Cr: creatine, NAA/Cr: N-Asetil aspartat/creatin, Cho/Cr:choline/ creatine, *Mann-Whitney U test, $p<0.05$ significantly.

performance studies including structured warming up sand familiar group games were conducted. Each patient played the role of the protagonist at least once during the process. In the course of these exercises, new roles that will replace old ones were examined, past life stories were rearranged and new possibilities for the future were evaluated. Each member was encouraged to engage with experiences relative to her own depression and to experiment with various means of coping. Group members enacted typical field situations such as marital problems (emotional distance with the spouse, anger towards the spouse, disappointments in spousal relations, anger towards the family of the spouse, etc.), relations with children (problems between a mother who could not reconcile her own expectations in life with those of her daughter), longing for mother (the sadness of a patient whose mother passed away when she was small), the emotional injury and disappointment of a woman with traumatic experiences (short term convicts), and loss of a father and the grief process. Awareness of symptoms arising from emotions was expressed and developed over the course of two group games

Table 2. Neurochemical metabolite levels and HAM-D scores by treatment group.

Metabolites	drug (n:8) mean±SD	drug+psychodrama grouptherapy (n:10) mean±SD	control (n:10) mean±SD	$\chi 2^*$	p
pre-treatment					
NAA	64.55±14.13	64.55±14.13	65.33±10.95	0.100	0.951
Cho	33.23±7.25	34.87±9.21	36.60±5.25	1.887	0.389
Cr	35.42±8.13	39.93±4.28	39.60±8.00	2.038	0.361
NAA/Cr	1.86±0.37	1.88±0.60	1.71±0.18	0.276	0.871
Cho/Cr	0.97±0.22	0.87±0.21	0.96±0.13	2.804	0.246
HAM-D	13.87±5.76	15.10±3.54	-		
post-treatment					
NAA	60.37±14.24	61.75±14.65	65.33±10.95	0.483	0.785
Cho	33.75±10.38	37.37±9.75	36.60±5.25	1.379	0.502
Cr	35.62±9.45	40.62±7.99	39.60±8.00	1.308	0.520
NAA/Cr	1.71±0.18	1.81±0.65	1.71±0.18	0.671	0.715
Cho/Cr	0.93±0.10	1.00±0.30	0.96±0.13	0.168	0.919
HAM-D	3.25±3.24	4.44±1.50	-		

NAA:N-acetyl aspartate, Cho:choline, Cr: creatine, NAA/Cr: N-Asetil aspartat/creatin, Cho/Cr:choline/ creatine, *Kruskal Wallis test, for all values $p>0.05$.

focusing on concentration and imagination . Each member examined her own life experiences including family relations during childhood, and experimented with new roles in which she could repair her social relationships and accept loss. The participants provided feedback indicating improved interactions with their own families and social environments during the course of the sessions. Unique relationships within the group and a variable therapeutic time interval applied to each individual participant.

DISCUSSION

The primary objective of this study was to evaluate neurochemical changes in the right prefrontal cortex of first episode major depression patients relative to a cohort of healthy control subjects. The depression severity of the 18 patients with a first episode of major depressive disorder participating in the study was mild-moderate (mean HAM-D score= 14.55±4.55). Prior to the treatment, the NAA levels (67.88±19.23), a parameter of neuronal integrity and healthy neuronal function, and choline levels, which reflect the degree of myelinization, proliferation and membrane functions (phosphorylcholine glycerophosphorylcholine total= 35.56±9.91) were found to be similar to the healthy control group. NAA/Cr (1.77±0.49) and Cho/Cr (0.97±0.23) ratios within the patient group were similar to the healthy control group, suggesting that neurodegeneration, which may occur in severe clinical manifestations of depression (Kumar et al. 2002), may not be a significant factor in the pathology of patients with mild depression.

Abnormalities in various neurochemical metabolites such as NAA, Cho related to neurodegenerative processes occur in the prefrontal cortex in patients with depression (Rao et al., 2011). Wang et al. (2012) suggest that DLPFK NAA/Cr and Cho/Cr, and right DLPFK NAA/Cr levels decrease in depression. This study of patients with first episode depression concluded that neurodegeneration occurs predominantly in patients with depressive symptom severities of mild and above who do not use anti-depressant medications. Other studies have proposed that depressive symptom severity and disease duration is related to neurochemical metabolite levels (Gönül et al., 2006, Husarova et al., 2012). Portella et al. (2011) have determined that prefrontal cortex NAA levels are reduced relative to first period depression patients in patients with recurring and chronic depression. Choline levels are elevated in patients with chronic depression i comparison to first period depression patients. Choline levels increase proportionally with disease duration. We propose that cellular abnormalities characteristic of depression may be more pronounced with disease duration, severity, and recurrence.

Additional studies have identified no neurochemical metabolic abnormalities in the prefrontal cortex during depression. In a study of mild to severe depression as well as patients with first episode disease or recurring depressive disorder, the levels of dorsolateral prefrontal cortex neurochemical metabolites such as NAA, Cho, Cr, glutamate and glutamine were similar to those of a healthy control group (Nery et al. 2009). Our results and the previous reports by other groups suggest that adult patients with non-chronic, first episode milk-moderate depression have a low prevalence of neurochemical change and no degenerative alteration in the function of prefrontal cortex NAA, Cho, Cr metabolites.

