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Cerebral Metabolism in Patients with Cognitive Disorders: a Combined Magnetic Resonance Spectroscopy and Positron Emission Tomography Study

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Objectives. Magnetic resonance spectroscopy (MRS) allows the contents of many metabolites in living tissues to be assessed. There is a good number of studies analyzing MRS data in Alzheimer's disease (AD), though their results are contradictory. In this regard, there is value in comparing MRS data with fluorodeoxyglucose (FDG) positron emission tomography (PET) results, which assess the functional state of nervous tissue. The present study provides a comparison of MRI scan data in AD and moderate cognitive impairment (MCI) with the characteristics of cerebral glucose metabolism assessed from FDG-PET data. **Materials and methods.** Multivoxel proton MRS of the supraventricular region was carried out in patients with AD ($n = 16$) and MCI ($n = 14$). The following metabolite ratios were determined: NAA/Cr, Cho/Cr, and NAA/Cho (NAA is N-acetylaspartate, Cr is creatine, and Cho is choline). Patients underwent neurological investigation, assessment of cognitive status, and PET scans with FDG. **Results.** Patients with AD showed decreases in NAA/Cr and Cho/Cr in the white matter of the medial cortex of the supraventricular areas of both hemispheres. The MCI group showed a decrease in the NAA/Cr ratio in only one area of the white matter of the left hemisphere, adjacent to the parietal cortex. Positive correlations were found between NAA/Cr and Cho/Cr with measures of cognitive status and with the rate of glucose metabolism measured from PET data in the frontal, parietal, and temporal areas and the cingulate cortex. **Conclusions.** The decrease in the NAA/Cr ratio in the supraventricular white matter and the medial cortex in AD and the correlation of this parameter with cognitive test results and cerebral glucose metabolism constitute evidence that it may have diagnostic value, reflecting the severity of cognitive impairments. Assessment of the NAA/Cr ratio should be carried out with consideration of the fact that dementia alters the concentrations of both metabolites (NAA and Cr).

Keywords: magnetic resonance spectroscopy, Alzheimer's disease, cognitive impairments, N-acetylaspartate, choline, creatine, positron emission tomography.

Introduction. The diagnosis of Alzheimer's disease (AD) is one of the most serious in psychiatry. As the most widespread form of dementia in patients over 65 years of age, this neurodegenerative disease has onset with extremely minor symptomatology, which becomes manifest as an unstoppable decline in cognitive functions as the disease progresses. Short-term memory is affected first, followed by long-term memory; speech functions are degraded; the ability to orient in the spatial environment is lost, as is the capacity for self-care; patients become desocialized [1].

Current methods for treating AD ameliorate the symptoms, but do not provide a cure, which significantly increases the role of the early diagnosis of the disease, preferably at the preclinical stage. Along with cognitive tests and laboratory investigations, the diagnosis of AD also uses neuroimaging methods: magnetic resonance imaging (MRI), and, more rarely (because of lower availability), positron emission tomography (PET) with different radiopharmaceuticals (RP) – both for assessment of β-amyloid accumulation, this

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being regarded as a key molecule in the pathogenesis of AD, and for assessment of glucose metabolism in the brain [2–4].

The use of PET in the diagnosis of AD in Russia is hindered by the small number of PET centers in operation, which limits the number of RP used, and the costs of the investigation itself. In the present report, PET and proton magnetic resonance spectroscopy (MRS) were used, the advantage over MRI being obvious, as functional changes at the molecular level precede structural pathology visible on MRI scans.

Proton MRS generally determines the content of N-acetylaspartate (NAA), choline (Cho), and creatine (Cr), assessing not their absolute concentrations but their relative contents. This is associated with the fact that although the concentration of a metabolite is linearly proportional to the area under the peak of the MR spectrogram, the latter depends on many of the technical characteristics of the MR tomograph and the algorithms used for processing the data, the overlapping of the peaks of different substances, displacement of the isoline, and the characteristics of the impulse sequence used for recording spectra [5, 6].

NAA is one of the most widespread amino acids in the central nervous system and is regarded as a surrogate marker for neural integrity, as it is present in neurons. NAA levels drop in diseases accompanied by nervous tissue damage. NAA levels can decrease both in irreversible lesions to nervous tissue and in transient functional disorders which can then be corrected by treatment or can settle spontaneously [5, 6]. There is also an age-related decline in NAA content [7].

The Cho peak is the sum of the peaks of the trimethylamine groups of phosphocholine and glycerophosphocholine and the small quantity of free Cho. Large quantities of these substance are also seen in glial cells. Changes in their concentrations are linked with membrane degradation and synthesis: increases in Cho are typical of active demyelination, neuroinflammation, and other processes in which membrane degradation takes place. In addition, it can also be induced by active processes synthesizing cell membrane components [8, 9]. In the white matter (WM) of the brain, Cho contents are greater than in the gray matter (GM) [10]. Cho levels increase with age [7].

The combined Cr + phosphocreatine peak is generally used as a reference, as its concentration in brain tissues is regarded as quite constant. Cr is involved in energy metabolism in muscle and nerve cells. Phosphocreatine probably operates as an energy buffer [6, 9]. Variation in Cr content is quite high: the level in the WM is significantly lower than that in the GM [10]. The Cr content gradually increases with age in the frontal and parietal areas [7].

