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Using proton magnetic resonance spectroscopy to identify mild cognitive impairment

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ABSTRACT

Background: Single-volume proton magnetic resonance spectroscopy (^{1}H MRS) has considerable diagnostic potential for Alzheimer's disease (AD). This study investigated ^{1}H MRS in specific regions of the brain, the posterior cingulate gyri (PCG) and the hippocampus, in patients with AD, amnestic mild cognitive impairment (aMCI), and in normal control subjects.

Methods: ^{1}H MRS analysis was carried out on 47 patients with AD, 32 patients with aMCI and 56 normal control subjects (NC group). Volumes of the PCG and hippocampus were assessed, and the metabolic signals of N-acetylaspartate (NAA), choline compounds (Cho), myo-inositol (mI), and creatine (Cr) were quantified.

Results: In the PCG, differences between the test groups were found in NAA/Cr, Cho/Cr, mI/Cr and NAA/mI ratios. Group differences were also found in mI/Cr and NAA/mI ratios in the left hippocampus, and in mI/Cr and NAA/mI ratios in the right hippocampus. NAA/Cr ratios increased in the PCG between AD and aMCI patients, and between aMCI and NC patients. Conversely, mI/Cr ratios in the PCG and left hippocampus decreased across AD, aMCI, and NC subjects. In discriminate and ROC (Receiver Operating Characteristic) analyses, a NAA/Cr ratio of ≤ 1.50 in the PCG indicated optimal potential for discriminating between aMCI patients and normal control subjects. Discriminating potential was also found to be high for a NAA/mI ratio in the PCG of ≤ 2.72. Despite significant differences between NC and aMCI patients in the mI/Cr ratio in the PCG and in the NAA/mI ratio in the left hippocampus, their sensitivity and specificity were all lower than 75%.

Conclusion: Proton MRS of the PCG using the NAA/Cr ratio as a metabolic marker indicates considerable potential for distinguishing between aMCI and NC subjects.

Key words: Alzheimer's disease, NAA/Cr, posterior cingulate gyri, hippocampus

Introduction

Amnestic mild cognitive impairment (aMCI) is generally accepted to include prodromal Alzheimer's disease (AD), as studies suggest that the majority of MCI patients progress to AD (Petersen *et al.*, 2001; 2010). Neuroimaging markers of MCI are clinically important to characterize such patients for early diagnosis and treatment. Single-volume proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive, convenient and rapid magnetic resonance imaging (MRI) technique that is sensitive to biologically relevant chemical changes in the brain. Prior studies have shown that levels of the neuronal integrity markers N-acetylaspartate (NAA) and NAA/Cr, as assessed by ^{1}H MRS, are lower in AD patients compared to healthy elderly individuals, and that decreased NAA/Cr levels can predict future conversion from MCI to AD (Chao *et al.*, 2005; Metastasio *et al.*, 2006). Previous studies have investigated ^{1}H MRS imaging of specific regions of the brain in patients with AD (Godbolt et al., 2006; Jessen et al., 2009). In one study, decreased NAA levels were found in the cortical gray matter of individuals with AD, relative to control subjects (Adalsteinsson et al., 2000). Another study showed that a reduced NAA/Cr ratio in the medial temporal lobe was correlated with low MMSE scores (Jessen et al., 2001).

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Measurements of NAA/Cr and mI/Cr ratios, as determined by 1H MRS analysis, correlate with neuropsychological measures of cognitive function in patients with AD (Huang et al., 2001). There is a region-specific association between neuropsychological performance and 1H MRS metabolite changes, depending on the cognitive domain being studied. For example, 1H MRS metabolite changes in patients with AD correlate with loss of verbal memory in the left medial temporal lobe and with language impairment and visuoconstructional abilities in the left parietotemporal cortex (Chantal et al., 2004). The association between 1H MRS measurements and neuropsychological performance suggests that 1H MRS may be a sensitive clinical marker for disease progression in AD. Since patients with AD show higher levels of mI and lower levels of NAA than cognitively normal elderly individuals, the ratio of NAA/mI is the most diagnostically accurate 1H MRS measurement used to differentiate between patients with AD and normal subjects. In prior studies, NAA/mI ratios have distinguished clinically diagnosed AD patients from normal elderly individuals with a sensitivity of 57–90% and a specificity of 73–95% for different cohorts, using distinct ^{1}H MRS acquisition parameters in specific regions of the brain (Kantarci et al., 2002; Martinez-Bisbal et al., 2004; Fernandez et al., 2005; Zhu et al., 2006). Since definitive diagnosis of AD requires histopathological confirmation, the diagnostic value of NAA/mI should ideally be correlated with AD pathology.

