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^{31}P magnetic resonance spectroscopy in the frontal lobe of major depressed patients

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Abstract Most research with ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS) in affective disorders has been done in the field of bipolar disturbances. Reduced frontal and temporal lobe phosphomonoester (PME) concentrations were measured in the euthymic state, whereas increased values were found in the depressed state. In bipolar-II patients reduced phosphocreatine (PCr) concentrations were reported in the euthymic, depressed, and manic state. The aim of the present study was to explore whether PME and PCr were also altered in the frontal lobe of major depressed, unipolar patients. Therefore, we used ^{31}P-MRS to investigate the relative phospholipid and high-energy phosphate concentrations in the frontal lobe of 14 unipolar patients, mostly medicated, and 8 age-matched controls. We found increased PME and decreased ATP values. Other ^{31}P-MRS parameters were not different in both groups. Phosphomonoester percentages correlated negatively with the degree of depression. Thus, the main alterations found in bipolar depressed patients could also be demonstrated in unipolar depressed patients. The results are discussed with regard to disturbed phospholipid and intracellular high-energy phosphate metabolism in depressed patients.

Key words ^{31}P magnetic resonance spectroscopy · Depression · Frontal lobe

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Introduction

^{31}P-magnetic resonance spectroscopy (^{31}P-MRS) is applied at present mainly in the investigation of the brain metabolism in schizophrenia. An increase in phosphodiesters (PDE) and a decrease in phosphomonoesters (PME) in frontal brain regions has already been demonstrated (e.g., Pettegrew et al. 1991; Stanley et al. 1994, 1995), but contradictory findings have also been reported (Fujimoto et al. 1992; Volz et al. 1997a, b). Far less research has been published thus far on affective disorders. Kato et al. (1991–1994) mostly investigated bipolar patients in different mood states and studied a 30-mm-thick slice between the frontal pole of the cortex and the anterior part of the corpus callosum. In bipolar patients treated with lithium, they found increased PME in the manic and depressed state, and decreased pH values as well as decreased PME in the euthymic state as compared with normal controls. No correlation to the brain lithium concentration could be verified. Deicken et al. (1995a) found reduced PME and increased PDE levels in the frontal cortex of unmedicated euthymic patients using a volume-selective technique. Deicken et al. (1995b) reported on decreased PME levels in the left and right temporal regions in euthymic bipolar patients, who had been drug free for at least 7 days. Major depressed monopolar patients were investigated only once (Kato et al. 1992); no differences to controls could be established.

Kato et al. (1992) further reported reduced phosphocreatine (PCr) levels in depressed bipolar patients with high scores on the Hamilton Rating Scale of Depression (HAMD) compared with those with low scores. Twelve patients with bipolar depression tended to have lower PCr values than patients with major (unipolar) depression or controls. In a subsequent paper, Kato et al. (1994) reported reduced PCr values in bipolar-II patients only (in the euthymic, depressed, and manic state), not in bipolar-I patients.

Deicken et al. (1995b) summarized these results as follows:

1. Reduced frontal and temporal lobe PME in the euthymic state may represent a trait abnormality, possibly related to membrane abnormalities in bipolar disorders, whereas PME increases in the frontal lobe might be state dependent (since it is measured only in the manic and depressed state).
2. In bipolar-II patients PCr decrease might be linked to disturbed metabolic processes of high-energy phosphates.
3. No such clear-cut disturbances exist in monopolar depressed patients.

The aim of the present investigation was to evaluate phospholipid and high-energy phosphate metabolism by means of ^{31}P-MRS in monopolar depressed patients vs controls. Based on the previously reported results, it was hypothesized that also in monopolar depressed patients PME would be observed to have increased, and pH and PCr to have decreased. In order to attempt a minimization of partial volume effects from muscle, skull bone, and cerebrospinal fluid, a volume-selective technique was applied.

