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Do multiple system atrophy and Parkinson's disease show distinct patterns of volumetric alterations across hippocampal subfields? An exploratory study

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Abstract

Objectives To investigate the volumetric alterations of hippocampal subfields and identify which subfields contribute to mild cognitive impairment (MCI) in multiple system atrophy (MSA) and Parkinson's disease (PD).

Methods Thirty MSA-MCI, 26 PD-MCI, and 30 healthy controls were administered cognitive assessment, along with hippocampal segmentation using FreeSurfer 6.0 after a 3-T MRI scan. Regression analyses were performed between the volumes of hippocampal subfields and cognitive variables.

Results Compared with healthy controls, the volume of the hippocampal fissure was enlarged in PD-MCI patients, while left Cornu Ammonis (CA2–CA3), bilateral molecular layer, bilateral hippocampus–amygdala transition area, right subiculum, right CA1, right presubiculum, right parasubiculum, and bilateral whole hippocampus were reduced in the MSA-MCI group. Moreover, volumetric reductions of the bilateral hippocampal tail, bilateral CA1, bilateral presubiculum, bilateral molecular layer, left CA2–CA3, left hippocampus–amygdala transition area, right parasubiculum, and bilateral whole hippocampus were found in MSA-MCI relative to the PD-MCI group. The volumes of the left CA2–CA3 ($B = -11.34$, $p = 0.006$) and left parasubiculum ($B = 4.63$, $p = 0.01$) were respectively correlated with language and abstraction functions. The volumes of the left fimbria ($B = 6.99$, $p = 0.002$) and left hippocampus–amygdala transition area ($B = 2.28$, $p = 0.009$) were correlated with visuospatial/executive function.

Conclusions The MSA-MCI patients showed more widespread impairment of hippocampal subfields compared with the PD-MCI group, involving trisynaptic loop and amygdala–hippocampus interactions. The alteration of CA, hippocampus–amygdala transition area, and fimbria still requires further comparison between the two patient groups.

Key Points

- *The atrophy patterns of hippocampal subfields differed between MSA and PD patients.*
- *MSA has widespread change in trisynaptic loop and amygdala–hippocampus interactions.*
- *The atrophy patterns may help to understand the differences of cognitive impairment in MSA and PD.*

Keywords Multiple system atrophy · Parkinson disease · Mild cognitive impairment · Hippocampus · Magnetic resonance imaging

Na Wang and Liang Zhang contributed equally to this work.

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Abbreviations

CA	Cornu Ammonis
H-Y	Hoehn and Yahr
HC	Healthy controls
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MPRAGE	Magnetization-prepared rapid acquisition gradient echo
MSA-MCI	MSA patients with MCI
MSA	Multiple system atrophy
PD-MCI	PD patients with MCI
PD-NCI	PD patients with no CI
PD	Parkinson's disease
PDD	Parkinson's disease dementia
UPDRS-III	The Unified Parkinson's Disease Rating Scale

Introduction

Multiple system atrophy (MSA) and Parkinson's disease (PD) are progressive neurodegenerative diseases with many overlapping symptoms, including cognitive impairment. Cognitive impairment has gained considerable attention, as numerous studies have shown that MSA and PD patients exhibit poor performance in memory, visuospatial ability, and verbal learning, even early in the disease. A number of studies have revealed that MSA patients have more severe cognitive impairment, shorter lifespans, and worse reactions to deep-brain stimulation procedures relative to PD patients [1, 2]. Moreover, cognitive impairment is heterogeneous, and MSA or PD patients with cognitive impairment could ultimately progress to dementia [3, 4]. Therefore, it is important to understand the underlying mechanism of cognitive impairment and distinguish the two patient groups for clinical intervention.

The hippocampal formation is known for the regulation of declarative and episodic memory and undergoes critical structural changes accompanying cognitive impairment in both MSA and PD patients [4–6]. Previous studies have shown that hippocampal volume was reduced more prominently in patients with mild cognitive impairment (MCI) or Parkinson's disease dementia (PDD) than in PD patients with no cognitive impairment (PD-NCI) [7, 8]. The volumetric reduction of the hippocampus could be a clue to the progression from MCI to PDD and predict the development of cognitive impairment [7, 9]. In MSA patients, pronounced atrophy in multiple brain regions, including the hippocampus, was reported in a volumetric structural MR study [6]. Pathological studies also demonstrated that glial cytoplasmic inclusions and neuronal cytoplasmic inclusions are confined to the hippocampus in MSA patients [10]. However, the hippocampus is composed of distinctive subfields, including the Cornu Ammonis (CA) subfields 1–4, the subiculum, the dentate gyrus, and the fimbria, which are interconnected, histologically heterogeneous, and functionally specialized [11]. This means that treating the hippocampus as a single entity may not adequately elucidate the mechanism of cognitive impairment in MSA and PD. Thus, researchers have become increasingly interested in exploring the specific changes in hippocampal subfields [12].