Patients with AD and MCI show degeneration of brain tissue, especially in the PCG and the hippocampus.The hippocampus is an important structure within the medial temporal lobe. It typically demonstrates marked pathological changes with AD and has exhibited reductions in NAA in postmortem studies of AD brains. In addition, posterior cingulate hypometabolism is a severe metabolic lesion that has been observed in early stage AD (Nestor *et al.*, 2003). Although posterior cingulate hypometabolism was originally interpreted as being a remote consequence of medial temporal lobe degeneration, recent volumetric MRI work has revealed that this area is also atrophic in incipient AD (Choo *et al.*, 2010; Pengas *et al.*, 2010).

Finding a valid brain imaging biomarker before the AD stage is imperative for early intervention, and metabolic markers in the posterior cingulate gyri (PCG) and hippocampus are promising candidates. The current study used ^{1}H MRS to investigate potential biomarkers of neuronal damage in AD and aMCI patients, as well as in normal control patients. Specifically, we assessed levels of N-acetylaspartate (NAA), choline compounds (Cho), myo-inositol (mI), and creatine (Cr) in the PCG and left and right hippocampi.

Methods

Participants and recruitment

We recruited 47 patients with AD, 32 patients with aMCI from the tertiary hospital of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine (Alzheimer's Disease and Related Disorders Center, ADRDC) and 56 cognitively normal elderly subjects from the Fenglin community of Shanghai Xu Hui district. Patients enrolled in the hospital via self-referral or referral from family or physician. The study was approved by the Institution's Ethical Committee and informed consent was obtained from all subjects and/or their legal guardians.

Probable AD was diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) criteria and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorder's Association (NINCDS/ADRDA) criteria.

Amnestic MCI was diagnosed based on the following criteria (Petersen *et al.*, 2001): (1) memory complaint, preferably corroborated by a spouse or relative, (2) objective memory impairment, (3) normal general cognitive function, (4) intact activities of daily living, and (5) absence of dementia. We have amended the amnestic MCI diagnostic criteria of the Petersen MMSE cut-off score in order to be consistent with the low level of education in elderly Chinese people. Research by Katzman *et al.* (1988) found that with the Chinese version of MMSE, AD subjects who had not been educated (NO ED) exhibited MMSE scores of <18, those with elementary school education exhibited MMSE scores of <21, and those with higher than middle school education exhibited MMSE scores of <25. In the present study, the aMCI analysis was carried out on NO ED subjects with MMSE cut-off scores of ≥ 18, elementary school educated subjects with MMSE cut-off scores of ≥ 21, and higher than middle school educated subject with MMSE cut-off scores of ≥ 25.

The cognitively normal elderly who formed the normal control (NC) group were independently functioning community dwellers with no neurological or psychiatric conditions.

All participants underwent a screening process that included a review of their medical history, physical and neurological examinations, laboratory tests, and MRI analysis. The clinical assessment of mild cognitive impairment or dementia included

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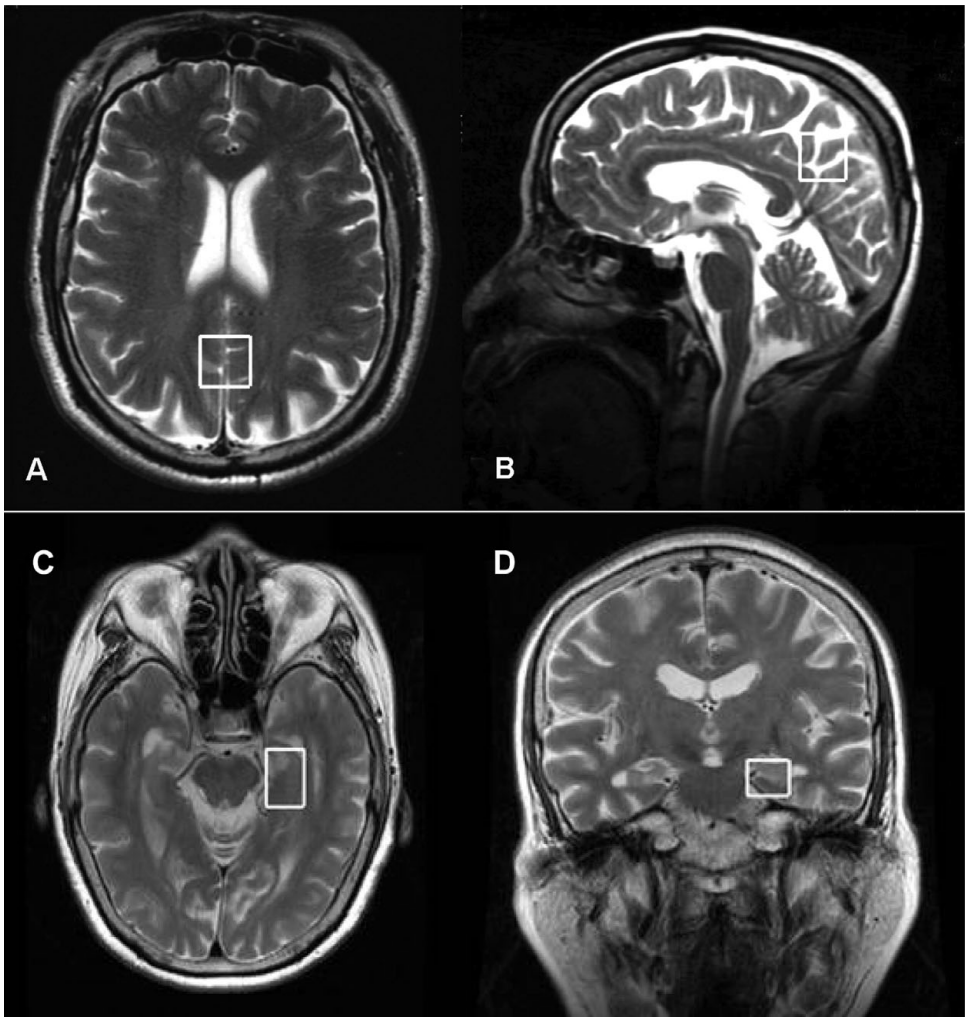


