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Increased Ventricular Cerebrospinal Fluid Lactate in Depressed Adolescents

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Abstract

Background—Mitochondrial dysfunction has been increasingly examined as a potential pathogenic event in psychiatric disorders, although its role early in the course of major depressive disorder (MDD) is unclear. Therefore, the purpose of this study was to investigate mitochondrial dysfunction in medication-free adolescents with MDD through in vivo measurements of neurometabolites using high-spatial resolution multislice/multivoxel proton magnetic resonance spectroscopy.

Methods—Twenty-three adolescents with MDD and 29 healthy controls, ages 12–20, were scanned at 3T and concentrations of ventricular cerebrospinal fluid lactate, as well as N-acetyl-aspartate (NAA), total creatine (tCr), and total choline (tCho) in the bilateral caudate, putamen, and thalamus were reported.

Results—Adolescents with MDD exhibited increased ventricular lactate compared to healthy controls [$F(1, 41) = 6.98, p = .01$]. However, there were no group differences in the other neurometabolites. Dimensional analyses in the depressed group showed no relation between any of the neurometabolites and symptomatology, including anhedonia and fatigue.

Conclusions—Increased ventricular lactate in depressed adolescents suggests mitochondrial dysfunction may be present early in the course of MDD; however it is still not known whether the presence of mitochondrial dysfunction is a trait vulnerability of individuals predisposed to psychopathology or a state feature of the disorder. Therefore, there is a need for larger multimodal studies to clarify these chemical findings in the context of network function.

Keywords

proton magnetic resonance spectroscopy; adolescent depression; mitochondrial dysfunction

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Conflicts of interest

All authors declare that they have no conflicts of interest.

1. Introduction

Major depressive disorder (MDD) is a debilitating mental illness and major public health concern that remains poorly understood. MDD often emerges in adolescence with devastating consequences, including suicide, the second leading cause of death in this age group [1–3]. However, there is a paucity of research targeting adolescents early in the course of illness. Nearly all pathophysiological models of adolescent MDD are based on evidence derived from research in adults, which may be confounded by disease chronicity, antidepressant exposure, and aging.

Recently, mitochondrial dysfunction has been increasingly scrutinized as a potential pathogenic event in MDD [4]. In support of this emerging model are phosphorous magnetic resonance spectroscopy (^{31}P MRS) studies of high-energy phosphate neurometabolites in adults with MDD, which have documented decreased levels of adenosine triphosphate (ATP)—the cell's energy currency—whose production is the primary biological function of the mitochondria [5, 6]. Additionally, recent proton magnetic resonance spectroscopy (^1H MRS) studies of brain lactate levels have reported elevations in adult patients with MDD [7], schizophrenia, and bipolar disorder [8, 9] compared to healthy control subjects. Brain lactate, the end product of anaerobic glycolysis, increases as a result of decreased mitochondrial energy production (Fig. 1), and is thus a sensitive index of mitochondrial dysfunction. However, these prior in vivo MRS assessments of the potential involvement of mitochondrial dysfunction in MDD were conducted in adult patients, so their relevance to depression in adolescence is unclear.

The primary aim of the present study was to investigate the potential role of mitochondrial dysfunction in depressed adolescents through in vivo measurements of neurometabolites using a high-spatial resolution multislice/multivoxel ^1H MRS technique, commonly referred to as MRS imaging or MRSI [10]. Specifically, based on our prior finding of elevations of ventricular cerebrospinal fluid (CSF) lactate in adults with MDD compared to healthy control subjects [7], we hypothesized that this metabolic marker of mitochondrial dysfunction would be similarly elevated in depressed adolescents. Secondly, we aimed to assess whether there were significant regional abnormalities (i.e., bilateral caudate, putamen, and thalamus) in the levels of other neurometabolites, including N-acetyl-aspartate (NAA), total choline (tCho), and total creatine (tCr), which are simultaneously measured with lactate by our MRSI technique. We specifically focused on metabolite concentrations within the striatum given mounting evidence linking this region to the reward circuitry, motivation [11–13], and anhedonia [14, 15].