Subjects and methods

Fourteen DSM-III-R major depressed, monopolar in-patients (8 females and 6 males; mean age 43.78 ± 12.53 years) and 8 age-matched controls (5 women and 3 men; mean age 41.5 ± 13.67 years) of comparable socioeconomic status, recruited by newspaper advertisement, were investigated after giving written informed consent to participate in the study. All probands were right-handed (Oldfield 1971). Diagnoses were made by an experienced psychiatrist (H.P.V.) and verified at the end of the in-patient treatment period. Data from patients whose diagnosis had to be changed at the end of hospital treatment were excluded from further analysis. The main demographic variables of the patients together with the medication status are given in Table 1. At the time of investigation, 3 patients were drug free, 2 were treated with antidepressants only, 6 had antidepressants and neuroleptics, 2 took a combination of antidepressants, neuroleptics, and lithium, and 1 patient received a tricyclic antidepressant and carbamazepine (see also Table 1). The Clinical Global Impression (CGI), the HAMD, the Montgomery Asberg Depression Rating Scale (MADRAS), and the Brief Psychiatric Rating Scale (BPRS) served as psychopathological rating scales. Main exclusion criteria for both groups were presence or history of substance abuse, organic brain diseases, and/or severe internal or neurological diseases. Controls were also thoroughly screened for the presence of psychiatric symptoms (using the same rating instruments that were applied to the patients), for a history of psychiatric illness, and for first-degree relatives suffering from a major psychiatric disorder. Any of these conditions led to exclu-

Table 1 Patient characteristics (*HAMD* Hamilton Rating Scale of Depression; *MADRAS* Montgomery Asberg Depression Rating Scale; *CGI* Clinical Global Impression; *BPRS* Brief Psychiatric Rating Scale; *F* female; *M* male)

Case no.	Gender	Age (years)	Duration of illness (years)	HAMD	MADRAS	CGI[a]	BPRS	Medication (mg/day)
1	F	53	20	16	22	4	34	Trimipramine (200)
2	F	53	16	29	32	6	51	Amitriptyline-oxide (180)
3	F	55	17	36	37	6	47	Carbamazepine (600) Clomipramine (125)
4	F	51	0.5	15	17	4	30	Paroxetine (30) Sulpiride (200) Prothazine (20)
5	F	52	2	23	19	5	34	Doxepine (100) Prothazine (25)
6	F	45	0.5	30	32	6	53	Maprotiline (100) Haloperidol (8)
7	F	28	0.5	25	31	5	41	–
8	F	45	5	22	35	6	48	Lithium (675) Amitriptyline (112) Haloperidol (8)
9	M	24	0.5	22	22	4	46	–
10	M	52	6	19	27	5	41	Amitriptyline (240) Levomepromazine (120) Haloperidol (5)
11	M	28	1.5	22	13	5	39	Lithium (900) Haloperidol (10) Levomepromazine (40)
12	M	55	0.5	21	22	5	40	–
13	M	19	0.5	15	16	4	30	Paroxetine (30) Prothazine (25)
14	M	53	0.5	18	20	5	34	Moclobemide (300) Levomepromazine (25)
Mean (SD)	43.78 (12.53)	5.07 (6.83)	22.36 (5.48)	24.64 (7.35)	5 (0.76)	40.37 (7.29)		

[a] Severity of illness score

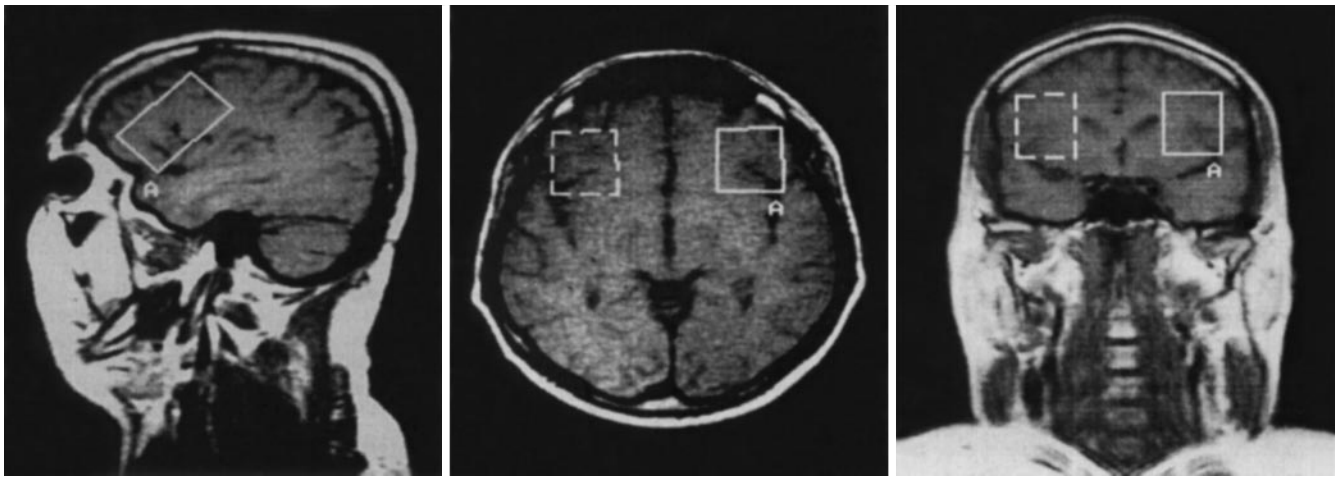

Fig. 1 Typical localization site of the region of interest measured with a volume-selective magnetic resonance spectroscopy technique