Published data indicate that decreases in the NAA/Cr ratio are nonspecific and can be seen in different types of dementia [6, 11]. Studies in 1992 identified a reduction in NAA in nervous tissue in autopsy investigations of the brains of patients with AD as compared with controls: the NAA level correlated with the number of amyloid plaques, tau protein, and nervous tissue density (cited in [12]). Decreases in NAA in the hippocampus, posterior cingulate cortex, and the GM of the parietal region are very characteristic of AD [12, 13]. Data reported by Kantarci et al. [12] indicate that the NAA/Cr ratio in the superior temporal lobe and posterior cingulate gyrus decreases in AD. As disease develops, changes in NAA become more widespread and are seen in the parietal, temporal, frontal, and occipital lobes [13, 14], i.e., virtually the whole cortex is involved in the process.

Along with decreases in the NAA level in AD, there are also increases in the ratio of myoinositol (mI) to Cr (mI/Cr). mI is believed to be linked with increases in glial proliferation [14]. Data from a number of studies indicate that AD is associated with increases in mI content in the parietal lobe and posterior cingulate cortex, while changes in its content in the frontal cortex or WM are not seen [13]. Several studies [15–17] have revealed a combination of an increased mI level with a decrease in NAA. The increase in mI precedes the decrease in NAA. Pathomorphological studies have shown that the premortal NAA/Cr and mI/Cr levels correlate with the severity of AD, the strongest predictor of the severity of pathological changes in AD being the NAA/mI ratio.

Views on the significance of changes in Cho concentrations in AD are contradictory. Some studies have observed increases in the Cho level [12, 18], while others have found no change [19]. Chantal et al. [20] reported a decrease in the Cho/H_2O ratio in the medial temporal lobe in AD, though this could be explained by an increase in signs of hydrocephaly and, as a result, an increase in the water concentration. Wang et al. [13] found frequent increases in the Cho/Cr ratio in the posterior cingulate cortex in AD, though studies in which the Cho concentration was determined rather than its ratio to the contents of other metabolites did not find any such changes.

Significant decreases in the NAA concentration and the NAA/Cr ratio in the hippocampus and posterior cingulate cortex were seen at the stage of moderate cognitive impairment (MCI) subsequently progressing to AD [21]. The posterior cingulate cortex also showed a decrease in the Cr content. The Cho/Cr ratio could increase, probably due to a decrease in Cr, as studies in which the Cr concentration was estimated identified a decrease [21]. Of particular practical interest is the ability to predict progression of MCI to dementia. Thus, Zhang et al. [22] reported that patients with MCI subsequently progressing to AD, as compared with patients with MCI progressing to Lewy body dementia, showed more marked decreases in NAA/Cr in the posterior cingulate cortex.

Despite numerous studies addressing MRS in cognitive impairments, the diagnostic value of MRS in this pathology remains unclear [24]. Clarification of this point and improvement of our understanding of the pathogenetic mechanisms of cognitive impairments requires comparison

TABLE 1. Measures from Cognitive Tests in the Groups Studied, Points

Diagnosis	Mean cognitive test value					
	MMSE	MoCA	FTB	clock drawing test	5 words memorization test	5 words memorization test, d/r
AD	18.79 ± 6.27	14.38 ± 5.40	13.0 ± 2.45	4.58 ± 2.17	3.58 ± 1.5	1 ± 0.71
MCI	26.72 ± 2.16	23.34 ± 3.76	14.81 ± 2.29	8.72 ± 1.71	4.78 ± 0.49	2.84 ± 1.65
AgeNorm	29.0 ± 1.0	28.40 ± 2.19	17.2 ± 0.84	10.0 ± 0.0	5.0 ± 0.0	4.0 ± 1.01

Here and Table 4: d/r – delayed reproduction of 5 words.

of MRS with FDG-PET data, as this would allow the functional state of nervous tissue to be evaluated. PET with FDG in AD shows a typical pattern of diffuse glucose hypometabolism in the temporal and parietal lobes, the angular gyrus being at the center of the metabolic dysfunction. The lateral frontal cortex is also often involved in the process, though the precentral gyrus remains relatively uninvolved. The extent of hypometabolism correlates with the severity of the cognitive impairment, the most sensitive marker of the severity of dementia being the decrease in glucose metabolism in the parietal lobes. The specific pattern of metabolic dysfunction differentiates AD from other types of dementia, the mean sensitivity of PET in the diagnosis of AD being 91.5% [25].

The aims of the present work were to carry out a complex study of cerebral metabolism using multivoxel proton MRS and PET with FDG and to compare the data with results of investigations of cognitive functions using the appropriate psychological tests and psychometric scales.

Materials and Methods. MRS data from 16 patients (five men and 11 women) with AD (mean age 70.3 ± 6.9 years) and 14 patients (six men and eight women) with MCI (mean age 63.53 ± 10.23 years) were analyzed. There were no statistically significant differences in age between the groups of patients. Controls consisted of MRS studies in healthy subjects of age similar to that of patients with cognitive impairments. This was the "age norm" (AgeNorm) group and consisted of 10 subjects (two men and eight women) of mean age 54.5 ± 8.1 years. All patients underwent standard neurological evaluation.

The severity of cognitive impairments was assessed using the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Frontal Test Battery (FTB) with a maximum of 18 points, the clock drawing test with a maximum of 10 points, and the five-word memorization test for short-term memory. Cognitive test results are shown in Table 1. Cognitive impairments were diagnosed in accordance with the modified criteria for MCI syndrome and ICD-10.

