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Value of magnetic resonance spectroscopy in geriatric patients with cognitive impairment

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Abstract

Background: Mild cognitive impairment is a transitional stage prior to dementia, and it is reported in depressed patients. Early diagnosis could predict the reversible etiologies and prevent further deterioration. Proton magnetic resonance spectroscopy has been used for early diagnosis and differential diagnosis of cognitive impairment.

Objective: We aimed to study the difference of hippocampal and frontal white matter metabolites between patients with Alzheimer's disease, mild cognitive impairment, and cognitive impairment associated with depression, and if those metabolites can differentiate between them.

Subjects and methods: Geriatric patients with cognitive impairment were recruited from neurology and psychiatry clinics. All subjects underwent comprehensive medical evaluations, neuropsychological testing, laboratory tests as well as brain MRI and ^{1}H-MRS studies.

Results: The present study included 85 subjects. Patients with MCI and AD had lower hippocampal NAA and NAA/Cr ratio than patients with depression and normal controls, while, frontal NAA and NAA/Cr ratio were lower in all patient's subgroups compared to normal control.

Conclusion: Hippocampal NAA and NAA/Cr ratio might help to differentiate between MCI and cognitive impairment associated with depression.

Keywords: Alzheimer's disease, Mild cognitive impairment, Spectroscopy, Geriatric patients

Introduction

Alzheimer's disease (AD) is the commonest cause of cognitive impairment in the geriatric population. It affects more than 35.6 million people living with dementia worldwide [1]. The transitional stage prior to dementia is mild cognitive impairment (MCI), with preserved activities of daily life [2], 20% of them develop dementia yearly [3]. MCI is reported in about 38% of depressed patients [4]. Furthermore, depression may be the early presenting feature of AD [5], and the diagnosis of depression can be difficult in the elderly [6]. The overall prevalence of depressive disorders among the geriatric population varies between10 and 20%, depending on the cultural situations [7, 8].

Several invasive neuroimaging tools such as PET or SPECT are useful to differentiate MCI from AD and healthy subjects [9, 10]. However, these tools might not have a strong specificity for clinical diagnosis. Structural neuroimaging tools like MRI is used to evaluate brain volume and degree of tissue atrophy in geriatric patients with cognitive impairment [11, 12]. But MRI usually misses the identification of early neuropathological changes. So, many new MRI techniques are currently used to evaluate the pathological processes underlying the development of cognitive impairment [13, 14]. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a recent technique that can, in vivo, evaluate human brain function, and it can measure the change of brain metabolite levels before structural changes. ^{1}H-MRS has been used for early diagnosis and differential diagnosis of cognitive impairment [15].

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Diagnosis of early signs of cognitive impairment is worth studying. It could predict the reversible etiologies and prevent further deterioration. In the elderly, cognitive deficit may be a sign of depression, MCI, or AD. Differentiation between functional and organic causes of dementia is a cornerstone for early therapeutic intervention and prevention of further progression of the disorder. Our goals were (a) to study the difference of hippocampal, frontal white matter *N*-acetylaspartate (NAA) concentrations, and *N*-acetylaspartate/creatine (NAA/Cr) ratio between patients with AD, MCI, and cognitive impairment associated with depression, (b) to study if these metabolites could differentiate between MCI and cognitive impairment associated with depression.