Figure 1. ^{1}H MR spectroscopy showing the location of the PCG volume of interest (VOI) on (A) an axial and (B) a mid-sagittal T2-weighted localizing image, and the hippocampal VOI on (C) an axial and (D) a coronal T2-weighted localizing image.

neuropsychological tests, as well as behavioral and psychiatric interviews conducted by the attending psychiatrist. AD patients recorded scores of < 4 on the Hachinski Ischemia Scale and showed no history of significant systemic or psychiatric conditions, or traumatic brain injuries that could compromise brain function. The neuropsychological battery which was used only to determine MCI subtype in the present study included: Wechsler Memory Scale (WMS) Verbal Associates immediate and 30-minute delayed test, Rey Auditory Verbal Learning and 30-minute Delayed Test, WMS-Digit Span, Category Naming Test-Animals, and Clock Drawing Test. We rated the MCI patients' cognitive impairment in seven domains: memory, attention, language, visual-spatial, orientation, calculation and executive function according to the neuropsychological battery and MMSE. Based on the assessment, we retained aMCI subjects and excluded subjects with impairment in a single non-memory domain (single, non-memory domain MCI subtype) and impairment in two or more domains (multiple domains, slightly impaired MCI subtype). NC subjects had no history of cognitive decline, neurological disorders, or uncontrolled systemic medical disorders. All subjects were required to have fewer than two lacuna ischemia (of diameter < 1 cm), as revealed by MRI fluid-attenuated inversion recovery (FLAIR) sequence scanning.

MRS image acquisition

All MRS scans were performed on a 3.0-Tesla Signa HD MR system (General Electric Medical Systems, Milwaukee, WI, USA) using Point-Resolved Spectroscopy (PRESS) pulse sequence. T2-weighted images were obtained to localize ^{1}H MRS voxels. Special attention was paid to the symmetric positioning of the patient's head. The parameters used were: echo time (ET) = 35 ms, repetition time (RT) = 1,500 ms, and acquisitions = 128. Typical voxel locations in the PCG and hippocampus

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Table 1. Demographic and clinical characteristics of subjects

	NC (n = 56)	aMCI (n = 32)	AD (n = 47)	*P*
Age (years)	71.4 ± 9.7	74.9 ± 7.6	70.9 ± 9.2	0.121
Male/Female	24/32	17/15	17/30	0.102
Education (years)	10.1 ± 4.0	8.6 ± 5.1	9.0 ± 4.5	0.271
CDR	0.0 ± 0.0	0.5 ± 0.0	2.1 ± 0.6	<0.001
MMSE	26.5 ± 3.5	23.9 ± 3.8	13.8 ± 5.4	<0.001
NPI (total score)	0.8 ± 3.3	5.2 ± 5.0	9.4 ± 9.6	<0.001