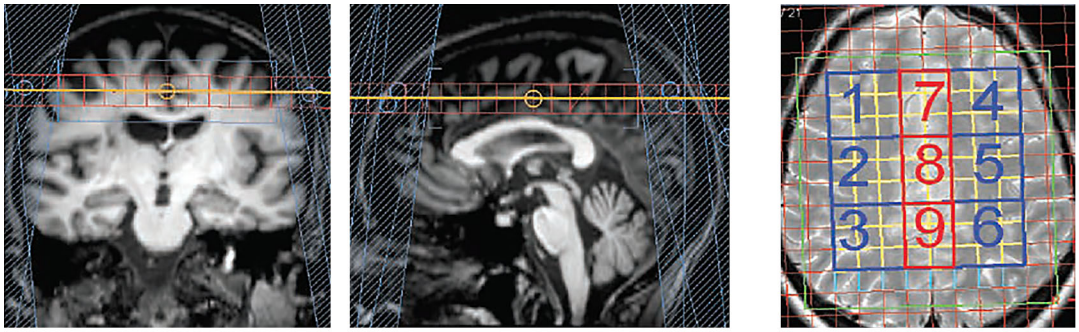
Multivoxel MRS in the supraventricular area (Fig. 1) was run in the 2D-PRESS H-MRS (TR = 2000 msec) program with voxel size 10 × 10 × 15 mm, with TE = 144 msec (TE is the time of echo, i.e., response time). Skull bone signals were suppressed using 10 saturation bands with automatic PencilBeam-auto shimming and suppression of the water signal. Data were evaluated in SpectroView. Regions subjected to spectroscopic studies consisted of 8 × 9 voxels and included the WM and GM of the cerebral hemispheres (see Fig. 1).

Voxels on tissue boundaries and those with low signal:noise ratios were not considered. Analysis of MRS determined the anatomical position of the voxel: the study area was divided into nine regions of interest (RoI), six of which included WM, three in each hemisphere, and three including the medial cortex (see Fig. 1, *b*). RoI in the medial cortex consisted mainly of the cingulate cortex (the dorsal part of the anterior cingulate cortex – part of Brodmann areas (BA) 32 and 24 and the posterior cingulate gyrus (BA 23 and 31) (see Fig. 1, *b*). This method of assessing MRS data and its advantages are discussed in greater detail in [26]. Metabolite ratios (NAA/Cr, Cho/Cr, and NAA/Cho) were calculated individually for each RoI.

Selection of the supraventricular area was due both to the functional role of the cingulate gyrus and the technical features of MRS studies, as this location allows distortion of the signal by the intracerebral CSF-containing spaces to be minimized, thus increasing the signal:noise ratio.

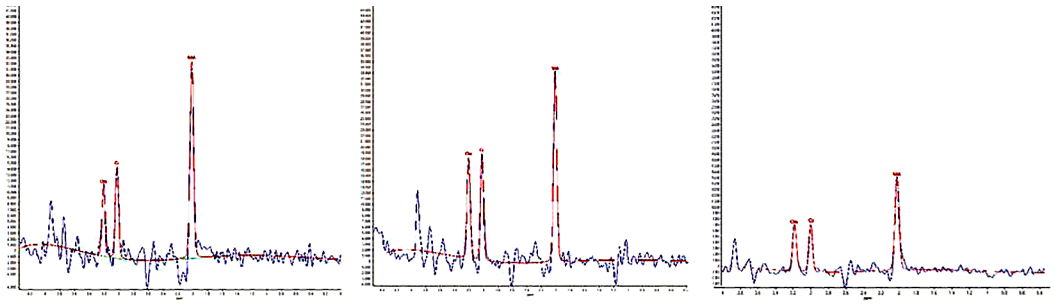
The cingulate gyrus was selected as a region of interest for comparison of MRI scan and PET data because it is involved in supporting many cognitive processes, including executive functions [27], impairments to which are an important component in the pathogenesis of cognitive impairments. Furthermore, a relationship between cognitive functions and metabolite contents in the centrum semiovale has been demonstrated [27]. Executive dysfunction in particular can serve as a factor with adverse effects on treatment efficacy, inducing decreases in patient compliance. Many studies have shown that one of the first areas impaired in AD is the posterior cingulate gyrus [12, 13]. Primary lesions of the anterior cingulate gyrus are more typical of frontal-temporal degeneration [28]. It is important for differential diagnosis to assess the state of the GM in all parts of the cingulate gyrus and the adjacent WM.

PET was performed only in groups with cognitive impairments (because of ethical issues related to administration of RP without medical indications). Studies were run on



a *b*

Fig. 1. Regions of interest subjected to MRI scanning. *a*) Anatomical locations of 2D-multivoxel MRI scan voxels in the supraventricular region; *b*) groups of voxels in the supraventricular area for 9 regions of interest, 1–6 in the WM and 7–9 in the medial cortex.



a *b* *c*

Fig. 2. Examples of MR spectrograms in the WM of the letter from hemisphere in the three groups studied. Abscissas show spectral peak positions, ppm; ordinates show peak height, units; *a*) control group; *b*) MCA; c) AD.

a Scanditronix PC2048 tomograph. FDG was given i.v. at a dose of 2–5 mCi, with scan duration 20 min starting 30–40 min after administration. Quantitative analysis of the glucose metabolic rate (GMR) was performed by transforming individual images to the coordinate space of the Talairach stereotaxic atlas [29] using Statistical Parametric Mapping software (SPM-8) [30]. The program WFU PicAtlas [31] was then used to compute the mean accumulation of RP in RoI corresponding to BA. Normalization used the primary sensorimotor cortex as the optimum reference for studies of dementia [32]. Thus, the statistical analysis used relative measures of GMR in the RoI listed above.

