Cognitive Impairment: Assessment With Brain Magnetic Resonance Imaging and Proton Magnetic Resonance Spectroscopy

Ulrike Weiss, M.D.; Reinhard Bacher, M.D.; Herbert Vonbank, M.D.; Georg Kemmler, Ph.D.; Albert Lingg, M.D.; and Josef Marksteiner, M.D.

Background: In vivo proton magnetic resonance spectroscopy is a safe and noninvasive tool that can be used to study aspects of brain chemistry and metabolism. This study was designed to evaluate its role in routine application to reveal the diagnostic reasons for cognitive impairment.

Method: 37 Alzheimer's disease patients (NINCDS-ADRDA criteria), 31 patients with subcortical ischemic vascular dementia (Chui et al. criteria), and 13 subjects with subjective cognitive impairment (DSM-IV criteria) were included in this retrospective study. Magnetic resonance images were used for atrophy rating; additionally, proton magnetic resonance spectroscopy was performed.

Results: Significantly reduced N-acetylaspartate levels ($p < .05$) were found in both patients with Alzheimer's disease and patients with subcortical ischemic vascular dementia compared to the group with subjective memory complaints. The ratios of N-acetylaspartate/creatine and N-acetylaspartate/myo-inositol were significantly lower in Alzheimer's disease patients compared to patients with vascular dementia ($p = .012$) or patients with subjective memory impairment ($p = .002$). N-acetylaspartate/creatine and N-acetylaspartate/myo-inositol ratios were positively correlated to the degree of cerebral atrophy. Disoriented patients displayed a low N-acetylaspartate/creatine ratio. In contrast, we were not able to relate concurrent psychotic or behavioral symptoms to any spectroscopic parameter.

Conclusion: This study indicates that proton magnetic resonance spectroscopy parameters could provide additional information in differentiating between Alzheimer's disease, subcortical ischemic vascular dementia, and subjective cognitive impairment. Therefore, this method can contribute to the routine diagnosis of dementia. Psychiatric and behavioral symptoms associated with dementia or due to a major psychiatric disorder cannot be related to changes in the measured proton magnetic resonance spectroscopy parameters.

(J Clin Psychiatry 2003;64:235–242)

Received Feb. 18, 2002; accepted June 26, 2002. From the Department of Psychiatry, University of Innsbruck (Drs. Weiss, Vonbank, Kemmler, and Marksteiner), Innsbruck, and Regional Hospital of Rankweil (Drs. Bacher and Lingg), Rankweil, Austria.

Supported in part by a grant from the Austrian National Bank (9295).

Corresponding author and reprints: Josef Marksteiner, M.D., Department of Psychiatry, Anichstraße 35, A-6020 Innsbruck, Austria (e-mail: j.marksteiner@uibk.ac.at).

Neuroimaging is increasingly being used to assess patients with dementia. Magnetic resonance imaging (MRI) of patients with Alzheimer's disease demonstrates accelerated total brain atrophy and greater enlargement of ventricular and sulcal cerebrospinal fluid spaces, compared with signs of normal aging.[1–3] Furthermore, MRI of the hippocampus in patients with Alzheimer's disease has demonstrated marked volume loss.[4,5]

The technique of in vivo proton magnetic resonance spectroscopy (1H-MRS) is able to monitor metabolic processes noninvasively in the brain. It is sensitive to the presence of several metabolites that provide a means for early detection of diseases and treatment responses. Proton MRS concurrently measures N-acetylaspartate and N-acetylaspartylglutamate (NAA), myo-inositol (mI), choline-containing compounds (Cho), and total creatine (Cr). Choline and Cr are present in all brain cells, whereas NAA has been localized mostly in neurons and therefore has been proposed as a neuronal marker.[6] Although the precise physiologic role of NAA remains uncertain, it may reflect mitochondrial function.[7] A recent in vitro report suggests that NAA may be involved in myelination processes in the adult human.[8] Proton MRS measures of brain metabolites in Alzheimer's disease have been demonstrated to be possible markers of neurodegeneration that have prognostic value even in the earliest stages of Alzheimer's disease.[9] Several cross-sectional invivo or postmortem 1H-MRS studies have reported decreased NAA and raised mI concentrations in Alzheimer's disease patients compared with matched controls. For the more challenging task of discriminating Alzheimer's disease from other possible dementia diagnoses, NAA/mI ratio was reported to yield a modest positive predictive

value (74%).[10] In the same study, an 80% negative predictive value was estimated.[10]

Vascular dementia is the second most common form of permanent cognitive impairment.[11] Subcortical ischemic vascular dementia (SIVD) is most commonly associated with subcortical lacunae and white matter signal hyperintensities. SIVD is hypothesized to be caused by a loss or disruption of subcortical neurons leading to a disconnection of cortical neurons from subcortical structures.[12]

Patients with dementia manifest not only progressive memory impairment, cognitive deficits, and functional alterations but also a variety of neuropsychiatric disturbances like agitation, aggression, hallucination, and delusions. These symptoms ultimately affect up to 75% of individuals with Alzheimer's disease and, once present, tend to be sustained or recurrent.[13–18]

It is still a very challenging task to differentiate between the various causes of subjective and/or objective cognitive impairment. For our patients, the most frequent diseases causing cognitive complaints are Alzheimer's disease, SIVD, and subjective memory impairment due to psychiatric illness. Therefore, we were interested in investigating in this retrospective study the applicability and validity of 1H-MRS as a routine diagnostic tool to discriminate between these diseases associated with objective and subjective memory complaints.