In the context of the present study, NAA was of particular interest because it is synthesized in neuronal mitochondria and localized almost exclusively in neuronal elements [16]. Reductions in NAA are generally interpreted as reflecting neuronal injury, dysfunction or loss and, germane to the present study, impaired mitochondrial function [17, 18]. Total choline is associated with cell membrane integrity, with increases indicative of membrane peroxidation and breakdown (Urenjak et al., 1993; Gabbay et al., 2007). Thus, we hypothesized that depressed adolescents would show decreased NAA and increased tCho in the striatum. Conversely, tCr is often constant and functions as an internal standard for

comparison in MRSI investigations [19], thus, no differences between groups were hypothesized. Lastly, potential associations between the neurometabolites and depressive symptoms (e.g., anhedonia and fatigue) previously documented in MDD [7, 20], were also explored.

2. Methods

2.1. Participants

Participants in this study consisted of 23 adolescents with MDD (mean age = 17.08, SD = 2.53, 14 females) and 29 healthy controls (HC; mean age = 15.86, SD = 1.96, 20 females). Groups were not specifically matched on age and gender, so these factors were explored as covariates in the statistical models.

Depressed adolescents and HC participants were recruited from academic institutions and by media advertisements in the New York City metropolitan area. Participants provided written informed consent, or parental consent and assent for subjects younger than 18 years old, before all procedures. Approval to conduct the study was granted by the institutional review boards of the participating institutions.

2.2. Inclusion and exclusion criteria

All adolescents with MDD met the DSM-IV-TR diagnosis of MDD with a current episode 6 weeks duration, and a raw severity score ≥ 36 on the Children's Depression Rating Scale-Revised (CDRS-R). Moreover, all participants with MDD were either medication naïve or psychotropic medication-free for at least 7 half-lives of the medication. In the MDD group, co-morbid diagnoses of attention-deficit/hyperactivity disorder (ADHD; $n = 3$) and anxiety disorders such as generalized anxiety disorder, overanxious disorder, and social anxiety disorder ($n = 8$) were inclusionary.

Exclusion criteria for all participants consisted of the presence of a significant medical or neurological disorder, IQ < 80 as assessed by the Kaufman Brief Intelligence Test [21], MRI contraindications as assessed by a standard safety screening form, a positive urine toxicology test, and in females, a positive urine pregnancy test on the day-of-scan. A lifetime diagnosis of bipolar disorder, conduct disorder, obsessive-compulsive disorder, panic disorder, pervasive developmental disorder, schizophrenia, or Tourette's disorder was exclusionary for adolescents with MDD. Diagnosis of a substance-related disorder within the past 12 months, or a current diagnosis of either post-traumatic stress disorder or an eating disorder was also exclusionary. The HC participants did not meet criteria for any major current or past DSM-IV-TR diagnosis and had never been treated with psychotropic medication.

2.3. Clinical assessments

A board-certified child/adolescent psychiatrist or a clinical psychologist conducted clinical assessments on all participants to determine psychiatric diagnosis and symptom severity. Clinical diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL [22], a

semi-structured interview performed with both the participants and their parents. Depression severity was assessed using the clinician-rated CDRS-R and the self-rated Beck Depression Inventory, second edition (BDI-II). Additionally, suicidality was assessed using the Beck Scale for Suicidal Ideation (BSSI).

2.4. Anhedonia

For all subjects, anhedonia severity was assessed by the sum of one item reflecting anhedonia in the clinician-rated CDRS-R (item 2: “Difficulty having fun,” rated 1–7) and two items from the self-rated BDI-II (item 4: “Loss of pleasure,” rated 0–3, and item 12: “Loss of interest,” rated 0–3), with the total score ranging from 1 to 13. This method of quantifying anhedonia has been used in our own studies [14, 23–27] as well as in others [28].

2.5. Fatigue

Fatigue severity was also quantified by the summation of clinician and self-rated scales. One item reflecting fatigue in the CDRS-R (item 6: “Excessive fatigue,” rated 1–7), and two items from the BDI-II (item 15: “Loss of energy,” rated 0–3, and item 20, “Tiredness or fatigue,” rated 0–3) were combined, with the total score again ranging from 1 to 13. Fatigue was chosen as a clinical characteristic of interest due to its prevalence in MDD and our prior finding of its relationship with lactate in adults [7].