sion from the study. The controls were free of any medication for at least 7 days before measurement took place.

^{31}P-MRS

The MRS measurements were performed on a Philips Gyroscan ACSII (Philips, Best, The Netherlands) system operating at 1.5 Tesla. In order to obtain spectra of defined volumes in the frontal cortex, we used an image-guided localization method with a transmit/receive ^{31}P quadrature head coil rather than a surface coil.

The method used was an image-selected in vivo spectroscopy (ISIS) sequence (Ordidge et al. 1986, 1988) with double volume selection (i.e., both volumes of interest measured simultaneously) using volume-selective adiabatic high-frequency pulses. The relaxation time was 3000 ms, the free induction decay (FID) sampling rate was 2000 Hz, and the number of sample points was 1024. Each spectrum was averaged over 768 measurements. The volumes of interest (VOIs) were slightly adapted to the size of the brain of each subject. The localization and size of each VOI was controlled with the help of anatomical landmarks. In the case of depressed patients, the size of the VOI was 39.4 ± 0.8 cm^3 (mean ± standard deviation), and for healthy controls the VOI size was 39.1 ± 0.4 cm^3.

For imaging we used a body coil. After a surface scan, T1-weighted images of 17 slices in transverse, sagittal, and coronal planes were obtained. These images were used for planning the VOIs in the left and right frontal lobe and exhibited reduced partial volume effects of ventricles, skull, muscle, or orbital region (Fig. 1) compared with surface-coil methods. The sampling time for one spectrum lasted 38 min; the whole experiment, including imaging, planing, and shimming, had a duration of approximately 1 h, 10 min.

The magnetic field homogeneity was shimmed prior to the ^{31}P-MRS measurements over a range containing both VOIs and then controlled by the half-height line width of the water signal from a ^{1}H-spectroscopic scan with the body coil. Shimming resulted in line widths of 0.05–0.15 ppm starting with shim sets determined from prior experiments.

The averaged signal of both VOIs was analyzed with the help of the software package included in the Philips Gyroscan operating system (Philips, Hamburg, Germany). Within the evaluation process the FID signal was direct-current (DC) corrected, zero-filled to 2048 data points, exponentially multiplied (8 Hz), and processed with a convolution difference procedure (80 Hz; e.g., see Oldfield et al. 1975). After Fourier transformation, a zero- and a linear-phase correction was applied. After this pre-processing procedure, the spectra were quantified in the frequency domain. Here the noise amplitude was used to discriminate between peak areas and noise. α-ATP and γ-ATP were modeled with their appropriate doublet structure and β-ATP with its appropriate triplet structure. Pi and PCr were modeled as single spectral peaks. Phosphomonoester was modeled by means of two fitting curves assuming that the measured signal is a superimposition of the main compounds phosphoethanolamine and phosphocholine, and PDE was modeled with three fitting curves, since the signal is formed by the main components glycerol-3-phosphoethanolamine, phosphocholine, and mobile phospholipids. Amplitude, line width, and frequency of all peaks were adapted to obtain a difference signal with a minimally disturbed baseline in the range of known signals. The analysis was performed blindly regarding proband status. Half of the spectra were analyzed twice in order to ascertain the reliability of the spectral analysis. As commonly used in the literature, the peak areas of all metabolites were normalized by dividing them by the total integrated area of the spectrum (Bottomley 1991; Rudin and Sauer 1992).

Statistics

In a first approach, we intended to test the pre-described findings of Kato et al. (1991–1994), i.e., increase of PME% and decrease of PCr% and pH. Therefore, for these parameters as a priori specified individual hypotheses, the Mann-Whitney U-test without Bonferoni correction was applied; for the remaining ^{31}P-MRS parameters the Bonferoni correction was used to correct for multiple testing. An explorative statistic was performed for the left and right VOIs analyzed separately with a repeated-measures ANOVA with group and side as factors.