Statistical analysis was run in Statistica for Windows 11.0. Nonparametric statistics methods were used: the Mann–Whitney test and the Kruskal–Wallis test for comparison of PET and MRS data in the different groups and the Spearman correlation coefficient to identify correlational relationships between MRS measures and PET data and cognitive tests.

Results and Discussion. Figure 2 shows typical spectra in the WM of the left hemisphere in patients of the three groups studied.

The overall picture of the state of cerebral metabolism in the groups of interest could be assessed in terms of the mean metabolite ratios in the WM and GM for the supraventricular plane (Table 2).

Statistical analysis showed that the most marked decreases in MRS measures were seen in AD. The results are consistent with published data on decreases in NAA/Cr in AD and MCI [12, 13, 21, 22], and are also consistent with our own observations [33].

FDG-PET data indicated that in AD (in contrast to the MCI group), GMR was decreased in the temporal (BA 20, 22, 37), parietal (BA 7, 39, 40), frontal (BA 6, 8, 9, 10), and cingulate (BA 23, 24, 32) areas of the cortex on both sides ($p < 0.001$), which is consistent with published data [27].

MRS results from different cerebral RoI (Table 3) showed that NAA/Cr and Cho/Cr values were different in different groups, the greatest decreases being seen in the AD group. In addition, regional variability was seen in the NAA content: both ratios including this metabolite were lower in the WM 1 and 4 than other areas of WM in all three groups. These results on decreases in NAA are consistent with data reported in [34], which addressed the NAA concentration in the supraventricular region and showed significantly lower levels in the anterior and medial cortex and adjacent WM in patients with AD, the decrease in the GM being more marked than that in the WM. There was no difference in

TABLE 2. Mean MRS Values in the Supraventricular Space

Metabolite ratio	AD		MCI		AgeNorm		p*
	mean	SD	mean	SD	mean	SD	
NAA/Cr							
WM	1.78	0.18	1.93	0.17	2.05	0.19	<0.05
GM	1.45	0.16	1.53	0.11	1.59	0.12	<0.05
NAA/Cho							
WM	1.97	0.25	2.02	0.29	2.11	0.23	<0.05
GM	1.68	0.19	1.80	0.24	1.83	0.20	<0.05
Cho/Cr							
WM	0.90	0.09	0.96	0.13	0.96	0.09	–
GM	0.87	0.07	0.86	0.10	0.88	0.08	–

*p, Mann–Whitney test, comparison between groups of patients with AD and the other two groups.

NAA levels in the middle part of the medial cortex and WM in the AD and control groups.

The only significant difference between the MCI and AgeNorm groups was in the NAA/Cr ratio in the WM of the right hemisphere, neighboring the medial parietal cortex (WM 6), and this ratio was lower in the MCI group. Decreases in the functional state of the parietal cortex determined by FDG-PET are known to depend on the severity of cognitive impairment in dementia of any etiology. This may explain why this area showed a decrease in NAA/Cr in the MCI group. No significant differences were seen in other parameters, which may be associated with the relatively high interindividual variability in metabolic indicators. This circumstance may also be linked with some subjects in the AgeNorm group having preclinical changes in brain tissues which in future would lead to cognitive decline.

The Cho/Cr ratio was lower in the AD group than the other groups in only two areas of WM. The Cho/Cr ratio did not differ between the AgeNorm and MCI groups.

As already noted, most studies evaluating MRS data use metabolite ratios rather than absolute concentrations. However, our observations indicate that the mean values of all peaks were lower in the AD group than the other groups, as can be seen in Fig. 2. This is probably associated with atrophic processes in nervous tissue (widening of perivascular spaces and decreases in neuron density), which were more marked in the AD group. Thus, although it is incorrect to use the area under the curve to determine metabolite concentrations, the visible decreases in the densities of all peaks can have practical value for specialists assessing MR spectrograms, evidencing increases in atrophic processes.

Metabolite ratios correlated negatively with patients' age: NAA/Cr in WM 1–4 and 6 and GM 9 (r from –0.4 to –0.6, $p < 0.05$), and Cho/Cr only in WM 4 ($r = –0.4$, $p < 0.05$).

Thus, NAA/Cr in the group of patients with dementia was significantly lower than on all other groups, the greatest differences being seen in comparison with the control groups. The Cho/Cr ratio was also lower in the group of patients with dementia, though only in two areas in the WM. The differences seen here were partially associated with age-related changes, as evidenced by the correlation with age, though it should be noted that patients' ages also correlated with the severity of cognitive impairment and greater duration of disease.

Comparison of metabolite ratios with measures from cognitive tests demonstrated multiple correlational relationships (Table 4).

Correlation of measures from cognitive tests with the Cho/Cr ratio were seen only in one area of the WM in the right hemisphere – WM 3 ($r = 0.5$, $p < 0.05$). Correlations obtained for these tests and NAA/Cr were consistent with the view that NAA is a marker for neuronal integrity.