Data represent number or mean ± SD. Data were analyzed by one-way ANOVA.
NC = normal control; aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory

are shown in Figure 1. The Prescan Algorithm of Proton Brain Exam (PROBE) automatically adjusted the transmitter and receiver gains and center frequencies. PRESS pulse sequence with automated shimming and water suppression and excellent reproducibility (Simmons *et al.*, 1998) was used to obtain spectra from each voxel after the chemical shift selective (CHESS) water suppression with high signal to noise ratio and the identification of NAA, Cho, ml, and Cr peaks among the other metabolites. Volumes of interest (VOI) were placed in a uniform manner by the same investigator and included 8 cm^3 (20 × 20 × 20 mm) of the PCG and 6.38 cm^3 (25 × 17 × 15 mm) of the hippocampus. VOI of the PCG were identified on a mid-sagittal T2-weighted image, below the cingulate sulcus and above the parieto-occipital sulcus, which included the PCG and inferior precuneus bilaterally. VOI of the hippocampus included both grey and white matter, as well as the parahippocampal gyrus. MRS is quite stable for the PCG, but it is not stable for the temporal lobe or hippocampus. Spectral data from either the left or right hippocampus (but not both) were obtained in 91.4% of the subjects. Since no significant differences were found in the metabolite content between the left and right hippocampi, metabolite ratios were averaged across the left and right hippocampi for subjects with data available for both sides.

Data analysis

Demographic and clinical characteristics across the AD, aMCI, and control groups were assessed by analysis of variance (ANOVA) followed by least significant difference (LSD) post hoc tests. Differences between the groups in metabolite ratios relative to Cr (NAA/Cr, Cho/Cr, mI/Cr) and in the NAA/mI ratio were tested by means of a two-way repeated ANOVA, with each group as the between-subject factor. For aMCI and NC subjects, discriminant and ROC (Receiver Operating Characteristic) analyses were also performed.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics for AD, aMCI, and NC subjects are shown in Table 1. No differences between the groups were observed in age, gender, or level of education. As expected, group differences were observed in the Mini-Mental Status Exam (MMSE) and in the Clinical Dementia Rating (CDR) scores ($P < 0.001$). Specifically, AD subjects had significantly lower scores on both scales compared to aMCI or NC subjects, and aMCI subjects had significantly lower scores on both scales compared to NC subjects ($P < 0.001$). The Neuropsychiatric Inventory (NPI) was applied to every subject before ^{1}H MRS scanning. Results revealed no detectable neuropsychiatric symptoms in 50 (89%), 8 (25%), and 8 (17%) subjects from the NC, aMCI, and AD groups, respectively. Anxiety was the most frequently displayed behavior in the aMCI group. Apathy was the most frequently displayed behavior in the AD group.

^{1}H MRS data

The representative proton MR spectra of the PCG for (a) the NC group, (b) the aMCI group and (c) the AD group are shown in Figure 2.

As shown in Table 2 and Figure 3, differences between the groups were found in the PCG for NAA/Cr, mI/Cr, NAA/mI (P's ≤ 0.01) and Cho/Cr ($P = 0.012$) ratios. Differences between the groups were found in the left hippocampus for mI/Cr and NAA/mI (P's < 0.01). Within the PCG, the NAA/Cr and NAA/mI ratios increased between the AD and MCI groups and between the MCI and the NC groups. Conversely, in the PCG and

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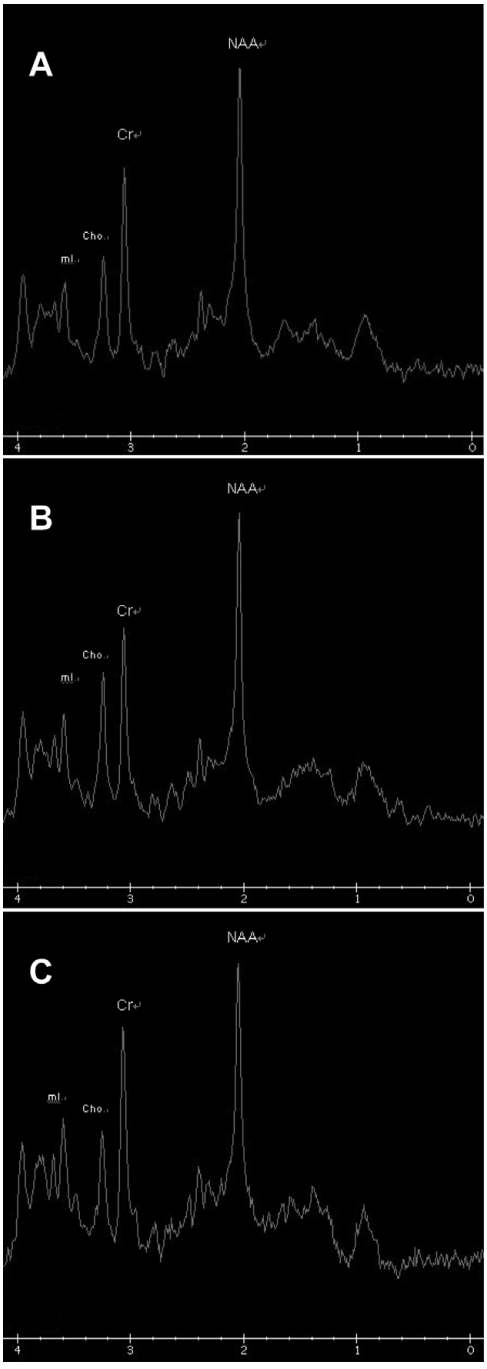