For correlation analyses (repeated analyses of spectra and MRS variables with psychopathology, etc.), the Spearman rank-correlation test was used.

Results

Typical spectra of a depressed medicated patient and a control are presented in Fig. 2. The main results are summarized in Fig. 3 and Table 2. We found increased values of PME% and decreased levels of the total ATP% and β-fraction in the depressed patient group in comparison with controls. No other difference was statistically significant. In our main evaluation, the FIDs of the right and left frontal lobe were added and subsequently analyzed in order to improve the quality of the spectra. To obtain tenta-

Table 2 Summary of the main results (mean ± SD). Presented are the individual peak area ratios in relation to the total peak area

	Controls	Depressed patients	*p*
PME%	8.52 ± 1.56	10.38 ± 1.52	0.026*
PCr%	10.62 ± 1.29	11.52 ± 1.57	0.891
pH	7.03 ± 0.03	7.04 ± 0.05	0.892
PDE%	32.59 ± 3.02	32.62 ± 3.60	0.891
PME/PDE	0.26 ± 0.06	0.32 ± 0.06	0.076
γ-ATP%	11.87 ± 1.31	12.43 ± 2.02	0.633
α-ATP%	16.54 ± 0.77	15.11 ± 0.83	0.152
β-ATP%	14.00 ± 0.80	11.63 ± 1.49	0.001**
ATP_{total}%	42.41 ± 1.84	39.17 ± 3.25	0.015[a]

The significance tests for the first three parameters are not corrected for multiple testing (see Statistics); the remaining values are corrected

* Significant difference without Bonferoni correction

** Significant difference after Bonferoni correction ($\alpha^* = \alpha/k$; α^* family-wise error rate, k number of tests, α is the nominal α-level. For the hypothesis that a test is significant at $\alpha = 0.05$, this results in a boundary of $\alpha^* = 0.008$)