The main goal of this study was to evaluate the use of 1H-MRS in routine diagnosis for patients admitted to a district hospital with objective as well as subjective memory impairment. We hypothesized that (1) decreased NAA levels would separate the Alzheimer's disease group from the SIVD and subjective cognitive impairment groups and (2) decreased NAA levels would be correlated with greater dementia severity. In addition, we compared 1H-MRS parameters in relation to psychiatric and behavioral symptoms.

METHOD

Subjects

This study was performed with subjects admitted to a district psychiatry hospital. Patients' characteristics are described in Table 1. Inclusion criteria were subjective and objective memory impairment. Criteria for exclusion included acute head trauma, history of head injury involving loss of consciousness, neurologic illness, substance abuse, acute infectious diseases, tumor, decompensated metabolic disease, or MRI scan evidence of diffuse or focal cerebral lesions.

Patients were assessed by standardized diagnostic procedures including neurologic, psychiatric, and general medical examination. All subjects underwent laboratory tests to exclude secondary causes of dementia, including a chest radiograph, electrocardiogram, chemistry profile, complete blood count, thyroid function tests, vitamin B_{12} level, folic acid level, and syphilis serology. Additional studies including a cerebrospinal fluid analysis and electroencephalogram were performed as the clinical situation indicated. Patients underwent an extensive battery of neuropsychological testing including Mini-Mental State Examination (MMSE),[19] Verbal Fluency Test,[20] Trailmaking A,[21] Trailmaking B,[21] Boston Naming Test,[22] Word-List memory,[23] Constructional Praxis,[24] Word-List recall,[23] and Word-List recognition.[25] Patients with mild cognitive impairment were staged on the Clinical Dementia Rating scale (CDR).[26] Magnetic resonance examination was part of the routine. All enrolled subjects gave their informed consent to undergo magnetic resonance assessment and to be included in this retrospective study.

According to the performed diagnostic steps, patients were assigned into 3 diagnostic groups: (1) Alzheimer's disease: patients fulfilled criteria for probable Alzheimer's disease on the basis of guidelines from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[27]; (2) subcortical ischemic vascular dementia: subjects were clinically diagnosed on the basis of criteria proposed by Chui et al.[28]; the presence of at least 1 lacunar infarction on MR images was mandatory; and (3) subjective cognitive impairment: diagnosis for these patients was established according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[29] In this group, 3 patients had a major depression, 1 had a depressive episode from a bipolar affective disorder, 1 had a neurotic disorder, and 1 had schizophrenia. Seven subjects had mild cognitive impairment according to the criteria published by Petersen et al.[30] These patients had a CDR score of 0.5. None of these patients fulfilled criteria for beginning Alzheimer's disease or vascular dementia.

Table 1. Characteristics of Patients With Alzheimer's Disease (AD), Subcortical Ischemic Vascular Dementia (SIVD), and Subjective Cognitive Impairment

	Diagnostic Group		
Variable	AD (N = 37)	SIVD (N = 31)	Subjective Cognitive Impairment (N = 13)
Age,[a] y, mean ± SD	75.6 ± 8.7	70.3 ± 8.5	68.2 ± 10.3
Sex, N (%)			
Men	11 (30)	10 (32)	7 (54)
Women	26 (70)	21 (68)	6 (46)
MMSE score,[b] mean ± SD	20.9 ± 6.0	23.2 ± 5.6	27.7 ± 1.6

[a]Patients in the AD group were significantly older than those in the 2 other diagnostic groups ($p < .05$, Kruskal-Wallis test; $p < .05$ in post hoc Mann-Whitney U tests).
[b]Patients in the AD and the SIVD groups had significantly lower MMSE scores than patients in the subjective cognitive impairment group ($p < .01$, Kruskal-Wallis test and post hoc Mann-Whitney U tests). No significant difference between the AD and SIVD groups ($p = .114$, Mann-Whitney U test).
Abbreviation: MMSE = Mini-Mental State Examination.

Assessment of Behavioral Symptoms

Behavioral symptoms were diagnosed according to DSM-IV. Additionally, impaired orientation was defined as being clearly impaired in at least 2 of 4 qualities of orientation (time, place, self, situation). For the analysis of the data, symptoms were grouped into 3 clusters: psychotic symptoms (hallucination, delusion), aggression and restlessness (wandering), and disorientation.