Figure 2. Representative proton MR spectra for (A) the NC group, (B) the aMCI group and (C) the AD group.

left hippocampus, the mI/Cr ratio decreased across the AD, MCI, and NC groups. Interestingly, the Cho/Cr ratio of PCG was reduced significantly only in AD subjects.

As shown in Table 3, in discriminant and ROC analyses, a NAA/Cr ratio in the PCG of $\leq$ 1.50 allowed optimal discrimination between aMCI patients and normal control subjects (sensitivity = 93.8% and specificity = 92.9%; Figure 4). A NAA/mI ratio in the PCG of $\leq$ 2.72 showed the next highest potential for discrimination (sensitivity = 75.0% and specificity = 80.0%). Despite significant differences between NC and aMCI patients in the mI/Cr ratio in the PCG and in the NAA/mI ratio in the left hippocampus, their sensitivity and specificity were low than 75%.

Discussion

NAA in the brain is primarily localized in neuron bodies, axons, and dendrites. In this way, NAA can be a sensitive marker for the loss of neuronal components, neuronal functional disruption, or both. NAA is reduced in both the cortical grey matter and the white matter in AD patients, and the cortex shows neuropathology in AD. The neurofibrillary pathology and associated neuronal damage in AD patients affects the limbic cortical regions earlier and more profoundly than the primary sensorimotor and visual cortices, which are affected only at the end stages of the disease (Zhu *et al.*, 2006). Following this progression, NAA/Cr ratios in cases of mild to moderate AD are decreased in the PCG, which is a paralimbic cortical region. NAA/Cr ratios in the PCG in the current study revealed clear brain tissue loss in MCI patients, which was exacerbated in AD patients. In the hippocampus, decreases in NAA and NAA/Cr ratios have been previously reported (Schuff *et al.*, 2002), but only in patients with AD. Our findings of regional metabolite changes in normal ageing individuals and those with MCI and AD reflect a gradual process of brain degeneration that initially affects the hippocampus. In older MCI patients, the severity of hippocampal and parahippocampal atrophy appears to be predictive of the rate of progression to AD. Reduction of NAA occurred even earlier than atrophy in MCI patients.

Conflicting reports exist on Cho levels in AD patients, as some studies have identified elevated levels (Kantarci *et al.*, 2004), while others have not (Krishnan *et al.*, 2003). The largest amount of Cho found in the brain is in the Cho-bound membrane phospholipids. Free Cho and acetylcholine are in low levels in brain tissue, and therefore do not contribute detectably to the nuclear magnetic resonance (NMR) signal. One possible explanation for the elevation of Cho in AD patients is increased membrane turnover due to neurodegeneration. It has also been postulated that the elevation of the Cho peak is the consequence of membrane phosphatidylcholine catabolism, to provide free choline for the chronically deficient acetylcholine production in AD. Cho/Cr levels decrease with cholinergic agonist treatment of AD, suggesting that downregulation of choline acetyltransferase activity may be responsible for the elevation of Cho. In our

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Table 2. Assessment of metabolic markers of neuronal damage by MRS

	NC (n = 56)	aMCI (n = 32)	AD (n = 47)	*P*	LSD POST HOC TESTS (*P* VALUE) 1 VS. 2	2 VS. 3	1 VS. 3
PCG							
NAA/Cr	1.62± 0.10	1.39± 0.09	1.23± 0.12	<0.001	<0.001	<0.001	<0.001
Cho/Cr	0.66± 0.07	0.65± 0.09	0.72± 0.11	0.012	0.723	0.009	0.007
mI/Cr	0.55± 0.10	0.60± 0.11	0.71± 0.13	<0.001	0.068	<0.001	<0.001
NAA/mI	3.01± 0.49	2.43± 0.58	1.81± 0.43	<0.001	<0.001	<0.001	<0.001
Left hippocampus							
NAA/Cr	1.36± 0.13	1.36± 0.24	1.31± 0.27	0.591	0.931	0.455	0.331
Cho/Cr	1.01± 0.11	1.01± 0.17	1.02± 0.16	0.944	0.929	0.826	0.735
mI/Cr	0.81± 0.14	0.91± 0.19	0.96± 0.20	0.002	0.034	0.353	0.001
NAA/mI	1.72± 0.28	1.58± 0.31	1.41± 0.37	0.002	0.128	0.092	<0.001
Right hippocampus							
NAA/Cr	1.33± 0.17	1.25± 0.16	1.21± 0.22	0.099	0.137	0.615	0.057
Cho/Cr	1.05± 0.14	1.03± 0.17	0.99± 0.19	0.514	0.670	0.518	0.252
mI/Cr	0.75± 0.13	0.82± 0.13	0.84± 0.16	0.102	0.090	0.146	0.071
NAA/mI	1.83± 0.46	1.63± 0.22	1.53± 0.43	0.053	0.060	0.395	0.040

