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Hippocampal metabolites and memory performances in patients with amnestic mild cognitive impairment and Alzheimer's disease

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ABSTRACT

In patients with amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD), previous studies have reported the decrease of N-acetylaspartate (NAA) concentration and the increase of myo-inositol (MI) concentration using proton magnetic resonance spectroscopy (1H-MRS). However, it remains to be investigated what aspects of cognition these metabolite changes reflect. In this study we evaluated the correlations between the subtests of Wechsler Memory Scale-Revised (WMS-R) and the concentrations of NAA and MI. The study group was composed of 42 patients with aMCI and 67 patients with AD. 1H-MR spectra with a single voxel-point resolved spectroscopy (PRESS) at a short echo time were acquired from the bilateral hippocampi and posterior cingulate gyrus. Positive correlations were shown between the NAA concentration in the left hippocampus and verbal memory, visual memory, general memory, attention and delayed recall; and furthermore, between the NAA concentration in the right hippocampus and verbal memory and general memory. Negative correlations were shown between the MI concentration in the left hippocampus and verbal memory, general memory, and delayed recall, and between the MI concentration in the right hippocampus and verbal memory. There was no significant correlation between any subtest of WMS-R and these two metabolite concentrations in the posterior cingulate gyrus. These findings suggest that bilateral, especially left hippocampal NAA and MI concentrations are associated with memory dysfunction observed in patients with aMCI and AD. In contrast, NAA and MI concentrations in the posterior cingulate gyrus may be less related to memory function than those in the hippocampus.

1. Introduction

Recent studies have investigated the relationship between episodic memory and neural basis using functional magnetic resonance imaging (fMRI) or event related potentials (Diana, Van den Boom, & Yonelinas, 2011; Yonelinas, Aly, Wang, & Koen, 2010). Several fMRI studies, especially, revealed that different medial temporal lobe regions including hippocampus and parahippocampal area process different types of episodic information (Diana & Yonelinas, 2010; Ranganath, 2010; Vanssay-Maigne et al., 2011). However, there have been few studies to investigate the associations between cerebral metabolite concentrations and episodic memory (Ross & Sachdev, 2004).

1H-MRS has been used to measure the metabolite concentrations in patients with aMCI and AD (Valenzuela & Sachdev, 2001; Watanabe, Shiino, & Akiguchi, 2010). Among various substances assessed by 1H-MRS, functional significances of two metabolites are interesting and have been discussed at length in literature: NAA and MI. NAA is predominantly intraneuronal and has been widely used as a marker of neuronal density and viability (Moffett, Ross, Arun, Madhavarao, & Namboodiri, 2007). MI is primarily located in astrocytes, and has been interpreted to be a marker of gliosis (Fisher, Novak, & Agronoff, 2002). In patients with aMCI and AD, previous studies reported the decrease of NAA concentrations and the increase of MI concentrations (Valenzuela & Sachdev, 2001; Watanabe, Shiino, & Akiguchi, 2010). However, it remains to be investigated what aspects of cognition these metabolite changes reflect. There is a strong interest in revealing the association between these two metabolite changes and episodic memory dysfunction that is considered to be the first symptom of AD. In our previous studies, we reported that absolute quantification in 1H-MRS is superior to relative ratios to discriminate AD and aMCI from healthy aging (Watanabe, Shiino, & Akiguchi, 2008; Watanabe, Shiino, & Akiguchi, 2010). In this study, we first assessed the absolute metabolite concentrations from patients with aMCI and AD in the bilateral hippocampi and posterior cingulate gyrus, and

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then evaluated the correlations between the subtests of Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987) and the concentrations of NAA and MI.

2. Methods

2.1. Participants

All patients were recruited consecutively and prospectively for longitudinal studies of cognitive disturbances at our outpatient clinic. They underwent comprehensive diagnostic evaluations, including medical histories, neurological and psychiatric examinations, neuropsychological testing, laboratory tests, as well as brain MRI and SPECT. The exclusionary criteria were medical histories of cortical stroke or other major neurological diseases, thyroid dysfunctions, seizures, alcohol abuse and psychiatric disorders. Dementia was diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (American Psychiatric Association, 1994). Patients with AD fulfilled the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984). Dementia severity in AD was assessed with the Clinical Dementia Rating (CDR) Scale (Morris, 1993) and only patients with mild to moderate severity (CDR 1 or 2) were studied. Patients with aMCI had to meet the operational criteria proposed by Grundman et al. (2004) including (1) memory complaint, corroborated by informants; (2) abnormal memory function, documented by delayed recall of one paragraph from the Logical Memory II subtest of the WMS-R; (3) normal general cognitive function, as determined by a clinician's judgment based on a structured interview with the patient and informant (CDR 0.5) and the Mini- Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score greater than or equal to 24; (4) minimal or no impairment in activities of daily living, as determined by a clinical interview with the patient and informants; and (5) not sufficiently impaired, cognitively or functionally, to meet NINCDS-ADRDA criteria for AD. Cognitive function was examined with the MMSE, Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (Mohs, 1994), Wechsler Adult Intelligence Scale-Revised (Shinagawa, Kobayashi, Fujita, & Maekawa, 1990; Wechsler, 1981), and WMS-R (Sugishita, 2001; Wechsler, 1987).