Subjects and methods

This study was a prospective cross-sectional case-control study of geriatric patients with cognitive disturbances attending Prince Sattam Bin-Abdulaziz University Hospital, outpatient clinics. Elderly patients were recruited from neurology and psychiatry clinics during the period from March 2016 to February 2019. Age- and sex-matched healthy volunteers were included as a control group. The study was approved by local Institutional Review Board. A written informed consent was taken from the patients or their caregiver. All subjects underwent comprehensive medical evaluations, including medical history, neurological and psychiatric examinations, neuropsychological testing, laboratory tests as well as brain MRI. Subjects were excluded from the study if they had symptoms or signs of cerebral strokes, major neurological diseases that could affect cognitive function, major psychiatric disorders other than depression, comorbid dementia with depression, thyroid dysfunctions, seizures, alcohol or drug abuse or dependence, or any contraindication to MRI. Diagnosis of probable Alzheimer's disease was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) group criteria [16]. Patients with mild to moderate severity according to the Clinical Dementia Rating Scale [17] were included. Patients with MCI must fulfill the criteria of Petersen et al. [18]: memory complaints, normal daily living activities, normal general cognitive function, and abnormal memory for age but no dementia. Memory complaints of the patients were corroborated by a family member. Diagnosis of depression was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders fifth edition [19]. In order to improve the classification of AD, MCI, and cognitive impairment associated with depression, we classified patients as follows: patients with clinical diagnosis (psychiatric interview, neuropsychiatric examination, and neuropsychological testing) of depression with memory domain improvement with repeated exposure, and with both control of encoding and retrieval cues were classified as cognitive impairment associated with depression. And patients with clinical diagnosis (psychiatric interview, neuropsychiatric examination, and neuropsychological testing) of AD or MCI with flat learning curve with repeated exposure, rapid forgetting, failure of recalling with cueing, and intrusions were classified as AD or MCI [20]. Patients with a confusing diagnosis were excluded from the study. All subjects were evaluated by The Geriatric Depression Scale (GDS) [21] and Montreal Cognitive Assessment Arabic version (MoCA) [22].

All subjects underwent MRI and ^{1}H-MRS studies on a 1.5-T scanner (1.5 T Philips Gyroscan Intera, 2 × 1.5 T Siemens Magnetom Vision, Best, Netherlands; 1.5 T Siemens Magnetom Sonata, Erlangen, Germany). Conventional MR images were obtained. ^{1}H-MRS voxel of interest measuring 20 × 10 × 10 mm^3 were defined in standard location in the left hippocampus. In a coronal slice, the voxel was started at the posterior margin of the amygdala and extended posteriorly for 20 mm (Fig. 1). The studied part of the hippocampus included both grey and white matter and the most posterior portion of the amygdala. The second location was the left frontal white matter, the voxel size was 20 × 20 × 20 mm^3, and the voxel was placed in normal-appearing left frontal white matter (Fig. 2).

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 13.0. Descriptive statistics were calculated. Difference between genders was evaluated by nonparametric chi-squared test. Group differences in age, GDS, MoCA, and metabolite concentrations were evaluated by one-way analysis of variance (ANOVA), Bonferroni post hoc analysis was used. Pearson's correlation coefficient (r) was employed to analyze the association between the different variables. Values of $P < 0.05$ were considered to be statistically significant.

Results

The present study included 73 subjects without age and gender significant differences between subjects' subgroups. Patients with AD and MCI had significantly lower hippocampal NAA than patients with cognitive impairment associated with depression and normal controls. Similarly, patients with AD and MCI had significantly lower hippocampal NAA/Cr ratio than patients with cognitive impairment associated with depression and normal controls. Hippocampal and frontal creatine levels were constantly stable among patients' subgroups.

Frontal NAA was significantly lower in patients with AD than patients with MCI and normal controls, at the same time, patients with cognitive impairment associated with depression and patients with MCI had significantly lower frontal NAA than normal controls.