MRI and 1H-MRS Data Acquisition

MRI and single voxel 1H-MRS data were acquired on a 1.5-T GE Signa scanner (GE Medical Systems, Milwaukee, Wis.) using a standard quadrature headcoil.

Each MRI examination included sagittal T1-weighted MR imaging (FMPSPGR), performed to exclude a diagnosis of obvious focal lesions and neurologic disease. A T2-weighted fast spin-echo (FSE) in the paracoronal plane parallel to the brain stem (slice thickness = 5 mm, interslice gap = 1 mm) and axial FLAIR images (slice thickness = 6 mm, interslice gap = 1 mm) were obtained to exclude a diagnosis of multi-infarct dementia, stroke, tumor, and other T2-sensitive abnormalities.

Brain MRS examinations were automated with a single voxel. First, an auto-prescan was performed to suppress the water signal (shim). The measurement parameters were repetition time (TR), 1700 ms; echo time (TE), 35 ms with point-resolved spectroscopy (PRESS) volume preselection; and number of acquisitions, 128. The voxel size was 8 cm^3. The PRESS volume, from which the MRS metabolite data were obtained, was located reproducibly in the midline of the occipital lobes (gray matter). The volume of interest (VOI) in each subject was placed in a uniform manner by the same investigator (H.V.), located medially of the perpendicular line between scull and the line connecting the backs of left and right splenium corporis callosi. This region was selected because it is the most reproducible place and not sensible to motion artifacts. The combined MR imaging and MR spectroscopy examination lasted approximately 20 minutes. Metabolite measurements were made blinded to clinical details.

Atrophy Rating

Images were assessed by an investigator who was blinded to diagnosis and age of the subjects. Essentially, rating was performed as described by Scheltens et al.[31] The degree of medial temporal lobe atrophy was judged on the slice that best depicted the hippocampal formation and surrounding structures. As we included in our study less severe patients, score 4 was not achieved. Rating was performed by the same, blinded investigator twice. When there was disagreement after the second rating, data were reanalyzed and a final assignment to a group was performed. Frontal cortex atrophy and generalized cerebral cortex atrophy were rated on a 4-point scale (0 = normal, 1 = mild atrophy, 2 = moderate atrophy, 3 = severe atrophy) in the same manner.

Data Analysis

Analysis of the spectra was performed using the manufacturer-supplied, semiautomated spectroscopy software package PROBE/SV of the MR system. Relative metabolite concentrations for NAA, Cho, Cr, and mI were determined.

Statistical Analysis

In an initial analysis, the 3 diagnostic groups were compared with respect to sociodemographic variables and MMSE score using the Kruskal-Wallis test (posthoc comparisons by Mann-Whitney U test) for continuous variables, and the chi-square test for dichotomous variables. Analysis of covariance (ANCOVA) was then applied for comparing the 3 diagnostic groups with regard to MR spectroscopy parameters, considering age and sex as covariates. In addition, ANCOVA with MMSE score as a further covariate was performed to check if the extent of dementia affected the results. A logarithmic or squareroot transformation was used, where appropriate, to obtain an approximately normal distribution of the dependent variable. Subsequent pairwise group comparisons were corrected for multiple testing using the Bonferroni method. Spearman correlation analysis was used to explore relationships between MR spectroscopy parameters and the degree of atrophy as well as behavioral and psychological symptoms.

RESULTS

All patients included in this study could be attributed to one of the following diagnostic groups: Alzheimer's disease patients; subcortical ischemic vascular dementia patients; and patients with subjective cognitive impairment but no evidence for either Alzheimer's disease or vascular dementia. Patients of this third group had various psychiatric illnesses, as described in Method.

NAA levels were significantly reduced in both patients with Alzheimer's disease and patients with SIVD compared to the control group ($p = .001$ and $p = .021$, respectively), whereas Cr, Cho, and mI levels did not differ significantly between the 3 groups (Table 2). Moreover, NAA levels were significantly lower in subjects with Alzheimer's disease than in those with SIVD ($p = .015$). When potential effects of MMSE score were adjusted for in the ANCOVA, the difference between the Alzheimer's disease and SIVD groups remained statistically significant ($p = .018$). The ratio of NAA/Cr and NAA/mI was significantly lower in the Alzheimer's disease group compared to patients with SIVD ($p = .012$) or the control group with subjective memory impairment ($p = .002$). The statistical significance of these findings is retained