Data represent mean ± SD and were analyzed by one-way ANOVA and LSD post hoc tests.
1 = NC (group 1), 2 = aMCI (group 2), 3 = AD (group 3)
NC = normal control; aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease; LSD = least significant difference; PCG = posterior cingulate gyri; NAA = N-acetylaspartate; Cho = choline; mI = myo-inositol; Cr = creatine

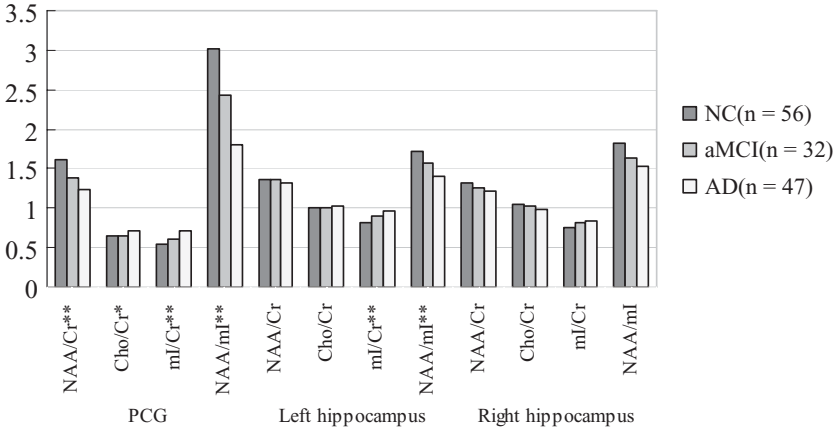


Figure 3. The metabolic markers of neuronal damage by ^{1}H MRS.
*significant at $p \leq 0.05$ level, **significant at $p \leq 0.01$ level by one-way ANOVA tests.

study, Cho/Cr levels were elevated only in the PCG of AD patients, while MCI patients had similar levels to those of the control subjects.

In the current study, NNA/Cr and mI/Cr ratios in the PCG were found to be significantly different across the AD, MCI and NC subject groups. Group differences were not as obvious in the hippocampus as in the PCG, although the mI/Cr ratio in the left hippocampus showed a significant effect. Significant group differences were found in the current study in the NNA/mI ratio of the PCG and left hippocampus. We speculate that metabolite changes may appear early in the PCG and later in the hippocampus, and that this theory may provide an interesting topic for investigation in future studies.

The syndrome of amnestic MCI was established to identify individuals with prodromal AD (Petersen, 2004). Such individuals have memory impairment but do not meet the clinical criteria for dementia, despite many of them having early AD pathology. For this reason, amnestic MCI is an important clinical group for the imaging of early AD and for early therapeutic intervention. Patients with aMCI show an increased mI/Cr ratio in the parietal lobes compared with elderly control subjects (Catani *et al.*, 2001), whereas NAA/Cr ratios are either mildly decreased or

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Table 3. Regional metabolite ratios as discriminators between aMCI and NC

METABOLITE RATIOS	LEVEL	SENSITIVITY (%)	SPECIFICITY (%)
PCG			
NAA/Cr	≤1.50	93.8	92.9
Cho/Cr	≥0.65	54.2	46.9
mI/Cr	≥0.58	62.5	72.7
NAA/mI	≤2.72	75.0	80.0
Left hippocampus			
NAA/Cr	≤1.37	56.5	53.5
Cho/Cr	>1.01	47.6	50.0
mI/Cr	≥0.85	50.0	74.4
NAA/mI	≤1.63	63.2	67.6
Right hippocampus			
NAA/Cr	≤1.28	68.8	63.2
Cho/Cr	≥1.03	64.7	57.5
mI/Cr	>0.82	78.6	76.7
NAA/mI	≤1.69	72.9	63.3

aMCI = amnestic mild cognitive impairment; NC = normal control; PCG = posterior cingulate gyri; NAA = N-acetylaspartate; Cho = choline; mI = myo-inositol; Cr = creatine