[a] Tendency toward significance

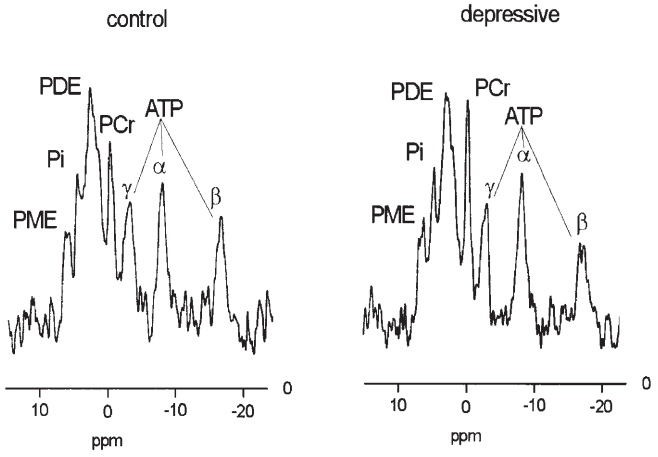

Fig. 2 Typical spectra of a depressed patient and a normal control

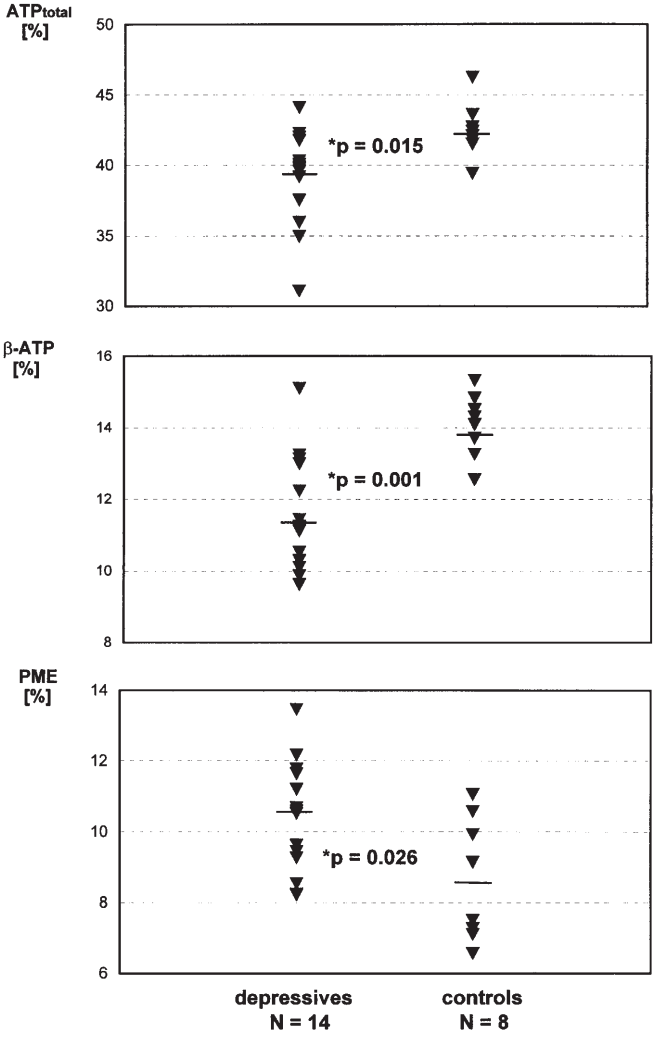

Fig. 3 Total ATP%, β-ATP%, and PME% values in controls and in depressed patients (*p*-values refer to the Mann-Whitney U-test, uncorrected, see also table 2)

tive information as to whether lateralization effects exist, in a second step, the spectra of the right and left frontal lobes were analyzed separately (multiple-measures ANOVA). No additional significant results were obtained. The described difference between depressed patients and controls regarding PME% was present predominantly on the left side.

No correlation between severity of depression (as measured with HAMD), duration of illness, and the MRS parameters could be established, with the exception of a negative correlation between PME% values and HAMD ($r = -0.55$, $p = 0.043$).

Half of the spectra of the double-volume approach were analyzed twice in order to ensure retest reliability. The obtained results were tested with the Spearman rank-correlation test and resulted in correlation coefficients between 0.80 and 0.95.

Discussion

To our knowledge, this is the first report of altered ^{31}P-MRS parameters in monopolar depressed patients. The main results are increased values of PME% and decreased levels of β-ATP% and total ATP% (as a trend).

Our results regarding the PME level are in good agreement with the reports of Kato et al. (1991–1994), who found an increased PME concentration in the depressed and manic state of bipolar-II patients. Those authors interpreted this finding as state dependent, mainly because in the euthymic state decreased levels were found. This hypothesis could not be verified in our study, since all our patients were depressed when examined. The negative correlation between PME level and HAMD score is a definite argument against decreased PME levels being a state marker.

Phosphomonoester contains various compounds, such as phosphoethanolamine, phosphocholine, and sugar phosphates, as well as glycerol-3-phosphate and inositol phosphates. By means of in vivo ^{31}P-MRS it is presently only possible to differentiate these compounds by proton decoupling (e.g., Murphy-Boesch et al. 1993; McNamara et al. 1994). Since we did not have this opportunity, the molecule which is mainly responsible for the observed difference remained undetermined; however, phosphoethanolamine seems to be the major constituent of PME (Gyulai et al. 1984; Brenton et al. 1985), and a precursor of membrane phospholipids. Evidence suggests extensive membrane abnormality in bipolar disorder (e.g., Meltzer 1991). Our findings propose similar alterations in monopolar depressed patients.

Kato et al. (1992) could not find differences between major (monopolar) depressed patients and controls, neither in the depressed nor in the euthymic state. The severity of depression (mean HAMD total score: 20.23) was nearly the same as in our sample. Also the medication status did not differ considerably. So the only explanation for the different results might be the different localization methods used in the studies.

As suggested by Kato et al. (1992–1994), lithium may increase PME levels by accumulation of inositol-1-phosphate. Thus, the apparent state-dependent alteration of PME may be caused by the state-dependent fluctuations of brain lithium concentration. However, in our study only 2 patients received lithium. If they are excluded from PME analysis, no significant change in the mean PME% values occurs (PME% without lithium treated patients: 10.62 ± 1.61; all patients: 10.38 ± 1.52). Therefore, a major influence of lithium on the measured PME% values is unlikely.