Table 2. Magnetic Resonance Spectroscopy (MRS) Parameters by Diagnostic Group

	Diagnostic Group						
	AD (1)		SIVD (2)		Subjective Cognitive Impairment (3)		
MRS Parameter	Mean	SD	Mean	SD	Mean	SD	Significant Group Differences[a]
NAA	91.1	17.1	100.9	20.2	112.4	25.0	(1) < (2),* (1) < (3),** (2) < (3)*
Cr	67.8	12.8	70.1	14.5	74.7	15.4	NS
Cho	40.0	8.7	41.2	9.0	41.2	8.8	NS
mI	45.1	11.2	43.9	9.7	45.5	9.1	NS
NAA/Cr ratio	1.35	0.14	1.45	0.11	1.50	0.11	(1) < (2),* (1) < (3)**
Cho/Cr ratio	0.59	0.09	0.59	0.08	0.56	0.08	NS
mI/Cr ratio	0.66	0.12	0.63	0.08	0.61	0.04	NS
NAA/mI ratio	2.09	0.46	2.34	0.31	2.47	0.29	(1) < (2),** (1) < (3)**

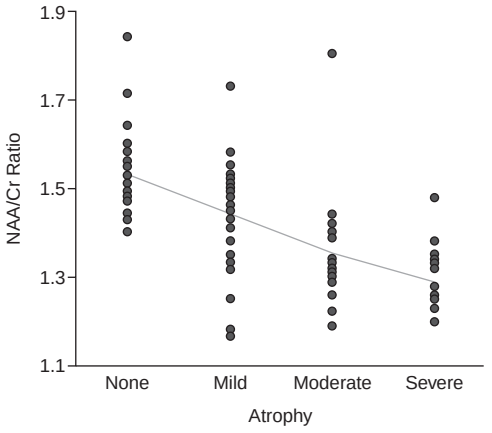
[a]Analysis of covariance with adjustment for age and sex.
*p < .05 (adjusted for multiple testing by Bonferroni method).
**p < .01 (adjusted for multiple testing by Bonferroni method).
Abbreviations: AD = Alzheimer's disease, Cho = choline-containing compounds, Cr = total creatine, mI = myo-inositol, NAA = N-acetylaspartate, NS = no significant group differences, SIVD = subcortical ischemic vascular dementia.

Table 3. Correlation of MRS Parameters With Atrophy for Patients With Alzheimer's Disease (N = 37), Subcortical Ischemic Vascular Dementia (N = 31), and Subjective Cognitive Impairment (N = 13)[a]

MRS Parameter	Degree of Atrophy	Frontal Atrophy	Medial Temporal Lobe Atrophy
NAA/Cr ratio	–0.67**	–0.24*	–0.41**
Cho/Cr ratio	0.09	0.21†	0.03
mI/Cr ratio	0.26*	0.17	0.24*
NAA/mI ratio	–0.51**	–0.25*	–0.40**

[a]Spearman rank correlation.
*p < .05; ** p < .01; †p < .1 (2-tailed significance levels).
Abbreviations: Cho = choline-containing compounds, Cr = total creatine, mI = myo-inositol, NAA = N-acetylaspartate.

Figure 1. Correlation Between Degree of Atrophy and NAA/Cr Ratio for Patients With Alzheimer's Disease (N = 37), Subcortical Ischemic Vascular Dementia (N = 31), and Subjective Cognitive Impairment (N = 13)[a]



[a]Spearman rank correlation, r = –0.67, p < .001.
Abbreviations: Cr = total creatine, NAA = N-acetylaspartate.

when adjusting for MMSE score. No difference between the SIVD group and the subjectively impaired group was found for NAA/Cr and NAA/mI, although NAA levels were significantly lower in the SIVD group.

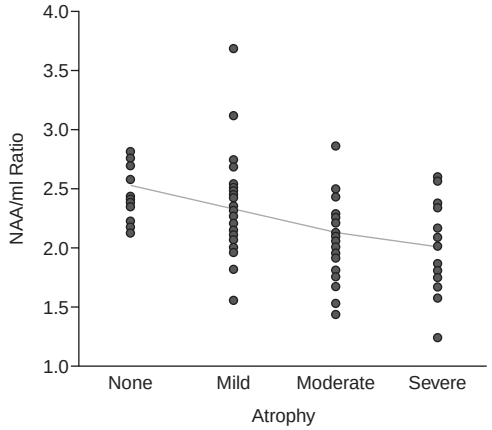
The ratio of NAA/Cr was positively correlated with the MMSE score (p = .029), while none of the other MRS parameters showed a significant correlation with MMSE score. A decreased ratio of NAA/Cr and NAA/mI correlated significantly with the degree of the cerebral atrophy (p < .001) (Table 3 and Figures 1 and 2). These ratios also correlated strongly with medial temporal lobe atrophy (p < .001 in both cases) (Figure 3) and, to a lesser extent, with frontal atrophy (p = .035 and p = .028, respectively) (Figure 4). Elevated levels of the mI/Cr ratio were found to correlate with general atrophy and medial temporal lobe atrophy (p = .014 and .035, respectively).