2.6. Structural MRI

A 3-plane, low-resolution, high-speed scout imaging series was first obtained, followed by a series of high-resolution scans. These included standard axial, coronal, and sagittal T1-, T2-, and spin density-weighted scans, which were used to prescribe the subsequent ^1H MRSI slices. In addition, a T1-weighted spoiled gradient-recalled echo (SPGR) volumetric scan and an axial fast fluid-attenuated inversion recovery (FLAIR) scan were performed for tissue segmentation and detection of exclusionary focal brain lesions, respectively.

2.7. ^1H MRSI

Multislice ^1H MRSI [10] scans were conducted in all participants using the same 3.0T GE MRI system as previously described [7, 29]. The MRSI data were recorded from four 15-mm axial-oblique brain slices with the second most inferior slice traversing the lateral ventricles at the genu and splenium of the corpus callosum. Multislice MRSI has the advantage of providing simultaneous acquisition of several sections with extended coverage of multiple brain regions [7, 10, 29, 30]. Each data set was acquired in 16 minutes using the following parameters: echo time/repetition time 280/2300 ms, 240 mm field of view, 24 x 24 phase-encoding steps with circular k-space sampling, and 512 sample points. The undesired pericranial lipid resonances were suppressed using octagonally tailored outer volume presaturation pulses [10]. Spectral resonances in a grid of voxels encompassing the lateral ventricles (Fig. 2) and in similar grids of voxels in a number of regions of interest within the brain parenchyma, particularly the striatum, were quantified by integration, and then the associated metabolite levels were expressed in institutional units, as peak area ratios relative

to the root mean square of the background noise in each voxel, as previously described [7, 29–31].

2.8. Brain tissue segmentation and volume of interest tissue heterogeneity

To estimate the proportions of gray matter, white matter and cerebrospinal fluid contained in the volume of interest (VOI), including in the bodies of the lateral ventricle, MEDx software (Medical Numerics, Germantown, MD) was used to segment the brain tissue based on the signal intensity histogram of each participant's volumetric SPGR MRI. In-house software developed in MATLAB (MathWorks, Natick, MA) was then implemented to generate a segmentation mask of each VOI, from which the relative volumes and proportions of gray matter, white matter, and cerebrospinal fluid were determined. These were then compared between the groups and in case of significant differences, included as covariates in the statistical model.

2.9. Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics, version 20 (SPSS Inc., Chicago, IL). Prior to the analyses, data normality was assessed using Shapiro-Wilks tests. Homogeneity of variance was assessed using Levene's test. Groups were compared on demographic and clinical variables using t-tests or chi-square tests, as appropriate. When normal distributional assumptions were not reasonably met, non-parametric analogs were used. Group differences in lactate, the primary metabolite of interest, were assessed using analysis of covariance (ANCOVA), with ventricular size, age, gender, and BMI examined as potential covariates. The level of significance was set at $p < 0.05$. Group differences in regional NAA, tCr, and tCho were also assessed with ANCOVA, controlling for factors that differed between groups; group differences were examined in age, gender, and gray matter, white matter and CSF content of each VOI. For these secondary analyses, significance was set at $p < 0.003$ (.05/18), to take into account the total number of bilateral subcortical regions (6; bilateral caudate, putamen, and thalamus) and metabolites (3; NAA, tCr, and tCho) that were examined. Lastly, Pearson/Spearman correlation coefficients were used to dimensionally explore the relationships between age, illness severity, depressive episode duration, anhedonia, fatigue, and brain metabolites in adolescents with MDD. For correlations between lactate and clinical variables, significance was defined as two-tailed, with a threshold of $p < 0.01$ (.05/5), to account for the number of analyses performed. For correlations between NAA, tCho, and tCr in the 6 subcortical regions of interest and clinical variables, a very conservative significance threshold of $p < 0.002$ (.05/30) was selected.

3. Results

3.1. Sample demographics and characteristics

The demographics and clinical characteristics of the current sample are summarized in Table 1. All subjects in the MDD group were in a current major depressive episode at the time of scan. The two groups differed significantly on age [$U(52) = 447.50$, $p = 0.036$] but not gender [$\chi^2 = .37$, $p = 0.54$] or BMI [$U(44) = 289$, $p = 0.22$]. Thus, age was included as a covariate in all group comparisons. The ventricular lactate data for 4 adolescents with MDD and 4 HCs were rejected from all analyses due to excessive subject head motion as

determined by the “smearing” of the residual pericranial lipid signals along the phase-encoding directions.