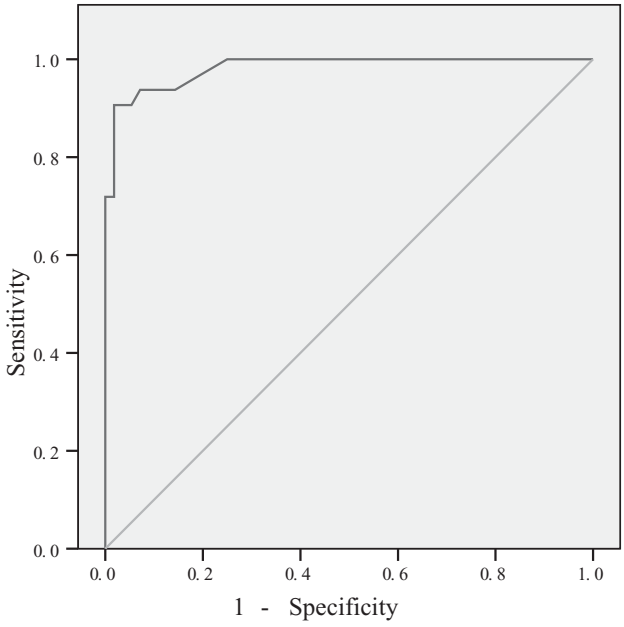


Figure 4. The NAA/Cr ratio in PCG as a predictor of aMCI.

normal. Conversely, NAA and NAA/Cr ratios are significantly decreased in the hippocampus of amnestic MCI patients (Ackl *et al.*, 2005). Regional elevation of mI/Cr ratios in prodromal AD suggests the following: (1) that 1H MRS may be sensitive to the biochemical changes that occur during the pathologic progression of AD, before there is a significant loss of neuronal integrity, and (2) that different brain regions and metabolites may identify different pathological stages in the course of AD. Therefore, mI/Cr and NAA/Cr ratios may be useful for predicting and monitoring prodromal AD in MCI patients. For example, NAA/Cr ratios have been reported to be lower at baseline in patients with aMCI who later progressed to AD than in those who remained stable at follow-up (Chao et al., 2005; Modrego et al., 2005; Metastasio et al., 2006). Our results support the clinical utility of proton MRS in diagnosing MCI and NC. NAA/Cr levels in the PCG show good diagnostic discrimination between MCI and NC patients. The clinical utility of NAA/Cr ratios, as determined by 1H MRS, has also been demonstrated by Fayed et al. (2008). Those authors found that NAA/Cr ratios in the PCG predicted the conversion of MCI to probable AD with a sensitivity of 82%

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and specificity of 72%, and that NAA/Cr ratios in the left occipital cortex (LOC) demonstrated a sensitivity of 78% and specificity of 69%. Kantarci et al. (2009) followed 151 subjects with MCI and found that NAA/Cr ratios, as determined by ^{1}H MRS, predicted progression to dementia. The authors' previous research showed that the Cho/Cr ratio was elevated in the paralimbic cortical region and in the PCG in MCI patients. Little research has compared MCI and NC subjects. Our study indicates that NAA/Cr ratios of ≤ 1.50 in the PCG show 93.8% sensitivity and 92.9% specificity in discriminating between MCI and NC patients.

Conclusions

Within the PCG, the NAA/Cr ratio showed increasing levels between the AD, MCI, and NC subjects. Conversely, the mI/Cr ratio in the PCG and left hippocampus showed decreasing levels across the AD, MCI, and NC subjects. A ratio of NAA/Cr ≤ 1.50 in the PCG, revealed by proton MRS, indicates considerable potential for distinguishing between MCI and NC patients. Future studies should examine the use of proton MRS in combination with other AD biomarkers to specify their individual contributions to the clinical pathology of AD and to predict the risk for developing MCI and AD.

Conflict of interest

None.

Description of authors' roles

Tao Wang contributed to the design of the project and writing of the paper. Shifu Xiao supervised the analysis and contributed to the design of the project. Xia Li, Bei Ding and Huawei Ling carried out the data collection of brain images. Kemin Chen and Yiru Fang supervised the data collection and analysis. All authors read and approved the final paper.

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References

Ackl, N., Ising, M., Schreiber, Y. A., Atiya, M., Sonntag, A. and Auer, D. P. (2005). Hippocampal metabolic abnormalities in mild cognitive impairment and Alzheimer's disease. *Neuroscience Letters*, 384, 23–28.

Adalsteinsson, E., Sullivan, E. V., Kleinhans, N., Spielman, D. M. and Pfefferbaum, A. (2000). Longitudinal decline of the neuronal marker N-acetyl aspartate in Alzheimer's disease. *Lancet*, 355, 1696–1697.