Patients with an impaired orientation had a significantly reduced ratio of NAA/Cr (p = .005) (Table 4). In patients with delusions and or hallucinations, no changes in any of the MRS parameters compared to patients with no psychiatric symptoms were found. Behavioral symptoms like aggression and wandering could not be correlated to changes in any of the MRS parameters.

DISCUSSION

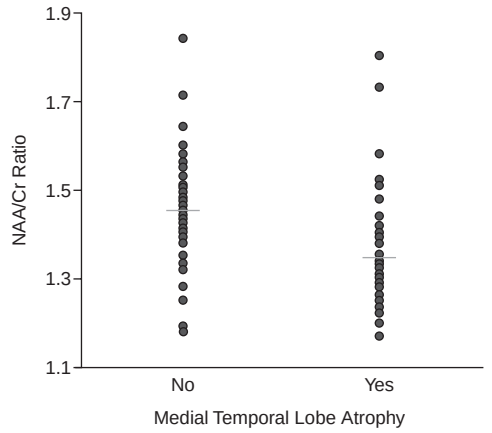
In vivo proton magnetic resonance spectroscopy of absolute metabolite concentrations in the occipital cortex revealed that concentrations of brain metabolites are significantly lower in patients suffering from Alzheimer's disease or subcortical ischemic vascular dementia when compared to patients reporting subjective memory impairment only. The reduction in levels of NAA, NAA/Cr, and NAA/mI ratios was significantly more pronounced in patients with Alzheimer's disease compared with the SIVD and subjective cognitive impairment groups. Our results are in line with several previous studies. The reduction of NAA levels in Alzheimer's disease brains has been demonstrated in the occipital lobe, temporoparietal region, temporal lobe, parietal lobe, and in the frontal

Figure 2. Correlation Between Degree of Atrophy and NAA/mI Ratio for Patients With Alzheimer's Disease (N = 37), Subcortical Ischemic Vascular Dementia (N = 31), and Subjective Cognitive Impairment (N = 13)[a]



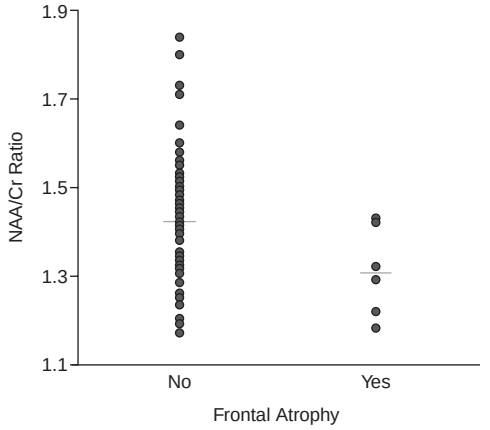
[a]Spearman rank correlation, r = –0.51, p < .001.
Abbreviations: mI = myo-inositol, NAA = N-acetylaspartate.

Figure 3. Correlation Between Medial Temporal Lobe Atrophy and NAA/Cr Ratio for Patients With Alzheimer's Disease (N = 37), Subcortical Ischemic Vascular Dementia (N = 31), and Subjective Cognitive Impairment (N = 13)[a]



[a]Mann-Whitney U test, p < .001.
Abbreviations: Cr = total creatine, NAA = N-acetylaspartate.

Figure 4. Correlation Between Frontal Atrophy and NAA/Cr Ratio for Patients With Alzheimer's Disease (N = 37), Subcortical Ischemic Vascular Dementia (N = 31), and Subjective Cognitive Impairment (N = 13)[a]



[a]Mann-Whitney U test, p = .035.
Abbreviations: Cr = total creatine, NAA = N-acetylaspartate.

Table 4. Correlation of MRS Parameters With Psychiatric Symptoms for Patients With Alzheimer's Disease (N = 37), Subcortical Ischemic Vascular Dementia (N = 31), and Subjective Cognitive Impairment (N = 13)[a]

	Delusions/ Hallucinations	Aggression/ Unrest	Disorientation
NAA/Cr ratio	0.16	–0.15	–0.32**
Cho/Cr ratio	–0.11	0.02	0.05
mI/Cr ratio	–0.03	0.12	–0.04
NAA/mI ratio	0.07	–0.19	–0.14

[a]Spearman rank correlation.
**p < .01
Abbreviations: Cho = choline-containing compounds, Cr = total creatine, mI = myo-inositol, NAA = N-acetylaspartate.

lobe.[32] In the present study, using the occipital cortex as the area of interest, no increase in mI levels was detected in any of the groups, whereas a correlation of general atrophy and medial temporal lobe atrophy with a significant elevation of the mI/Cr ratio was found. This is in line with a previous study in patients with mild Alzheimer's disease (5 patients with MMSE score of ≥ 20) in which mI levels were unchanged in the occipital cortex but increased in the parietal cortex.