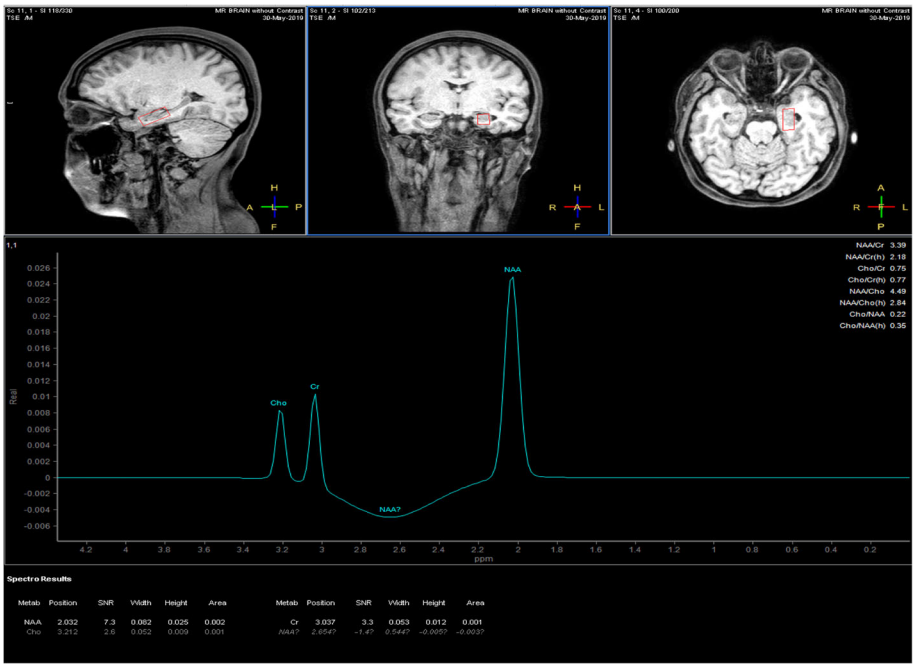

Fig. 1 The location of MRS voxel with a representative spectrum in the left hippocampus

Patients with AD and patients with cognitive impairment associated with depression had significantly lower frontal NAA/Cr ratio than patients with MCI and normal controls. On the other hand, frontal NAA/Cr ratio was significantly lower in patients with MCI than normal controls. The highest GDS score was reported among patients with cognitive impairment associated with depression. Regarding MoCA scores, patients' subgroups had significantly lower MoCA scores compared with normal controls, within patients' subgroups; patients with AD had the lowest MoCA scores (Table 1).

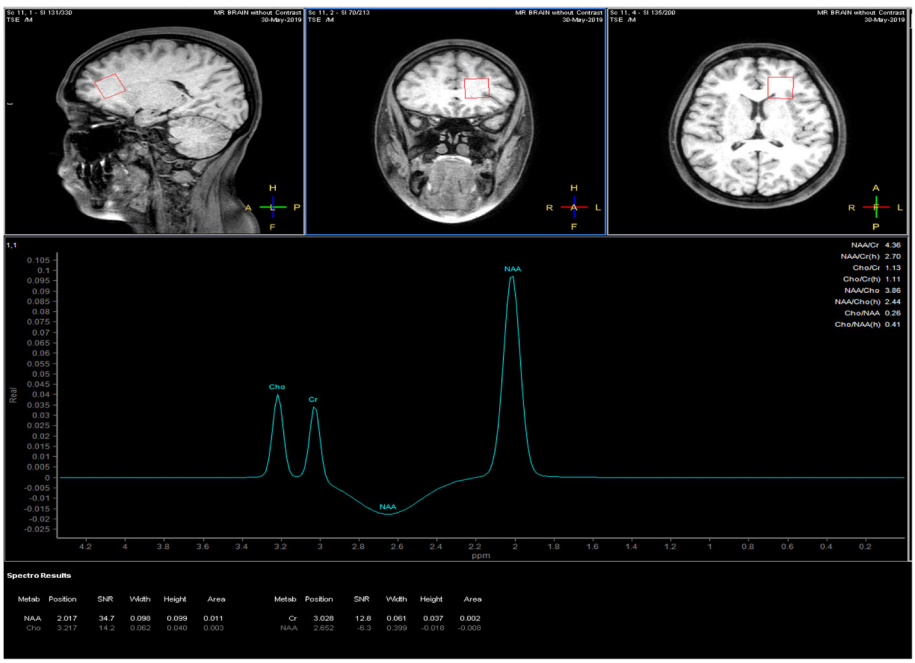

Fig. 2 The location of MRS voxel with a representative spectrum in the left frontal white matter