As to the influence of other psychotropic medication, the effects of tricyclic antidepressants and serotonin reuptake inhibitors on ^{31}P-MRS data have not yet been investigated. Regarding neuroleptics, it could be possible that these compounds decrease PDE levels via inhibition of phospholipase A_2 (Volz et al. 1997a, b); however, Keshavan et al. (1989) reported on ten schizophrenics who exhibited increased PDE% levels when drug free and after 4 weeks of neuroleptic treatment. Effects of neuroleptics on PME levels have not been reported, and in the investigation of Keshavan et al. (1989) lowered PME% levels were even more pronounced after neuroleptic treatment. Our results speak against a major influence of psychotropic medication on PME levels, since PME% values remained constant after having dropped the three medication-free patients from statistical analysis (10.26 ± 1.61 without patients on psychotropic medication, 10.38 ± 1.52 all patients). We are aware of the fact that due to the small sample size such subanalyses are only of very limited value; therefore, our remarks on the potential influence of psychotropic drugs on ^{31}P-MRS parameters should be regarded as very preliminary.

The second important finding is the reduction of β-ATP and total ATP (as a trend) in depressed patients, mainly attributable to a reduction of the α- and β-ATP fraction. The reduction of the β-ATP level is particularly noteworthy, since this fraction probably correlates best with the total ATP concentration in tissues. Unlike the α- and γ-resonance, it is not contaminated by signal contributions from other phosphate-containing metabolites, such as adenosine diphosphate and nicotinamide adenine dinucleotide phosphates. In this context the finding of Kato et al. (1994) of reduced PCr% levels in all three psychopathological states of bipolar-II patients is interesting. As one possible explanation they mentioned a reduction of ATP synthesis, since PCr is metabolized from ATP and creatine with the creatine kinase (CPK) as the catalyzing enzyme according to the following reaction:

$$\text{Creatine} + \text{ATP} \underset{\text{CPK}}{\longleftrightarrow} \text{PCr} + \text{ADP}$$

Thus, the point of view of Kato et al. (1994) is supported by our results. Impaired ATP production has been observed in conditions such as ischemia, hypoglycemia, and hypoxia (Erecinska and Silver 1989) and in genetic abnormalities of mitochondrial function, such as mitochondrial cytopathy (Barbiroli et al. 1993). Depletion of mitochondrial DNA has been reported in depressive disorders (Stine et al. 1993) and may correspond to our observation of reduced ATP levels in the frontal lobe of depressed patients, since diminished ATP levels may be the consequence of disturbed mitochondrial function. An objection against this interpretation is that normally ATP is highly conserved and a fall in PCr occurs before a decrease in ATP is seen. This condition is explained by the fact that PCr acts as an energy shuttle between sites of ATP production and ATP utilization and the creatine kinase reaction prevents short-term ATP deficits without consuming oxygen. If this is true, only a reduced CPK activity in the depressed patients could explain the findings.

However, the potential methodological pitfalls of the present investigation have to be addressed: Differences between patients and controls might not only be due to different concentrations of phosphorus metabolites, but also to alterations in the T1 and T2 relaxation times of depressed patients. It can therefore not be excluded that altered PME and ATP levels might not reflect different concentrations of these metabolites, but differences in metabolite variability as a consequence of relaxation differences.

Moreover, the region of interest selected for each subject contains varying percentages of white and gray matter. This may contribute to the measured differences of PME and ATP levels, since their distribution might be different in gray and white matter. In future experiments MRI segmentation software should be applied to determine the percentage of gray and white matter in the selected voxels, as already proposed by Deicken et al. (1995b). The ISIS procedure tends to increase the amount of white matter in relation to gray matter compared with surface-coil techniques. Kato et al. (1994) also used a surface coil method, however, with depth-resolved surface-

coil technique (DRESS). The respective VOI was determined as the center 30-mm slice between the frontal pole and the frontal edge of the corpus callosum. Thus, the amount of white matter included in their investigations seems to be comparable to the amount included in the VOIs used in our investigation.

However, the localization method applied by Kato and collaborators (1994) is not precise, since the measured VOI includes large amounts of extracerebral tissue, which might have confounded their results. The more precise localization technique used in our study, which minimized partial volume effects, improves data quality. Nevertheless, since partial volume effects still exist at the edges of the VOIs for a certain distance, such effects are not completely ruled out, even when using ISIS with small VOIs as in our study. Another possibility to minimize partial volume effects is spectroscopic imaging (SI, also called chemical shift imaging, CSI), used, for example, in the investigation of patients with affective disorders by Deicken et al. (1995). By this approach, the VOIs can be selected and separated after the measurement, which is not possible with ISIS or DRESS.

In summary, altered PME% and high-energy phosphate levels in the frontal brain of depressed patients are new findings that should be confirmed by future studies. Follow-up investigations of patients in depressed and euthymic states are further called for to determine whether these alterations are state- or trait dependent.

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