In moderate and severe Alzheimer's disease patients (11 subjects with MMSE scores between 10 and 19 and 5 subjects with MMSE scores between 1 and 9, respectively), mI levels were also significantly elevated in the occipital cortex compared to levels in healthy controls.[33] Studies reporting elevated levels of mI also in the occipital cortex[10,34,35] have mostly investigated patients with a more advanced stage of Alzheimer's disease (MMSE scores between 5 and 25 in the largest trial published by Shonk et al.,[10] with 114 patients with dementia included), whereas in the present study patients were examined having a mean MMSE score of 20.9 and 23.2 in the Alzheimer's disease and the SIVD groups, respectively. Neuropathologic studies in correlation to clinical parameters also indicate that key features for Alzheimer's disease are found late in the course of the disease.[36]

What Can Be Expected From the Use of 1H-MRS in the Diagnosis of Cognitive Impairment?

As demonstrated in this study and in others, proton magnetic resonance spectroscopy is a valuable tool to de-

tect ongoing metabolic changes leading to cognitive decline. N-acetylaspartate/creatine measured in the occipital cortex correlates with the degree of atrophy in the frontal cortex and medial temporal lobe as well as with the degree of general atrophy. Magnetic resonance imaging studies of hippocampal atrophy including larger numbers of subjects showed some overlap between Alzheimer's disease patients and healthy elderly.[37,38] A possible reason for this overlap, resulting in difficulties in detecting Alzheimer's disease patients, is that, to the degree degenerating neurons are replaced by glial cells,[39] tissue atrophy in Alzheimer's disease is attenuated. It was demonstrated that measurement of hippocampal NAA taken together with volume provides better discrimination between Alzheimer's disease patients and control subjects than either measure alone.[40] In Alzheimer's disease, neuronal dysfunction is likely to occur before neuronal loss, and chemical changes measured by MRS may occur before tissue volume loss in Alzheimer's disease. This study provides evidence for a different mechanism in subjects with subjective cognitive impairment, as NAA levels were higher in these patients than in patients with Alzheimer's disease and SIVD.

Thus, MRI and 1H-MRS may be useful in discriminating between degenerative and non-degenerative pathologic processes leading to cognitive impairment. For example, it may have a potential as a diagnostic tool in differentiating between psychiatric diseases associated with subjective cognitive impairment and cognitive deficits due to Alzheimer's disease. Although significant differences were found in this study between patients suffering from Alzheimer's disease compared to patients with SIVD, there remains uncertainty whether MRS is able to differentiate between these different diseases. For example, Capizzano et al.[41] showed a reduction in cortical NAA among patients with dementia with lacunes independent of atrophy and tissue composition and hypothesized that these changes represent neuronal loss or metabolic impairment or both caused by subcortical injury. In a study using a lower-field (1.0 Tesla) MR scanner, Alzheimer's disease patients had a significantly higher ratio of mI/Cr (data were obtained in the midline of the occipital lobe) compared with patients with multi-infarct dementia.[42] Significantly lower levels of NAA/Cr and NAA/Cho were observed across both gray and white matter voxels in subjects with Alzheimer's disease.[43] In the same study, in patients with SIVD, NAA/Cr levels were significantly lower in frontal gray and white matter voxels.[43] Nevertheless, a valuable role for 1H-MRS, which seems to be able to detect subtle neurobiological abnormalities in mental disorders, for monitoring disease progression and treatment response is suggested.

The reasons for behavioral changes associated with dementia are manifold and poorly understood.[44] In the present study, 1H-MRS measurement was done only in the occipital lobe, which is a limitation of the present study since data acquisition in the prefrontal lobe and amygdalo-hippocampal complex could have lead to correlations with behavioral symptoms and MRS parameters. At the neurobiological level, damage to the prefrontal lobe has been associated with increased hostility, impulsivity, and aggression.[45–47] Abnormal neuronal activity in medial temporal lobe—as in temporal lobe epilepsy—has been associated with increased aggression and violence,[48–50] whereas damage to medial temporal lobe structures may reduce aggression.[51,52] Recently, in violent patients with mild mental retardation, significantly lower levels of NAA in the prefrontal lobe and a lower ratio of NAA/Cr in the amygdalo-hippocampal complex were found.[53] In patients with schizophrenia, hallucinations are thought to be mediated by a distributed network of cortical and subcortical areas.[54,55] To our knowledge, it is not demonstrated yet if the same brain regions are involved in patients with dementia suffering from behavioral symptoms. In the present study, no evidence could be found that different behavioral symptoms are caused by metabolic changes that can be determined in the occipital lobe, since no correlation exists between the presence of delusions/hallucinations or aggression/unrest and changes in the ratios of the investigated metabolic parameters.