Ninety-eight patients with AD, 73 patients with aMCI and 58 age-matched healthy control (HC) subjects recruited during May 2001 and December 2010. The HC subjects were volunteers for the study project of MCI in our facilities. None of the control subjects had any severe neurological or medical diseases. On the basis of the above-mentioned criteria, however, we studied 67 patients with AD, 42 patients with aMCI and 54 HCs. They were all right handed. The protocol was approved by the local ethics committee, and informed consent was obtained from all participants and their responsible caregivers in accordance with the Declaration of Helsinki.

Table 1
Clinical characteristics of patients with Alzheimer's disease (AD), amnesic mild cognitive impairment (aMCI), and healthy control (HC) subjects.

	HC	aMCI	AD
No. of subjects	54	42	67
Women/men	34/20	20/22	49/18
Age (years)[a]	69.5 ± 6.2	71.3 ± 7.4	72.3 ± 7.5
Age range	60–81	56–83	56–82
Education (years)[a]	10.9 ± 0.6	11.7 ± 0.5	11.2 ± 0.4
MMSE score[a]	29.1 ± 1.4	27.3 ± 1.8[A,B]	20.6 ± 3.5[A]
Verbal Memory[b]	NA	80[B]	67
Visual Memory[b]	NA	87[B]	64
General Memory[b]	NA	82[B]	64
Attention/Concentration[b]	NA	94[B]	86
Delayed Memory[b]	NA	68[B]	54

NA: not assessed.
[a] Data are given as the mean ± SD.
[b] Data from subtests of WMS-R are given as the median.
[A] $p < 0.01$ relative to HC.
[B] $p < 0.01$ relative to AD.

Table 2
Absolute concentrations of metabolites from patients with aMCI, AD, and healthy controls (HC).

Metabolites	Group	RH	LH	PC
NAA	HC	8.65 ± 1.01	8.70 ± 1.02	9.76 ± 1.02
	aMCI	7.64 ± 1.04[A,B]	7.53 ± 0.87[A,B]	8.99 ± 1.46[A]
	AD	6.82 ± 1.10[A]	6.84 ± 1.12[A]	8.88 ± 1.34[A]
MI	HC	7.22 ± 1.31	7.27 ± 1.14	5.05 ± 0.64
	aMCI	7.63 ± 1.19	7.54 ± 1.47	5.33 ± 1.30
	AD	8.01 ± 1.82[a]	7.90 ± 1.62[a]	5.37 ± 1.04

Note: Data are given as the mean ± SD (mmol/L). RH: right hippocampus; LH: left hippocampus; PC: posterior cingulate gyrus.
[A] $p < 0.01$ relative to HC.
[a] $p < 0.05$ relative to HC.
[B] $p < 0.01$ and relative to AD.

2.2. MRI and 1H-MRS

The study protocol has been previously described in detail (Watanabe et al., 2008). Briefly, both MRI and 1H-MRS were performed on a 1.5 Tesla apparatus (Signa LX, General Electric Medical System, Milwaukee, WI) using a standard head coil suited for MRI and MRS. The protocol for structural MRI included axial FLAIR images with repetition time (TR)/echo time (TE)/inversion time (TI) = 4000/124/2000 ms with a slice thickness of 4 mm. As shown in Fig. 1, the volumes of interests (VOIs) for 1H-MRS were assigned to the bilateral hippocampi and posterior cingulate gyrus (PCG). To establish the VOIs for the hippocampi, sagittal images were obtained, followed by tilted T2-weighted (TR/TE 4000/107 ms) coronal images perpendicular to the long axis of the hippocampus

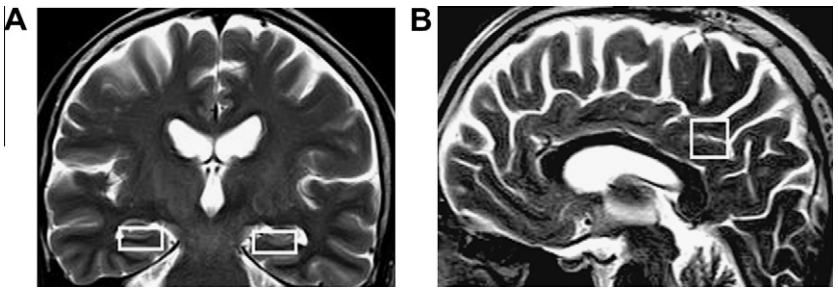

Fig. 1. Locations of volumes of interest (VOI) for 1H-MRS: (A) bilateral hippocampi; (B) posterior cingulate gyrus. In the posterior cingulate gyrus, the VOI was located in a paramedian position.