Table 1 Demographic, clinical, and spectroscopic data of the studied groups

		I No. 20	II No. 23	III No. 15	IV No.15	*P* value				
Age in years						0.074				
Mean ± SD		67.5 ± 4.3	64.9 ± 3.1	64.3 ± 3.7	64.4 ± 3.2					
Male	No.	9	13	7	9	0.233				
	%	45	56.5	46.7	60					
Female	No.	11	10	8	6					
	%	55	43.5	53.3	40					
Hippo NAA						I vs II *P* = 0.000	I vs IV *P* = 0.000	II vs III *P* = 0.000	III vs IV *P* = 0.000	
Mean ± SD		6.7 ± 1	10.6 ± 0.5	7.5 ± 1.5	10.9 ± 0.8					
Hippo Cr.										
Mean ± SD		5.1 ± 0.4	4.9 ± 0.2	4.8 ± 0.2	4.9 ± 0.2					
Hippo NAA/Cr						I vs II *P* = 0.000	I vs IV *P* = 0.000	II vs III *P* = 0.000	III vs IV *P* = 0.000	
Mean ± SD		1.3 ± 0.2	2.1 ± 0.1	1.5 ± 0.2	2.2 ± 0.1					
Frontal NAA						I vs III *P* = 0.000	I vs IV *P* = 0.000	II vs IV *P* = 0.000	III vs IV *P* = 0.011	
Mean ± SD		7.7 ± 1.4	8.4 ± 1.6	9.7 ± 1.3	11.4 ± 0.6					
Frontal Cr.										
Mean ± SD		4.9 ± 0.2	5.1 ± 0.4	4.9 ± 0.2	4.8 ± 0.2					
Frontal NAA/Cr						I vs III *P* = 0.000	I vs IV *P* = 0.000	II vs III *P* = 0.002	II vs IV *P* = 0.000	III vs IV *P* = 0.002
Mean ± SD		1.6 ± 0.3	1.7 ± 0.3	1.9 ± 0.3	2.4 ± 0.2					
GDS						I vs II P = 0.000	II vs III P = 0.000	II vs IV P = 0.000		
Mean ± SD		3.1 ± 1.4	10.3 ± 2.5	2.1 ± 1	1.7 ± 0.7					
MoCA						I vs II *P* = 0.000	I vs III *P* = 0.000	I vs IV *P* = 0.000	II vs IV *P* = 0.000	III vs IV *P* = 0.000
Mean ±SD		8.6 ± 4.6	20.3 ± 2	22.7 ± 2.4	27.9 ± 1					

I = Alzheimer's disease, II = Cognitive impairment associated with depression, III = Mild cognitive impairment, IV = Control subjects
Hippo Hippocampus, *NAA*: *N*-acetylaspartate, *Cr.*: Creatine, *NAA/Cr*: *N*-acetylaspartate /creatine ratio, *GDS*: The Geriatric Depression Scale, *MoCA*: Montreal Cognitive Assessment Arabic version
Significance level is set at $P < 0.05$

Patients with AD showed significant positive correlation between MoCA and both hippocampal NAA and hippocampal NAA/Cr ratio. No other significant correlations were reported between clinical data and the radiological parameters in this group of patients (Table 2). On the other hand, patients with cognitive impairment associated with depression showed a significant negative correlation between GDS in one arm and hippocampal NAA, hippocampal NAA/Cr ratio, frontal NAA, and frontal NAA/Cr ratio in the other arm (Table 3).

Patients with MCI had a positive significant correlation between MoCA and hippocampal NAA and hippocampal NAA/Cr ratio (Table 4). While normal controls showed no significant correlation between the clinical and the spectroscopic data (Table 5).

Discussion

The present study showed that hippocampal NAA level and NAA/Cr ratio could differentiate patients with MCI from elderly depressed patients with cognitive impairment.

Patients with AD and patients with MCI had significantly lower hippocampal NAA and NAA/Cr ratio than other groups. In accordance with our results, Watanabe et al. [23] reported an intermediate hippocampal NAA level in patients with MCI that was lower than normal control but higher than AD patients. The meta-analysis study of Tumati et al. [24] revealed a lower hippocampal NAA level in MCI group compared with healthy controls. In partial contradiction to our results, Jessen et al. [25] reported a higher medial temporal lobe NAA concentration in MCI patients than in patients with AD, but no difference was observed between MCI and healthy subjects. Another study reported a lower hippocampal NAA in patients with AD compared to patients with MCI and healthy control and a tendency towards a significant difference in NAA between MCI and healthy controls [26]. However, no difference was observed between MCI, AD, and healthy subjects in the study of Rupsingh et al. [27]. Previous studies reported also a significant reduction of NAA levels in patients with AD compared with age-matched normal subjects [28, 29]. Many previous studies did not find differences in hippocampal NAA in patients with depression compared with healthy subjects [30–32]. Although Venkatraman et al.