However, a significant correlation was detected between MMSE scores and the ratio of NAA/Cr indicating that the metabolic changes detected by 1H-MRS are more likely to reflect an underlying pathology responsible for the observed cognitive decline. Accordingly, impaired orientation as a cognitive function also correlated with a low NAA/Cr ratio. This is consistent with previous studies, in which the NAA/Cr ratio in patients with Alzheimer's disease has also been shown to significantly correlate with MMSE scores,[56] and even to significantly predict change in MMSE score 12 months later.[57] A recent longitudinal study confirmed a correlation of NAA/Cr ratio with cognitive decline.[58] In contrast to these results and the present study, another group was not able to detect significant correlations between 1H-MRS parameters with MMSE scores in subjects with Alzheimer's disease or SIVD.[43]

The present study has several limitations. Our patients were diagnosed according to established guidelines. Nevertheless, without pathologic confirmations, we do not know whether the patients with clinically diagnosed probable Alzheimer's disease have the characteristic Alzheimer's disease pathology of neuritic plaques and neurofibrillary tangles. In the SIVD group, there may be some subjects with neuropathologic changes found in Alzheimer's disease. Although all subjects were normotensive at the time of examination, some subjects with Alzheimer's disease may have had some cerebrovascular damage due to an unidentified history of hypertension. Another drawback is that there was only 1 person rating atrophy. This

was due to the fact that data were collected in a district hospital. Our control group suffering from subjective memory complaints, including different psychiatric diseases, is more heterogeneous than the Alzheimer's disease and SIVD groups.

Automated 1H-MRS shows potential as an accessible adjunct to clinical assessment and structural imaging in discrimination of objective and subjective cognitive impairment. Except disorientation, psychiatric and behavioral symptoms associated with dementia or due to a major psychiatric disorder cannot be related to changes in the measured 1H-MRS parameters in this study. To our knowledge, we are the first to correlate behavioral symptoms associated with dementia with 1H-MRS parameters. As our study was spatially limited to the occipital region, this is an area for further research, to examine if there are more regionally specific neurobiological abnormalities that might contribute to these symptoms. MRS is certain to play an important role in correlating cognitive improvements as a response to antidementia drugs. For interpreting its role in monitoring behavioral symptoms, which produce more stress for caregivers than the cognitive impairments, further work is needed.

REFERENCES

1. Jernigan TL, Salmon DP, Butters N, et al. Cerebral structure on MRI, pt 2: specific changes in Alzheimer's and Huntington's diseases. Biol Psychiatry 1991;29:68–81
2. Luxenberg JS, Haxby JV, Creasey H, et al. Rate of ventricular enlargement in dementia of the Alzheimer type correlates with rate of neuropsychological deterioration. Neurology 1987;37:1135–1140
3. Tanabe JL, Amend D, Schuff N, et al. Tissue segmentation of the brain in Alzheimer disease. AJNR Am J Neuroradiol 1997;18:115–123
4. Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. Neurology 1991;41:51–54
5. Seab JP, Jagust WJ, Wong ST, et al. Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. Magn Reson Med 1988;8:200–208
6. Miller BL. A review of chemical issues in 1H NMR spectroscopy: N-acetyl-L-aspartate, creatine and choline. NMR Biomed 1991;4:47–52
7. Bates TE, Strangward M, Keelan J, et al. Inhibition of N-acetylaspartate production: implications for 1H MRS studies in vivo. Neuroreport 1996;7:1397–1400
8. Bhakoo KK, Pearce D. In vitro expression of N-acetyl aspartate by oligodendrocytes: implications for proton magnetic resonance spectroscopy signal in vivo. J Neurochem 2000;74:254–262
9. Kantarci K, Jack CR Jr, Xu YC, et al. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: a 1H MRS study. Neurology 2000;55:210–217
10. Shonk TK, Moats RA, Gifford P, et al. Probable Alzheimer disease: diagnosis with proton MR spectroscopy. Radiology 1995;195:65–72
11. Geldmacher DS, Whitehouse PJ. Evaluation of dementia. N Engl J Med 1996;335:330–336
12. Brown GG, Garcia JH, Gdowski JW, et al. Altered brain energy metabolism in demented patients with multiple subcortical ischemic lesions: working hypotheses. Arch Neurol 1993;50:384–388
13. Borson S, Raskind MA. Clinical features and pharmacologic treatment of behavioral symptoms of Alzheimer's disease. Neurology 1997;48:S17–S24
14. Mega MS, Cummings JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–135
15. Patterson MB, Bolger JP. Assessment of behavioral symptoms in Alzheimer disease. Alzheimer Dis Assoc Disord 1994;8(suppl 3):4–20
16. Reisberg B, Borenstein J, Salob SP, et al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987;48(suppl 5):9–15
17. Reisberg B, Ferris SH, de Leon MJ, et al. The stage specific temporal course of Alzheimer's disease: functional and behavioral concomitants based upon cross-sectional and longitudinal observation. Prog Clin Biol Res 1989;317:23–41
18. Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. Am J Psychiatry 1989;146:577–587
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
20. Isaacs B, Kennie AT. The Set Test as an aid to the detection of dementia in old people. Br J Psychiatry 1973;123:467–470
21. Reitan R. Validity of the Trail-Making Test as an indication of organic brain damage. Percept Mot Skills 1958;8:271–276
22. Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test. 2nd ed. Philadelphia, Pa: Ley & Febiger; 1983
23. Atkinson RC, Shiffrin RM. The control of short-term memory. Sci Am 1971;225:82–90
24. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364
25. Mohs RC, Kim Y, Johns CA. Assessing change in Alzheimer's disease: memory and language tests. In Poon LW, ed. Handbook for Clinical Memory Assessment of Older Adults. Washington DC: American Psychological Association; 1986:149–155
26. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull 1988;24:637–639
27. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944
28. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42: 473–480
29. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC: American Psychiatric Association; 1994
30. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308
31. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992;55:967–972
32. Valenzuela MJ, Sachdev P. Magnetic resonance spectroscopy in AD. Neurology 2001;56:592–598
33. Huang W, Alexander GE, Chang L, et al. Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study. Neurology 2001;57:626–632
34. Miller BL, Moats RA, Shonk T, et al. Alzheimer disease: depiction of increased cerebral myo-inositol with proton MR spectroscopy. Radiology 1993;187:433–437
35. Moats RA, Ernst T, Shonk TK, et al. Abnormal cerebral metabolite concentrations in patients with probable Alzheimer disease. Magn Reson Med 1994;32:110–115
36. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–259
37. Jack CR Jr, Petersen RC, O'Brien PC, et al. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 1992;42:183–188
38. Lehericy S, Baulac M, Chiras J, et al. Amygdalohippocampal MR volume measurements in the early stages of Alzheimer disease. Am J Neuroradiol 1994;15:929–937
39. Terry RD, Peck A, DeTeresa R, et al. Some morphometric aspects of the brain in senile dementia of the Alzheimer type. Ann Neurol 1981;10:184–192
40. Schuff N, Amend D, Ezekiel F, et al. Changes of hippocampal N-acetyl aspartate and volume in Alzheimer's disease: a proton MR spectroscopic imaging and MRI study. Neurology 1997;49:1513–1521
41. Capizzano AA, Schuff N, Amend DL, et al. Subcortical ischemic vascular dementia: assessment with quantitative MR imaging and 1H MR spectroscopy. Am J Neuroradiol 2000;21:621–630