Ventricular volume and the proportions of gray matter, white matter, and CSF in the regions of interest did not differ between the groups (see Table A.1 in Appendix A), so these variables were not included as covariates in the statistical analyses. Additionally, while there were no differences in gender between groups, this variable was nevertheless included as a covariate in ANCOVA models due to known associations between gender and neuroimaging measures [32, 33].

3.2. Metabolite group comparisons

Adolescents with MDD ($n = 19$) had higher ventricular CSF lactate levels than HC participants [$n = 25$; 0.60 (0.81) versus 0 (0.72); $F(1, 40) = 8.92$, $p = 0.005$]. This finding remained significant [$F(1,39) = 7.64$, $p = 0.009$] even after excluding one clear outlier in the MDD group ($n = 18$), which was identified because the value was more than 2 standard deviations higher than the mean value for the depressed group. Group differences are illustrated in Fig. 3. On the other hand, no significant differences were found between adolescents with MDD ($n = 23$) and HC ($n = 29$) in our three additional metabolites of interest, NAA, tCho, or tCr in the bilateral caudate, putamen, or thalamus (see Tables A.2–A.4 in Appendix A).

3.3. Dimensional relationships between metabolites and clinical variables in MDD

There were no significant correlations between ventricular lactate and age [$\rho(19) = 0.05$, $p = 0.85$], or between striatal NAA, tCho, tCr and age (all $p > .05$); therefore, age was not included as a covariate in any of the correlational analyses. Moreover, no significant correlations were found between any of the neurometabolites and depression severity, depressive episode duration, anhedonia, or fatigue (all $p > .01$).

4. Discussion

Using state-of-the-art multislice ^1H MRSI technology, this study compared neurometabolites in adolescents with MDD and healthy control participants, with the primary objective being to uncover in vivo evidence to support the role of mitochondrial dysfunction early in the course of depression. Our main finding of increased ventricular CSF lactate is suggestive of impaired mitochondrial function in adolescent MDD and is consistent with our prior report of a similar elevation in depressed adults [7]. Despite this indication of potential mitochondrial dysfunction in adolescent MDD, this study was negative with respect to group differences in striatal NAA, tCr, and tCho, or their relationships to depressive symptomatology, including anhedonia and fatigue.

4.1. Increased ventricular CSF lactate in adolescent MDD

Elevations of brain lactate are generally indicative of increased anaerobic glycolytic rates to compensate for insufficient energy production in the respiratory chain under conditions of ischemia, hypoxia, or mitochondrial dysfunction [34]. In our prior studies of patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)—a

primary mitochondrial disorder with a known pathogenic mitochondrial DNA mutation—we established that elevations of ventricular CSF lactate are one of the earliest signs of an actual, impending, or perceived mitochondrial dysfunction, even in mutation carriers who had not yet developed a full clinical syndrome [31, 35]. Elevation of lactate in adolescent psychiatric illness implies that these alterations may be independent of chronicity or long-term exposure to antidepressants, and thus could serve as a potential biomarker for early metabolic dysfunction in MDD. Additionally, both preclinical and clinical evidence support a relationship between elevations in brain lactate and mitochondrial dysfunction [4, 36–38]. In animal models, induced states of oxidative stress have been associated with mitochondrial dysfunction and decreased ATP production [39]. For example, lactate levels increased 5-fold above baseline in a study in which cerebral mitochondrial metabolism was specifically impaired using cyanide perfusion in the feline brain [40]. Furthermore, lactate elevations have been documented in a number of adult psychiatric populations, including MDD [7], schizophrenia, and bipolar disorder [8, 9], suggesting mitochondrial dysfunction is not specific to major depression. This neurochemical alteration may therefore reflect a general pathophysiology related to CNS impairment across psychiatric disorders.