Comparison of MRS and PET data in specific study areas identified correlations only for NAA/Cr and NAA/Cho in GM 8 and GMR in BA 24 ($r = 0.4$, $p < 0.01$). GMR in functionally significant areas – BA – was also comparable, as was the ratio of the main MRS of metabolites in the WM of the corresponding hemisphere. Positive correlational relationships ($r = 0.4$–0.6, $p < 0.05$) were seen between NAA/Cr and GMR in many BA; summary results are presented in Fig. 3.

The NAA/Cho ratio in WM (WM 1, 2, 4, 5) and the medial cortex (GM 8, 9) correlated with GMR in the cingulate cortex (BA 24), with $r = 0.4$, $p < 0.01$ on the right and left. Published data indicate that a decrease in glucose metabolism occurs in the cingulate gyrus in AD. In addition, we found a link between the NAA content and GMR in the cingulate gyrus in HIV-associated cognitive deficit [29]. This suggests that the involvement of the cingulate gyrus

TABLE 3. MRS Data in Different Structures of the Supraventricular Region in Groups of Patients

RoI	AD		MCI		AgeNorm		p (Kruskal–Wallis test)
	mean	SD	mean	SD	mean	SD	
NAA/Cr							
WM 1	1.70	0.18	1.85	0.14	1.96	0.21	<0.01
WM 2	1.79	0.16	1.98	0.17	2.05	0.19	<0.01
WM 3	1.75	0.15	1.93	0.16	1.98	0.18	<0.01
WM 4	1.69	0.18	1.94	0.19	2.02	0.18	<0.01
WM 5	1.86	0.24	2.01	0.18	2.16	0.20	<0.01
WM 6	1.85	0.14	1.85	0.15	2.10	0.18	<0.01
GM 7	1.46	0.17	1.50	0.11	1.58	0.11	<0.01
GM 8	1.45	0.18	1.52	0.09	1.56	0.14	<0.01
GM 9	1.45	0.14	1.57	0.12	1.62	0.11	<0.01
Cho/Cr							
WM 1	0.99	0.09	1.04	0.16	1.05	0.11	–
WM 2	0.91	0.08	0.97	0.15	0.94	0.10	–
WM 3	0.81	0.08	0.91	0.11	0.89	0.07	<0.05
WM 4	0.96	0.12	1.04	0.14	1.04	0.09	–
WM 5	0.88	0.06	0.96	0.12	0.96	0.09	–
WM 6	0.84	0.10	0.85	0.09	0.90	0.07	<0.05
GM 7	0.96	0.08	0.96	0.11	0.98	0.10	–
GM 8	0.88	0.05	0.87	0.10	0.89	0.07	–
GM 9	0.78	0.07	0.76	0.09	0.77	0.07	–
NAA/Cho							
WM 1	1.72	0.21	1.80	0.29	1.87	0.18	–
WM 2	1.98	0.27	2.07	0.32	2.20	0.25	–
WM 3	2.16	0.22	2.12	0.27	2.22	0.24	–
WM 4	1.76	0.21	1.87	0.25	1.92	0.18	–
WM 5	2.09	0.29	2.09	0.31	2.22	0.25	–
WM 6	2.12	0.27	2.16	0.28	2.25	0.26	–
GM 7	1.52	0.18	1.58	0.25	1.63	0.19	–
GM 8	1.65	0.19	1.76	0.22	1.76	0.20	–
GM 9	1.86	0.20	2.07	0.24	2.11	0.20	<0.05

is nonspecific and reflects the general components in the mechanism of cognitive impairments of different etiologies.

Studies comparing MRS and FDG-PET are few in number. Weissenborn et al. [36] reported positive correlations between glucose metabolism in the motor cortex with the Cr ratio in the WM, GM, and basal ganglia in patients with hepatic encephalopathy. Mielke et al. [37] compared FDG-PET data and MRS in 18 patients with AD and found weak correlations between GMR and Cho/Cr and NAA/Cho. O'Neill et al. [38] studied the interaction between cerebral glucose metabolism in the cerebral cortex using FDG-PET data and MRS in a group of 19 people including patients with dementia and cog-

TABLE 4. Correlations of NAA/Cr with Cognitive Test Measures

RoI	MMSE		MoCA		FTB		Clock drawing test		5 word memorization test	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
WM 1	0.5274	0.0013	0.5517	0.0007	0.4226	0.0128	0.5184	0.0017	0.6333	0.0001
WM 2	0.6104	0.0001	0.6289	0.0001	0.5480	0.0008	0.5407	0.0010	0.6511	0.0000
WM 3	0.6212	0.0002	0.5741	0.0009	–	–	0.5426	0.0019	0.4915	0.0058
WM 4	0.5133	0.0019	0.5690	0.0004	–	–	0.5918	0.0002	0.5694	0.0004
WM 5	0.5112	0.0020	0.5681	0.0005	0.5698	0.0004	0.5335	0.0012	0.6120	0.0001
WM 6	–	–	–	–	–	–	–	–	0.4999	0.0031
GM 7	–	–	–	–	–	–	–	–	0.4274	0.0117
GM 8	–	–	–	–	–	–	–	–	0.4732	0.0047
GM 9	0.5169	0.0021	0.4783	0.0049	–	–	0.4052	0.0193	0.4784	0.0049