A secondary objective of the present study was to evaluate neurochemical changes using the 1H-MRS method, including metabolites such as NAA, Ch that may be affected by depression treatment (Caverzasi et al.2012). One patient group was prescribed essitalopram (10-20mg/d) only, whereas in the second patient group participated in psychodrama group psychotherapy in addition to receiving essitalopram treatment; depressive symptoms recovered and symptom intensity decreased in both patient groups. The prefrontal cortex chemical metabolite levels did not change in the anti-depressant medication treatment only group or the combined treatment group following several weeks of therapy. Both biological and psychological elements contribute to the development of depression. The lack of altered neurometabolism in depressed patients with clinical symptom improvements may suggest a greater role for psychological factors in the pathogenesis of depression.

A study conducted by Nery et al. (2009) reported no change in metabolite levels in the prefrontal cortex following treatment. Another study examined SSRI over an 8 week period, concluding that there was no difference between the pre- and post- treatment NAA/Cr and Cho/Cr levels, while left DLPFK myo-inositol/Cr ratios were significantly decreased (Ulusoy-Kaymak et al., 2009). Another study conducted by by Gönül et al. (2006) presented a contradictory result, indicating that medial prefrontal cortex NAA/Cr levels are lower in depression patients in comparison to healthy individuals, but are increased by pharmacological treatment. In severe and chronic depression patients, left DLPFK metabolite levels increase following electro convulsive treatment (Michael et al. 2003). Others have proposed that patients with frontal lobe NAA/Cr ratios greater than 1.91 have a more robust response to pharmacological treatment and NAA/Cr may be helpful prognostic indicators (Kado et al., 2006). Frontal cortex neurochemical metabolite studies normalized following treatment in these studies, with effectiveness varying across patient groups. Psychotherapeutic approaches with various theoretical and application techniques are effective in the treatment of depression and can help resolve abnormalities that occur in prefrontal cortex metabolism, similar to pharmacologic treatment. In a functional imaging study regarding the neurobiological effects of CBT and SSRI treatments on major depression patients, Goldapple et al. (2004) reported that

PFC activity was reduced to within normal limits in the CBT group but increased in the pharmacologic treatment group. Psychotherapy treatment results in recovery of thought with the suppression of limbic activity. In a study carried out to examine the effect of interpersonal psychotherapy and paroxetine treatment on major depression in patients with increased PFC activity as indicated by PET, PFC activity was decreased in right side by psychotherapy whereas paroxetine treatment results in PFC activity decrease in both sides (Brody et al., 2001). Psychodynamic psychotherapy applied for 15 months decreases prefrontal cortex activity in patients with major depression, with the greatest effect seen in the brain hemisphere that had the greatest activity prior to treatment(Buchheim et al., 2012). In summary, these studies indicate that abnormal PFC activities in depression can be regulated by way of psychotherapy.

Huntley et al. (2012) have conducted a systematic review and meta-analysis study examining the effectiveness of group based psychological treatment that psychotherapies excluding CBT, concluding that such methods had limited effect. objective secondary objective of the present study was to determine whether psychodrama group treatment added to anti-depressant treatment would improve clinical recovery. The results have shown that the application of psychodrama group psychotherapy provides a similar clinical recovery to treatment with anti-depressants only and results in similar neurochemical metabolism. Although previous studies have identified decreases in depressive symptoms and increased social adaptation following psychodrama group psychotherapy (Costa et al. 2006, Hamamcı 2006), the number of studies in this field is insufficient. The objective of psychodrama is to define the inhibiting factor affecting emotion and thought processes in the patient and to overcome depression and resolve problematic interactions through the use of interactive games (Farmer 2005). The administrators of the present study noted that the factors underlying depressive status tended to surface in participating patients with the advancement of the group therapy process. As group activities were conducted involving contradictory emotions and complex thoughts, the ability to articulate disease-related awareness and emotions increased in these patients. The patients themselves reported that they could better interact with their own families and social environment. The exclusion ratio of patients who participated in the group therapy was less than half that of the group treated with anti-depressant pharmacologic treatments only. Our experience indicates that psychotherapy increased regular participation and adaptation to the therapeutic process, willingness to participate in treatments, and personal responsibility. Further studies on this patient group might contribute to the evaluation of prognosis and coping in these patients.

The limitations of our study include the small number of cases, the inclusion of mild and moderate level depression patients only, technical limitations which permitted only a single 1HMRS scan in the control group, and the measurement of neurochemical anomalies only right prefrontal cortex metabolites.

In conclusion, adult, non-chronic, first episode mild/moderate level depression is associated with a low probability of degenerative change in prefontal cortex NAA, Cho, Cr metabolite levels. Pre-treatment prefrontal cortex metabolite levels did not change following anti-depressant treatment only or medical treatment with psychotherapy. Short and long term target driven studies that are applied with a more structured treatment framework may enhance understanding of the nature of depressive symptoms and their biological projections.

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