Inflammation may be a key component of these frequent findings of suspected mitochondrial dysfunction across psychiatric conditions. There is strong support for the role of inflammation in the pathogenesis of both MDD [41–43] and other psychiatric disorders [44]. Work in our lab has documented immune system dysregulation and increased levels of proinflammatory cytokines—proteins that function as signaling molecules to modulate immune responses—in adolescent MDD [41, 45]. Cytokines also interact with mitochondria to increase the production of reactive oxygen species (ROS), and ROS, through a recurring cycle, further activate cytokines and evoke an inflammatory response [46, 47]. At high levels, ROS and oxidative stress can result in cell death [42] and exacerbate mitochondrial dysfunction [4]. The recent discovery of a CNS lymphatic system that functions as a gateway for immune cells to travel to the brain further suggests that neuroinflammatory processes that subsequently disrupt mitochondrial function may be a more plausible contributor to psychiatric disease than previously thought [48].

The absence of other significant metabolic abnormalities detectable by ^1H MRS suggests that mitochondrial impairment and neuronal damage in adolescent MDD may be relatively subtle. In our ^1H MRSI study in adults with MDD [7], we likewise failed to detect neurometabolic differences other than in levels of ventricular lactate. Similarly, several studies, including our laboratory's prior work [20, 49–51], found no alterations in NAA in depressed adolescents, while others have documented decreased NAA [52, 53]. Furthermore, our lack of findings of augmented striatal tCho and tCr in MDD contradicts our laboratory's prior results [49], as well as others that have reported increased tCho in depressed adolescents [50, 54, 55]. Several additional explanations for these divergent outcomes include the heterogeneous presentation of MDD, small sample sizes of depressed adolescents in many of these studies, a lack of multiple comparisons correction, as well as different proportions of gray matter, white matter, and CSF in the various brain regions examined, as neurometabolites are susceptible to tissue makeup in ^1H MRS [56].

4.2. Dimensional relationships between neurometabolites and symptomatology

Finally, while there were significant group differences in ventricular lactate, there was no relation between any of the neurometabolites and symptomatology in the depressed group. The lack of a correlation between lactate levels and depressive symptoms fits our previous findings in adults [7]. The clinical correlations that we found between CSF lactate and clinical variables in adults [7] were only significant across three diagnostic groups—patients with MDD, chronic fatigue syndrome, and healthy controls—but not within the MDD group alone. This observation again suggests that mitochondrial impairment in adolescent MDD may be relatively subtle.

Alternatively, it is also possible that the absence of significant correlations could indicate that mitochondrial dysfunction is a subtle trait vulnerability of some individuals with psychopathology rather than a state related to the pathogenesis of major depression. The presence of lactate elevations across psychiatric populations [7–9] may otherwise suggest that certain individuals with psychopathology may simply be more vulnerable to slight impairments in mitochondrial function. Future studies are needed to examine previously depressed adolescents or adults during euthymic periods in order to clarify whether alterations in mitochondrial function are transient manifestations of the pathophysiology of depression or simply subtle, enduring traits of certain individuals predisposed to psychopathology.

The present study is the first to our knowledge to examine brain lactate in psychotropic medication-free adolescents with MDD. This work has the potential to examine neurobiological underpinnings early in the course of the illness prior to chronicity or aging effects. Despite this study's strengths, there are several limitations. Our sample size was modest, although similar to other imaging studies. Additionally, while substance abuse disorders were exclusionary and a drug toxicology test was completed on the day-of-scan, information on nicotine and alcohol use immediately prior to the scan was not obtained. It is unclear how these factors may affect neurometabolite levels, as preliminary evidence suggests NAA, and possibly tCho, tCr, and lactate, may be altered by nicotine usage and alcohol consumption [57, 58]. Moreover, our multislice ^1H MRSI protocol did not yield voxels that were small enough to completely eliminate contamination from tissues outside of the ventricles. However, there were no significant differences in ventricular volume between groups (see Table A.1 in the Appendix), so lactate alterations could not be due to partial volume effects caused by different fractions of CFS being sampled. Furthermore, lactate was only found in the CSF and not the brain parenchyma. This could indicate limitations of the ^1H MRSI acquisition protocol due to narrower resonance linewidths, longer T2 relaxation times in the CSF compared to the brain, and greater lactate concentration in the CSF than in parenchyma [31]. Alternatively, it is possible that CSF lactate could originate in the parenchyma and be transported to the ventricles via circulating CSF, where it becomes visible in higher concentrations using the MRSI protocol [31]. Lastly, the fatigue measure used in the current study was a combination of questions taken from other scales to reflect fatigue, but not a validated, stand-alone assessment, which could have contributed to our lack of correlational findings with brain metabolites. Despite these limitations, our study demonstrates that CSF lactate is elevated early in depression, prior to the accumulation

effects of aging and chronicity, and suggests a need to further investigate whether mitochondrial dysfunction is a trait vulnerability of individuals with psychopathology or a state related to the manifestation of depression. In light of the connections between inflammatory processes, mitochondrial function, and depression [42], future studies should attempt to combine immune and both chemical and functional imaging techniques to provide a better interpretation of these findings in the context of network function.