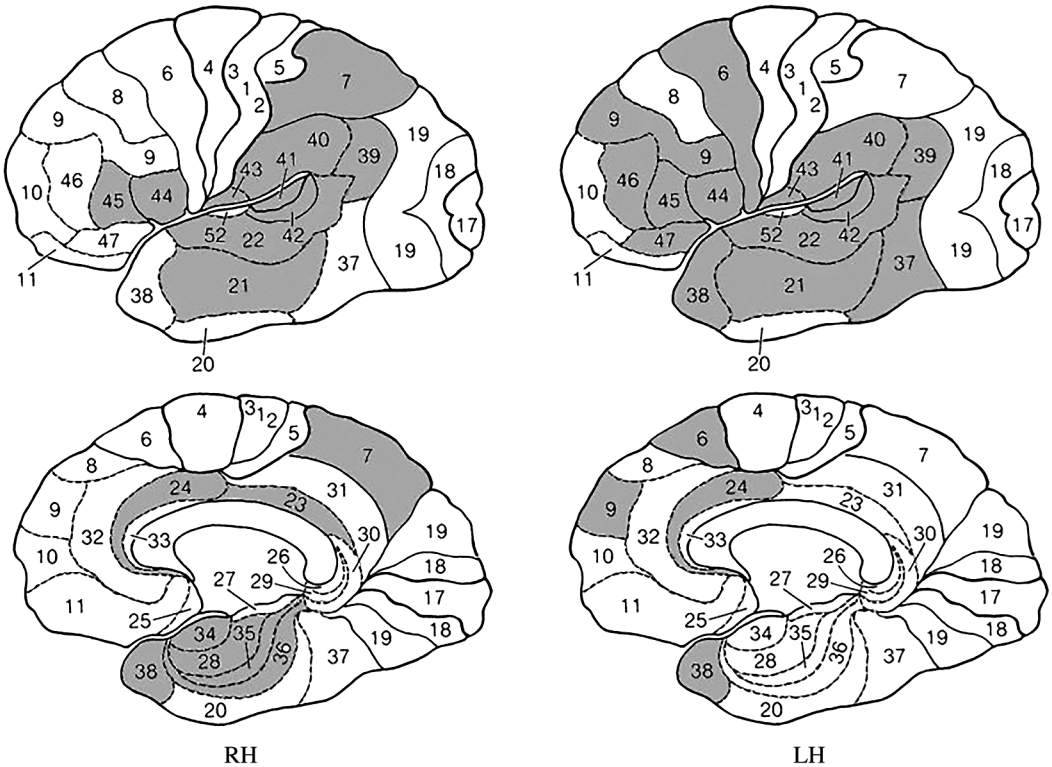


Fig. 3. BA in which GMR correlated positively with the NAA/Cr ratio. RH – right hemisphere; LH – left hemisphere.

nitively normal patients. The relationships found between NAA concentration and GMR were interpreted as a link between GMR and neuron density in the cortex. Coutinho et al. [24] studied metabolism in the cingulate cortex in 32 patients with AD and 27 with MCI and found a decrease in NAA/mI and GMR in the posterior cingulate gyrus in AD, with regional glucose metabolism correlating with the NAA/mI ratio.

Correlation of Cho/Cr with GMR was found only for areas WM 3 and 5 (those in which Cho/Cr was decreased in the AD group), mainly with GMR in the ipsilateral parietal cortex (decreased glucose metabolism here is shown by published data to provide the most specific reflection of increases in the severity of impairment in AD [25]: on the right – WM 3 with GMR in BA 5, 7, 39–40 ($r = 0.4$, $p < < 0.05$); on the left – WM 5 with BA 7; in the frontal cortex – BA 9 ($r = 0.4$, $p < 0.05$). The positive correlations found in this study between Cho/Cr and GMR were at first sight contradict the concept of Cho as a marker of membrane dis-

ruption. However, this may be associated with atrophy of nervous tissue, with the result that there are decreases in all peaks on MR spectrograms in AD. The Cho peak probably decreases more strongly than the Cr peak, which is present in quite large quantities not only in neurons, but also in glial cells [5, 8].

A limitation of this study is the fact that analysis of MRS data is performed using traditional ratios between metabolite concentrations rather than their absolute values, and the magnitudes of parameters in this situation depend on the values of both the numerator and the denominator. However, determination of the absolute concentrations in MRS in vivo is technically difficult and is not generally used in clinical practice, while the analysis procedure used here can easily be included in the standard investigation protocol for this group of patients.

Conclusions. Thus, results from studies of the supraventricular region using MRS showed that NAA/Cr and Cho/Cr were decreased in patients with AD and correlated with measures of cognitive status. In addition, MRS measures correlated with glucose metabolism (FDG-PET data) in areas of the frontal, parietal, and temporal cortex key for AD, as well as in the cingulate cortex. As NAA is regarded as a surrogate marker for neuronal integrity, the correlations found here reflect the interaction between the functional state of the cortex and the integrity of neural conductors in the supraventricular WM. The correlations with the results of cognitive tests provide evidence that the NAA/Cr ratio may have diagnostic value, reflecting the severity of the cognitive impairments. However, the decrease in the NAA content in the supraventricular area was nonspecific for AD and correlated not only with cognitive impairments, but also with patients' ages, and was also characterized by interindividual variability. The use of multivoxel spectroscopy with a larger region of interest, along with use of other MRS protocols providing for determination of a wider range of metabolites, might allow a more specific metabolic pattern typical of AD to be identified.