Catani, M. *et al.* (2001). (1)H-MR spectroscopy differentiates mild cognitive impairment from normal brain aging. *NeuroReport*, 12, 2315–2317.

Chantal, S., Braun, C. M., Bouchard, R. W., Labelle, M. and Boulanger, Y. (2004). Similar 1H magnetic resonance spectroscopic metabolic pattern in the medial temporal lobes of patients with mild cognitive impairment and Alzheimer disease. *Brain Research*, 1003, 26–35.

Chao, L. L. *et al.* (2005). Reduced medial temporal lobe N-acetylaspartate in cognitively impaired but nondemented patients. *Neurology*, 64, 282–289.

Choo, I. H. *et al.* (2010). Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, 31, 772–779.

Fayed, N., Dávila, J., Oliveros, A., Castillo, J. and Medrano, J. J. (2008). Utility of different MR modalities in mild cognitive impairment and its use as a predictor of conversion to probable dementia. *Academic Radiology*, 15, 1089–1098.

Fernandez, A. *et al.* (2005). Proton magnetic resonance spectroscopy and magnetoencephalographic estimation of delta dipole density: a combination of techniques that may contribute to the diagnosis of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 20, 169–177.

Godbolt, A. K. *et al.* (2006). MRS shows abnormalities before symptoms in familial Alzheimer disease. *Neurology*, 66, 718–722.

Huang, W. *et al.* (2001). Brain metabolite concentration and dementia severity in Alzheimer's disease: a (1)H MRS study. *Neurology*, 57, 626–632.

Jessen, F. *et al.* (2001). Decrease of N-acetylaspartate in the MTL correlates with cognitive decline of AD patients. *Neurology*, 57, 930–932.

Jessen, F. *et al.* (2009). A multicenter (1)H-MRS study of the medial temporal lobe in AD and MCI. *Neurology*, 72, 1735–1740.

Kantarci, K. *et al.* (2002). Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 14, 198–207.

Kantarci, K. *et al.* (2004). 1H MR spectroscopy in common dementias. *Neurology*, 63, 1393–1398.

Kantarci, K. *et al.* (2009). Risk of dementia in MCI: combined effect of cerebrovascular disease, volumetric MRI, and 1H MRS. *Neurology*, 72, 1519–1525.

Katzman, R. *et al.* (1988). A Chinese version of the Mini-Mental State Examination: impact of illiteracy in a Shanghai dementia survey. *Journal of Clinical Epidemiology*, 41, 971–978.

https://doi.org/10.1017/S1041610211000962 Published online by Cambridge University Press

Krishnan, K. R. *et al.* (2003). Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *American Journal of Psychiatry*, 160, 2003–2011.

Martinez-Bisbal, M. C., Arana, E., Marti-Bonmati, L., Mollá, E. and Celda, B. (2004). Cognitive impairment: classification by 1H magnetic resonance spectroscopy. *European Journal of Neurology*, 11, 187–193.

Metastasio, A. *et al.* (2006). Conversion of MCI to dementia: role of proton magnetic resonance spectroscopy. *Neurobiology of Aging*, 27, 926–932.

Modrego, P. J., Fayed, N. and Pina, M. A. (2005). Conversion from mild cognitive impairment to probable Alzheimer's disease predicted by brain magnetic resonance spectroscopy. *American Journal of Psychiatry*, 162, 667–675.

Nestor, P. J., Fryer, T. D., Smielewski, P. and Hodges, J. R. (2003). Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Annals of Neurology*, 4, 343–351.

Pengas, G., Hodges, J. R., Watson, P. and Nestor, P. J. (2010). Focal posterior cingulate atrophy in incipient Alzheimer's disease. *Neurobiology of Aging*, 31, 25–33.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, 256, 183–194.

Petersen, R. C.*et al.* (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, 58, 1985–1992.

Petersen, R. C. *et al.* (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*, 74, 201–209.

Simmons, A., Smail, M., Moore, E. and Williams, S. C. (1998). Serial precision of metabolite peak area ratios and water referenced metabolite peak areas in proton MR spectroscopy of the human brain. *Magnetic Resonance Imaging*, 16, 319–330.

Schuff, N. *et al.* (2002). Selective reduction of N-acetylaspartate in medial temporal and parietal lobes in AD. *Neurology*, 58, 928–935.

Zhu, X. *et al.* (2006). Effects of Alzheimer disease on fronto-parietal brain N- acetyl aspartate and myo-inositol using magnetic resonance spectroscopic imaging. *Alzheimer Disease and Associated Disorders*, 20, 77–85.

https://doi.org/10.1017/S1041610211000962 Published online by Cambridge University Press