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Appendix

Table A.1

Ventricular volume and segmentations of striatal gray matter, white matter, and CSF.

Structure	MDD (<i>n</i> = 23)		HC (<i>n</i> = 29)		U(52)	<i>p</i> ^a
	Mean	SD	Mean	SD		
Ventricular Volume*	10.17	0.722	9.94	0.413	231	0.88
Left Striatum Gray Matter (%)	0.172	0.003	0.175	0.002	296	0.49
Left Striatum White Matter (%)	0.826	0.003	0.823	0.002	392	0.28
Left Striatum CSF (%)	0.0008	0.0001	0.0009	0.0002	362	0.60
Right Striatum Gray Matter (%)	0.176	0.004	0.173	0.002	311.5	0.69
Right Striatum White Matter (%)	0.823	0.004	0.825	0.002	358.5	0.65
Right Striatum CSF (%)	0.001	0.0002	0.001	0.0002	341	0.89

^aResults of Mann-Whitney U-tests. There were no significant ($p < 0.05$) group differences in ventricular volume, gray matter, white matter, or cerebrospinal fluid (CSF) segmentations.

* 4 subjects were excluded from ventricular volume comparisons due to a lack of reliable lactate data ($n = 19$ MDD and 25 HC).

MDD = major depressive disorder; HC = healthy controls.

Table A.2

NAA group comparisons.

Structure & Side	MDD (<i>n</i> = 23)		HC (<i>n</i> = 29)		F(1,48)	<i>p</i> ^a
	Mean	SD	Mean	SD		
Caudate						
Left	30.96	8.81	31.53	7.73	.196	.660
Right	30.84	9.02	33.11	7.89	.069	.793
Putamen						
Left	39.08	9.54	38.38	6.32	1.60	.212
Right	38.38	9.21	39.46	6.78	.271	.605
Thalamus						
Left	30.77	8.88	33.07	9.48	.080	.778
Right	31.83	9.20	34.47	8.40	.103	.750

^aResults of the NAA ANCOVAs, controlling for age and gender. There were no significant ($p < 0.003$) group differences.

MDD = major depressive disorder; HC = healthy controls.

Table A.3

tCho group comparisons.

Structure & Side	MDD (<i>n</i> = 23)		HC (<i>n</i> = 29)		F(1,49)	<i>p</i> ^a
	Mean	SD	Mean	SD		
Caudate						
Left	16.10	3.74	18.53	4.57	2.22	.143
Right	16.80	4.73	19.24	4.55	1.81	.185
Putamen						
Left	17.06	3.75	17.90	3.24	.045	.833
Right	16.55	3.68	17.72	3.64	.321	.574
Thalamus						
Left	15.58	3.80	17.09	3.93	.564	.456
Right	16.68	3.79	17.09	3.51	.035	.853

^aResults of the tCho ANCOVAs, controlling for age and gender. There were no significant ($p < 0.003$) group differences.

MDD = major depressive disorder; HC = healthy controls.

Table A.4

tCr group comparisons.

Structure & Side	MDD (<i>n</i> = 23)		HC (<i>n</i> = 29)		F(1,48)	<i>p</i> ^a
	Mean	SD	Mean	SD		
Caudate						
Left	10.68	3.55	10.66	3.21	0.79	.380
Right	11.42	3.04	10.67	2.51	3.49	.068
Putamen						
Left	13.61	2.96	13.13	2.92	2.31	.135

Structure & Side	<u>MDD (<i>n</i> = 23)</u>		<u>HC (<i>n</i> = 29)</u>		F(1,48)	<i>p</i> ^a
	Mean	SD	Mean	SD		
Right	13.60	2.75	13.46	2.63	1.06	.307
Thalamus						
Left	10.29	2.59	10.77	3.10	.017	.896
Right	11.15	2.75	11.95	3.04	.040	.842

^aResults of the tCr ANCOVAs, controlling for age and gender. There were no significant ($p < 0.003$) group differences.