Table 2 Correlations between age, clinical, and spectroscopic data in patients with AD

		Age in years	GDS	MoCA
Hippo NAA	Pearson correlation	.184	−.019	.710
	Significance	.438	.937	.000
Hippo Cr.	Pearson correlation	−.351	−.319	.095
	Significance	.129	.170	.689
Hippo NAA/Cr	Pearson correlation	.359	.143	.599
	Significance	.120	.548	.005
Frontal NAA	Pearson correlation	.195	.060	.325
	Significance	.411	.802	.162
Frontal Cr.	Pearson correlation	−.031	.140	−.010
	Significance	.898	.556	.968
Frontal NAA/Cr	Pearson correlation	.204	.018	.317
	Significance	.388	.940	.173

Hippo: Hippocampus, *NAA*: *N*-acetylaspartate, *Cr.*: Creatine, *NAA/Cr*: *N*-acetylaspartate /creatine ratio, *GDS*: The Geriatric Depression Scale, *MoCA*: Montreal Cognitive Assessment Arabic version
Significance level is set at $P < 0.05$

Table 3 Correlations between age, clinical, and spectroscopic data in patients with cognitive impairment associated with depression

		Age in years	GDS	MoCA
Hippo NAA	Pearson correlation	−.051	−.598	−.219
	Significance	.817	.003	.315
Hippo Cr.	Pearson correlation	.352	−.187	.246
	Significance	.100	.392	.258
Hippo NAA/Cr	Pearson correlation	−.292	−.450	−.393
	Significance	.176	.031	.063
Frontal NAA	Pearson correlation	−.123	−.864	−.241
	Significance	.575	.000	.268
Frontal Cr.	Pearson correlation	.221	−.155	.079
	Significance	.312	.480	.718
Frontal NAA/Cr	Pearson correlation	−.223	−.816	−.289
	Significance	.306	.000	.181

Hippo: Hippocampus, *NAA*: *N*-acetylaspartate, *Cr.*: Creatine, *NAA/Cr*: *N*-acetylaspartate /creatine ratio, *GDS*: The Geriatric Depression Scale, *MoCA*: Montreal Cognitive Assessment Arabic version
Significance level is set at $P < 0.05$

Table 4 Correlations between age, clinical, and spectroscopic data in patients with mild cognitive impairment

		Age in years	GDS	MoCA
Hippo NAA	Pearson correlation	.265	.226	.568
	Significance	.341	.418	.027
Hippo Cr.	Pearson correlation	.307	.369	.411
	Significance	.266	.176	.128
Hippo NAA/Cr	Pearson correlation	.241	.151	.576
	Significance	.387	.592	.024
Frontal NAA	Pearson correlation	.164	.269	.235
	Significance	.560	.331	.399
Frontal Cr.	Pearson correlation	−.273	.175	.499
	Significance	.325	.532	.058
Frontal NAA/Cr	Pearson correlation	.262	.220	.112
	Significance	.346	.430	.690

Hippo: Hippocampus, *NAA*: *N*-acetylaspartate, *Cr.*: Creatine, *NAA/Cr*: *N*-acetylaspartate /creatine ratio, *GDS*: The Geriatric Depression Scale, *MoCA*: Montreal Cognitive Assessment Arabic version
Significance level is set at $P < 0.05$

Table 5 Correlations between age, clinical, and spectroscopic data in normal controls

		Age in years	GDS	MoCA
Hippo NAA	Pearson correlation	−.251	.033	−.102
	Significance	.366	.907	.717
Hippo Cr.	Pearson correlation	−.233	.068	.105
	Significance	.404	.810	.711
Hippo NAA/Cr	Pearson correlation	−.105	−.009	−.148
	Significance	.709	.975	.599
Frontal NAA	Pearson correlation	.123	−.293	.084
	Significance	.662	.289	.767
Frontal Cr.	Pearson correlation	.375	−.105	.297
	Significance	.168	.710	.282
Frontal NAA/Cr	Pearson correlation	−.115	−.138	−.094
	Significance	.684	.623	.738

Hippo: Hippocampus, *NAA*: *N*-acetylaspartate, *Cr.*: Creatine, *NAA/Cr*: *N*-acetylaspartate /creatine ratio, *GDS*: The Geriatric Depression Scale, *MoCA*: Montreal Cognitive Assessment Arabic version
Significance level is set at $P < 0.05$

[33] reported an increased left medial temporal lobe NAA in late-life depression, without any change in the right one.