42. Rai GS, McConnell JR, Waldman A, et al. Brain proton spectroscopy in dementia: an aid to clinical diagnosis. Lancet 1999;353:1063–1064
43. MacKay S, Meyerhoff DJ, Constans JM, et al. Regional gray and white matter metabolite differences in subjects with AD, with subcortical ischemic vascular dementia, and elderly controls with 1H magnetic resonance spectroscopic imaging. Arch Neurol 1996;53:167–174
44. Finkel SI. Behavioral and psychological symptoms of dementia: a current focus for clinicians, researchers, and caregivers. J Clin Psychiatry 2001;62(suppl 21):3–6
45. Anderson SW, Bechara A, Damasio H, et al. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat Neurosci 1999;2:1032–1037
46. Damasio H, Grabowski T, Frank R, et al. The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science 1994;264:1102–1105
47. Grafman J, Schwab K, Warden D, et al. Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. Neurology 1996;46:1231–1238
48. Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. Arch Neurol 1977;34:454–467
49. Herzberg JL, Fenwick PB. The aetiology of aggression in temporal-lobe epilepsy. Br J Psychiatry 1988;153:50–55
50. Rodin EA. Psychomotor epilepsy and aggressive behavior. Arch Gen Psychiatry 1973;28:210–213
51. Geschwind N. Effects of temporal-lobe surgery on behavior. N Engl J Med 1973;289:480–481
52. Kiloh LG, Gye RS, Rushworth RG, et al. Stereotactic amygdaloidotomy for aggressive behaviour. J Neurol Neurosurg Psychiatry 1974;37: 437–444
53. Critchley HD, Simmons A, Daly EM, et al. Prefrontal and medial temporal correlates of repetitive violence to self and others. Biol Psychiatry 2000;47:928–934
54. Silbersweig DA, Stern E, Frith C, et al. A functional neuroanatomy of hallucinations in schizophrenia. Nature 1995;378:176–179
55. Shergill SS, Brammer MJ, Williams SCR, et al. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 2000;57:1033–1038
56. Rose SE, de Zubicaray GI, Wang D, et al. A 1H MRS study of probable Alzheimer's disease and normal aging: implications for longitudinal monitoring of dementia progression. Magn Reson Imaging 1999;17: 291–299
57. Doraiswamy PM, Charles HC, Krishnan KR. Prediction of cognitive decline in early Alzheimer's disease. Lancet 1998;352:1678
58. Jessen F, Block W, Traber F, et al. Decrease of N-acetylaspartate in the MTL correlates with cognitive decline of AD patients. Neurology 2001;57:930–932