MDD = major depressive disorder; HC = healthy controls.

Fig. 1.

Anaerobic formation of lactate and aerobic energy production. Lactate is the end product of anaerobic glycolysis. ATP = adenosine triphosphate; ADP = adenosine diphosphate; NAD⁺ = oxidized nicotinamide adenine dinucleotide; NADH = reduced nicotinamide adenine dinucleotide.

Fig. 2.

MRSI ventricular voxel placement and ^1H spectra. A) The ventricle volume of interest is shown on a T1-weighted axial image. B) A sagittal view of the four inferior-superior spectroscopic imaging-encoded slices that cover the ventricles and subcortical regions of interest on a T1-weighted image. C) A coronal view of the four spectroscopic imaging-encoded slices on a T2-weighted image. D) Sample ^1H MR spectrum from a voxel in the right posterior horn of the lateral ventricle, showing a clear lactate (Lac) doublet peak at 1.33 ppm, along with model-fitting of the experimental spectrum to derive the metabolite peak areas. The other identified resonances are for N-acetyl-L-aspartate (NAA), total creatine (tCr) and total choline (tCho), which appear with greatly decreased intensity in ventricular spectra because they arise from partial volume-averaging with surrounding brain tissue.

Fig. 3.

Group differences in ventricular CSF lactate. Lactate is presented in institutional units (i.u.), as peak area ratios relative to the root mean square of the background noise in each voxel. There was one outlier in the group with major depression ($n = 19$) and no outliers in the healthy control group ($n = 25$). Group differences were still significant when excluding the single outlier in the depressed group ($n = 18$). MDD = major depressive disorder; HC = healthy controls.

Table 1

Demographic and clinical characteristics of the study sample.

Characteristic	MDD (<i>n</i> = 23)	HC (<i>n</i> = 29)
Age [mean ± SD]	17.08 ± 2.53 ^a	15.86 ± 1.96 ^a
Gender [<i>n</i> female] (%)	14(61)	20 (69)
BMI [mean ± SD] (Range)	24.36 ± 4.58 (18–32)	22.23 ± 2.73 (18–30)
Ethnicity [Caucasian/ African American/ Other] <i>n</i>	10/3/10	10/11/8
Illness History		
Episode Duration in Months [mean ± SD] (Range)	26.13 ± 21.41 (1.5–72)	0
Number of Previous Episodes [0/1/2/3] (%)	0/65/30/5	100/0/0/0
Medication Status [<i>n</i>] (%)		
Medicated	0	0
Medication Free	6	0
Medication Naïve	17	29
CDRS-R [mean ± SD] (Range)	53.26 ± 6.99 (43–68) ^b	18.69 ± 1.34 (17–22) ^b
BDI-II [mean ± SD] (Range)	28.61 ± 12.32 (10–51)	2.55 ± 3.00 (0–10)
BSSI [mean ± SD] (Range)	5.68 ± 7.88 (0–28)	.07 ± 0.26 (0–1)
Anhedonia [mean ± SD] (Range)	7.65 ± 2.21 (3–11) ^c	1.34 ± 0.67 (1–3) ^c
Fatigue [mean ± SD] (Range)	8.05 ± 2.23 (2–11) ^d	1.67 ± 0.92 (1–4) ^d
Current Comorbidity [<i>n</i>] (%)		
ADHD	3 (13)	0
Any Anxiety Disorder	8 (35)	0

Abbreviations : ADHD = attention-deficit/hyperactivity disorder; BDI-II = Beck Depression Inventory, Second Edition; BSSI = Beck Scale of Suicidal Ideation; BMI = body mass index; CDRS-R = Children's Depression Rating Scale-Revised; HC = healthy controls; MDD = major depressive disorder.

^aMDD and HC groups were significantly different, $U(52) = 447.50$, $p = 0.036$

^bMDD and HC groups were significantly different, $U(52) = 667$, $p < 0.0005$

^cMDD and HC groups were significantly different, $U(52) = 665.5$, $p < 0.0005$

^dMDD and HC groups were significantly different, $U(44) = 472$, $p < 0.0005$