The correlations found here for MRS measures and the rate of glucose metabolism and the results of cognitive tests suggest that monitoring of these values during the development of cognitive deficit may have diagnostic and prognostic value. This could easily be achieved by supplementing standard MRI investigations with the MRS protocol, which contrasts with PET, which is expensive and requires the synthesis and administration of rapidly degrading RP and the associated radiation load on the patient.

The authors have no conflicts of interests.

REFERENCES

1. M. Tabert, X. Liu, R. Doty, et al., "A 10-item smell identification scale related to risk for Alzheimer's disease," *Ann. Neurol.*, **58**, No. 1, 155–160 (2005).
2. G. Verdile, S. Fuller, C. Atwood, et al., "The role of beta amyloid in Alzheimer's disease: still a cause of everything or the only one who got caught?" *Pharmacol. Res.*, **50**, 397–409 (2004).
3. C. Mathis, N. Mason, B. Lopresti, and W. Klunk, "Development of positron emission tomography β-amyloid plaque imaging agents," *Semin. Nucl. Med.*, **42**, No. 6, 423–432 (2012), https://doi.org/10.1053/j.semnuclmed.2012.07.001.
4. P. Trzepacz, P. Yu, J. Sun, K. Schuh, et al., Alzheimer's Disease Neuroimaging Initiative, "Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia," *Neurobiol. Aging*, **35**, No. 1, 143–151 (2014), https://doi.org/10.1016/j.neurobiolaging.2013.06.018.
5. M. Modo and J. Bulte (eds.), *Magnetic Resonance Neuroimaging. Methods in Molecular Biology*, Springer (2011), https://doi.org/10.1007/978-1-61737-992-5_9.
6. P. B. Barker, A. Bizzi, N. De Stefano, et al., *Clinical MR Spectroscopy: Techniques and Applications*, Cambridge University Press (2009).
7. K. K. Haga, Y. P. Khor, A. Farrall, and J. M. Wardlaw, "A systematic review of brain metabolite changes, measured with ^{1}H magnetic resonance spectroscopy, in healthy aging," *Neurobiol. Aging*, **30**, 353–363 (2009), https://doi.org/10.1016/j.neurobiolaging.2007.07.005.
8. C. Stagg and D. Rothman (eds.), *Magnetic Resonance Spectroscopy. Tools for Neuroscience Research and Emerging Clinical Applications*, Elsevier (2014).
9. N. A. Semenova, T. A. Akhadov, A. V. Petryaikin, et al., "Metabolic impairments and the interaction of metabolic processes in the frontoparietal cortex of the brain in severe craniocerebral trauma. A study using local ^{1}H magnetic resonance spectroscopy," *Biokhimiya*, **77**, No. 4, 493500 (2012).
10. H. P. Hetherington, G. F. Mason, J. W. Pan, et al., "Evaluation of cerebral gray and white matter metabolite differences by spectroscopic imaging at 4.1T," *Magn. Reson. Med.*, **32**, No. 5, 565–571 (1994), https://doi.org/10.1002/mrm.1910320504.
11. A. Shiino, M. Matsuda, S. Morikawa, et al., "Proton magnetic resonance spectroscopy with dementia," *Surg. Neurol.*, **39**, No. 2, 143–147 (1993), https://doi.org/10.1016/0090-3019(93)90093-g.
12. K. Kantarci, R. C. Petersen, and B. F. Boeve, "^{1}H-MR spectroscopy in common dementias," *Neurology*, **63**, No. 8, 1393–1398 (2004), https://doi.org/10.1212/01.wnl.0000141849.21256.ac.
13. H. Wang, L. Tan, H. F. Wang, et al., "Magnetic resonance spectroscopy in Alzheimer's disease: systematic review and meta-analysis," *J. Alzheimers Dis.*, **46**, No. 4, 1049–1070 (2015), https://doi.org/10.3233/JAD-143225.
14. B. B. Frederick, A. Satlin, D. A. Yurgelun-Todd, and P. F. Renshaw, "In vivo proton magnetic resonance spectroscopy of Alzheimer's disease in the parietal and temporal lobes," *Biol. Psychiatry*, **42**, No. 2, 147–150 (1997), https://doi.org/10.1016/s0006-3223(97)00242-4.
15. A. Bitsch, H. Bruhn, V. Vougioukas, et al., "Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy," *AJNR Am. J. Neuroradiol.*, **20**, No. 9, 1619–1627 (1999).
16. F. Jessen, W. Block, and F. Traber, "Proton MR spectroscopy detects a relative decrease of N-acetylaspartate in the medial temporal lobe of patients with AD," *Neurology*, **55**, No. 5, 684–688 (2000), www.ajnr.org/content/20/9/1619, acc. May 15, 2018.
17. W. Huang, G. E. Alexander, L. Chang, et al., "Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study," *Neurology*, **57**, No. 4, 626–632 (2001), https://doi.org/10.1212/wnl.57.4.626.
18. A. Pfefferbaum, E. Adalsteinsson, D. Spielman, et al., "In vivo spectroscopic quantification of the N-acetyl moiety, creatine, and choline from large volumes of brain gray and white matter: effects of normal aging," *Magn. Reson. Med.*, **41**, No. 2, 276–284 (1999), https://doi.org/10.1002/(sici)1522-2594(199902)41:2<276::aid-mrm10>3.3.co.
19. K. R. Krishnan, H. C. Charles, P. M. Doraiswamy, et al., "Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease," *Am. J. Psychiatry*, **160**, No. 11, 2003–2011 (2003), https://doi.org/10.1176/appi.ajp.160.11.2003.