It was reported that hippocampal NAA/Cr ratio decreased significantly in AD patients, but not in patients with MCI, compared with healthy control [27]. In other studies, the hippocampal NAA/Cr ratio was decreased in patients with AD [25, 27] and MCI compared to healthy subjects [15, 24, 29]. A lower NAA/Cr ratio was reported in the left hippocampus in AD and MCI patients [15, 34], and both hippocampi in AD patients [35] compared with healthy subjects.

In patients with major depressive disorder, the hippocampal NAA/Cr ratio did not differ from the control group [31]. However, in patients with post-stroke depression, the ratio decreased in both hippocampi [36], it also decreased in the left hippocampus in patients with first-episode major depressive disorder [37].

Hippocampal complex plays an important role in memory [38]. The initial pathological changes of AD first occur in the entorhinal cortex, then the hippocampus, and spread to other areas [39]. Structurally, hippocampal atrophy occurs early in Alzheimer's disease [40]. The most affected site in patients with MCI is the anterior hippocampal formation [41]. Moreover, marked cortical atrophy in the temporal region including the hippocampus had been reported in MCI patients [42]. Patients with depression had been reported to have hippocampal-dependent memory deficits that were exacerbated with the progression of depression [32]. Hypothalamic pituitary dysfunction occurs in patients with depression, which could affect the hippocampus with subsequent reduction of hippocampal volume [43]. Hippocampal volume changes might explain the metabolic abnormalities reported in previous studies.

Frontal NAA and NAA/Cr ratio were significantly lower in all patient groups than normal controls. A previous study reported lower frontal NAA in patients with AD than control subjects [44]. Similarly, the left prefrontal cortex NAA was decreased in patients with MCI compared to healthy control [45]. Other study reported no difference between patients with MCI, AD, and healthy control regarding the frontal NAA level [46].

Lower frontal NAA was reported in the frontal white matter in patients with late-life depression [47]. However, no significant difference was reported in patients with MDD in other studies [30, 48]. Olvera et al. [49], studied patients with MDD and found decreased NAA level in right medial prefrontal cortex, and a trend towards the decreased level in the left dorsolateral prefrontal gray matter and right dorsolateral prefrontal white matter.

For AD relative to healthy subjects, there was a strong tendency toward a statistically significant reduced NAA/Cr ratio in the left frontal region [50]. In patients with MCI, NAA/Cr ratio was mildly reduced but it dropped as MCI progressed to AD, in addition, a lower NAA/Cr could predict progression to AD [51, 52].

NAA/Cr was significantly lower in bilateral dorsolateral prefrontal white matter in MDD patients than healthy control [53, 54]. NAA/Cr was reduced also in the right prefrontal cortex in moderate MDD patients but it did not change in patients with mild MDD [48]; however, other study did not show significant changes on NAA/Cr ratio in bilateral ventral prefrontal white matter in patients with major depressive disorder [55]. In the study of Chen et al. (2009), patients with late-life major depressive disorder had a significantly lower NAA/Cr ratio in the frontal white matter than healthy subjects. A lower NAA/Cr ratio might indicate a neurodegenerative process in frontal white matter in late-life depression [47, 56].

The amygdala and the prefrontal cortex interconnected with many areas and play a major role in mood regulation [57]. Neuronal or glial loss in the frontal cortex and connectivity impairment between left frontal and limbic structure have been reported in late-life depression. These changes support theories of frontolimbic dysregulation in depression [33, 58, 59]. Accordingly, the metabolic changes reported in the hippocampus might be related to decreased frontal lobe inhibition of the amygdala.