20. S. Chantal, M. Labelle, R. W. Bouchard, et al., "Correlation of regional proton magnetic resonance spectroscopic metabolic changes with cognitive deficits in mild Alzheimer disease," *Arch. Neurol.*, **59**, No. 6, 955962 (2002), https://doi.org/10.1001/archneur.59.6.955.
21. S. Tumati, S. Martens, and A. Aleman, "Magnetic resonance spectroscopy in mild cognitive impairment: systematic review and meta-analysis," *Neurosci. Biobehav. Rev.*, **37**, No. 10, Pt 2, 2571–2586 (2013), https://doi.org/10.1016/j.neubiorev.2013.08.004.
22. B. Zhang, T. J. Ferman, B. F. Boeve, et al., "MRS in mild cognitive impairment: early differentiation of dementia with Lewy bodies and Alzheimer's disease," *J. Neuroimaging*, **25**, No. 2, 269–274 (2015), https://doi.org/10.1111/jon.12138.
23. K. Kantarci, D. S. Knopman, D. W. Dickson, et al., "Alzheimer disease: postmortem neuropathologic correlates of antemortem ^{1}H MR spectroscopy metabolite measurements," *Radiology*, **248**, No. 1, 210–220 (2008), https://doi.org/10.1148/radiol.2481071590.
24. A. M. N. Coutinho, F. H. G. Porto, P. F. Zampieri, et al., "Analysis of the posterior cingulate cortex with [^{18}F]FDG-PET and Naa/mI in mild cognitive impairment and Alzheimer's disease: Correlations and differences between the two methods," *Dement. Neuropsychol.*, **9**, No. 4, 385–393 (2015), https://doi.org/10.1590/1980-57642015DN94000385.
25. S. V. Medvedev, T. Yu. Skvortsova, and R. N. Krasikova, *PET in Russia: Positron Emission Tomography in the Clinic and Physiology*, St. Petersburg (2008).
26. A. A. Bogdan, Yu. G. Khomenko, G. V. Kataeva, and T. N. Trofimova, "Principles of data grouping in assessment of the results of multivoxel spectroscopic investigations of the brain," *Luch. Diagnost. Ter.*, **4**, No. 7, 15–19 (2016).
27. R. A. Charlton, D. J. McIntyre, F. A. Howe, et al., "The relationship between white matter brain metabolites and cognition in normal aging: The GENIE study," *Brain Res.*, **1164**, 108–116 (2007), https://doi.org/10.1016/j.brainres.2007.06.027.
28. J. M. Allman, N. A. Tetreault, A. Y. Hakeem, et al., "The von Economo neurons in frontoinsular and anterior cingulate cortex," *Ann. N. Y. Acad. Sci.*, **1225**, 59–71 (2011), https://doi.org/10.1111/j.1749-6632.2011.06011.x.
29. J. Talairach and P. Tournoux, *Co-Planar Stereotactic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging*, Thieme, New York (1988).
30. *Statistical Parametric Mapping*, www.fil.ion.ucl.ac.uk/spm/, acc. May 15, 2018.
31. *WFU PickAtlas*, www.nitrc.org/projects/wfu_pickatlas/, acc. May 15, 2018.
32. I. Yakushev, C. Landvogt, H. G. Buchholz, et al., "Choice of reference area in studies of Alzheimer's disease using positron emission tomography with fluorodeoxyglucose-F18," *Psychiatry Res.*, **164**, No. 2, 143–153 (2008), http://dx.doi.org/10.1016/j.pscychresns.2007.11.004.
33. Yu. G. Khomenko, A. A. Bogdan, G. V. Kataeva, and E. M. Chernysheva, "Use of multivoxel magnetic resonance spectroscopy in investigations of patients with cognitive disorders," *Vestn. Stankt-Peterburg. Univ. Ser. 4, Fiz, Khim.*, **3**, No. 1, 82–89 (2016).
34. N. Schuff, D. L. Amend, D. J. Meyerhoff, et al., "Alzheimer disease: Quantitative H-1 MR spectroscopic imaging of frontoparietal brain," *Radiology*, **207**, No. 1, 91–102 (1998).
35. E. A. Gromova, A. A. Bogdan, G. V. Kataeva, et al., "Characteristics of the functional state of brain structures in HIV-infected patients," *Luch. Diagnost.*, **1**, 41–48 (2016).
36. K. Weissenborn, B. Ahl, D. Fischer-Wasels, et al., "Correlations between magnetic resonance spectroscopy alterations and cerebral ammonia and glucose metabolism in cirrhotic patients with and without hepatic encephalopathy," *Gut*, **56**, No. 12, 1736–1742 (2007), http://dx.doi.org/10.1136/gut.2006.110569.
37. R. Mielke, H. H. Schopphoff, H. Kugel, et al., "Relation between ^{1}H MR spectroscopic imaging and regional cerebral glucose metabolism in Alzheimer's disease," *Int. J. Neurosci.*, **107**, No. 34, 233–245 (2001), https://doi.org/10.3109/00207450109150687.
38. J. O'Neill, J. L. Eberling, N. Schuff, et al., "Method to correlate ^{1}H MRSI and ^{18}FDG-PET," *Magn. Reson. Med.*, **43**, No. 2, 244–50 (2000), https://doi.org/10.1002/(sici)1522-2594(200002)43:2<244::aid-mrm11>3.3.co.