Frontal lobe atrophic changes and hyperactivation had been reported in patients with MCI and AD [60–68]. However, frontal cortex hypoactivation was reported in MCI patients with prominent cognitive decline [65, 69–

71]. Changes in frontal lobe activation in patients with MCI might be a compensatory mechanism to maintain normal cognitive ability [72].

In the present study, hippocampal NAA and NAA/Cr ratio correlated positively with cognitive ability (as measured by MoCA) of patients with AD and patients with MCI. A previous study reported a significant correlation between NAA/Cr ratio and cognitive testing in Alzheimer's disease [29]. NAA/Cr ratio in the medial temporal lobe correlated with Mini-Mental State Examination (MMSE) and the cognitive part of the Alzheimer Disease Assessment Scale scores [73]. NAA/Cr ratio correlated also with verbal memory testing and general cognition [74]. Hippocampal metabolic concentration had strong correlations with MMSE and Revised Wechsler Memory Scale in patients with AD [23]. A strong relation was also reported between hippocampal NAA and cognitive tests, specifically the memory subtests of the Consortium to Establish a Registry for Alzheimer's Disease(CERAD) neuropsychological battery in patients with AD [26, 27]. Moreover, low gray matter NAA level was related to poor performance on recognition memory tests [75].

Levels of NAA in medial temporal lobe had been reported to have a positive association with verbal memory ability both in MCI and AD [26, 76]. A significant positive correlation was reported between hippocampal NAA, hippocampal NAA/Cr ratio, and MMSE in patients with MCI [26, 27]. Hippocampal NAA was clearly related to delayed recall of a learned word list and the delayed praxis subtests of the CERDA battery [26]. It had been reported that right and left hippocampal NAA levels correlated positively with subtests of Wechsler Memory Scale-Revised, and the correlation was more prominent for the left hippocampus than the right hippocampus, which might suggest the importance of the left hippocampus in episodic memory function, moreover, NAA levels might reflect memory performance of patients with MCI and AD [76].

In depressed patients, we observed a negative correlation between depression scores and hippocampal and frontal metabolite levels. A significant positive correlation was observed between Beck Depression Inventory (BDI) and hippocampal NAA but not with NAA/Cr ratio [31]. A significant correlation was reported also between the memory quotient and NAA/Cr ratio in bilateral dorsolateral prefrontal white matters. Correlations with statistical significance were determined between NAA/Cr in the left dorsolateral prefrontal white matter and visual regeneration, and associative learning. The right dorsolateral prefrontal white matter NAA/Cr ratio correlated significantly with personal experience, visual recognition, and associative learning in depressed patients [54].

The point of strength in this study is that, although, MCI and depression are common in the geriatric population and differentiation between them is a challenging issue. Our study showed that MRS could help in solving this challenging situation. Our study was limited by some factors including, the relatively small number of patients that might be explained by the few numbers of elderly patients who fulfilled the criteria of inclusion in the study, and MRS is a costly procedure. Also, a considerable number of patients could not tolerate or refused to do an MRI brain. Other brain areas, as cingulate gyrus, and occipital lobe, were not studied to avoid too long time of brain scan. We recommend further study that includes other brain areas which might improve the classification of cognitive impairment in geriatric population.

Conclusions

In conclusion, patients with MCI and AD had lower hippocampal NAA and NAA/Cr ratio than patients with depression and normal controls, while, frontal NAA and NAA/Cr ratio were lower in all patient's subgroups compared with normal control. Hippocampal NAA and NAA/Cr ratio might help to differentiate between MCI and cognitive impairment associated with depression.

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Authors' contributions
All authors contributed to the research idea. MAK, AMK, and AAA contributed to the data collection. MAK, AMK, and AAA analyzed the data and along with NMD who interpreted the data. Further, MAK and YMA completed the first draft of the article. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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Availability of data and materials
All datasets generated and analyzed during the current study are not publicly available but are available by reasonable request from the corresponding author.

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of College of Medicine, Prince Sattam Bin Abdulaziz University, KSA on 4 January 2016. A written consent was taken from all of the participants or their caregiver after explaining the details, benefits, and risks to them.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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