To date, a growing body of literature indicates that the volumetric reductions in several subfields of PD patients [4, 13–16]. Previous studies found that the decreased volume of the including the subiculum, CA1, and CA2–CA3 corresponds at least partly to pathological evidence showing greater α-synuclein-containing inclusion concentrations in these subregions in PD patients [13–16]. Foo and colleagues also compared the volumetric alteration of the hippocampal subfields between PD-MCI and PD-NCI groups at both baseline and follow-up over 18 months; they found that the volumes of several hippocampal subfields particularly in the CA sectors were decreased in PD-MCI patients, and the changes could serve as early biomarkers for the detection cognitive impairment [4]. Interestingly, a recent study showed that neuronal cytoplasmic inclusions were prominently deposited in the dentate gyrus and were associated with cognitive impairment in MSA patients [17]. These findings suggest that MSA and PD patients may possess distinct hippocampal subfield atrophy patterns. It is imperative to investigate the volumetric changes of hippocampal subfields in MSA or the atrophy patterns compared with PD; however, few MRI studies have been performed, and no conclusion has been made.

In the present study, we hypothesized that the atrophy patterns of hippocampal subfields would differ between MSA and PD patients and that these differences might contribute to cognitive impairment. We explored the volumetric alterations of bilateral hippocampal subfields in MSA patients with MCI (MSA-MCI) and the different atrophy patterns between MSA-MCI and PD patients with MCI (PD-MCI). We also investigated the association between hippocampal volume and cognitive rating scores.

Materials and methods

Subjects

The Institutional Review Board of China Medical University approved the present study. All subjects signed an informed consent form with a detailed description of the study prior to participation. All subjects were right-handed and had no contraindications for MRI. None of the participants had a history of neurological surgery. No history of neurological illness was reported in the healthy control participants.

Fifty-six patients (30 MSA-MCI and 26 PD-MCI patients) from the neurology outpatient clinic at the First Affiliated

Hospital of China Medical University were enrolled between February 2016 and August 2017. Thirty age-, gender-, and education-matched healthy controls were recruited from the community. MSA patients were diagnosed with "probable MSA" on the basis of the second consensus clinical criteria [18]. PD patients met the UK PD Society Brain Bank diagnostic criteria [19]. All patients were diagnosed after at least a 1-year follow-up to reconfirm the diagnosis by an advanced movement specialist.

Global cognitive function was measured with the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The components of the MoCA were extracted to assess the seven cognitive domains, including visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation function. Movement Disorders Society Task Force criteria were used to rate the MCI [20]. For the level I criteria, a MoCA score < 26 was defined as cognitive impairment. For the modified level II criteria, 1.5 SD below the normative values (healthy controls) was used as a cutoff. Patients who fulfilled the MDS criteria for PDD (MMSE ≤ 25, cognitive deficiency severe enough to impair daily life, and impairment in more than one cognitive domain) were excluded. Healthy controls showing cognitive decline based on a MoCA score < 26 or < 25 for secondary school–educated subjects (12 years of education) were excluded. Based on the Fazekas scale for the 3D fluid-attenuated inversion recovery sequence, patients with severe white matter hyperintensities were excluded. In addition, the Unified Parkinson's Disease Rating Scale (UPDRS-III) and Hoehn and Yahr (H-Y) stage were measured to rate the extent of movement impairment.

3D T1 image acquisition

Imaging data were obtained on a 3.0-T MRI scanner (Magnetom Verio, Siemens Healthineers) equipped with a 32-channel head coil in the Department of Radiology. A high-resolution 3D sagittal magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted sequence with the following parameters was performed: repetition time = 5000 ms, echo time = 2960 ms, flip angle = 12°, field of view = 256 × 256 mm^2, matrix size = 256 × 256, slice thickness = 1 mm, voxel size = 1.0 × 1.0 × 1.0 mm.

Imaging data preprocessing

The structural T1-weighted image data were processed with the FreeSurfer 6.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The detailed process of hippocampal subfield volumetric segmentation has been described previously [21]. First, multiple steps were performed to reconstruct the cortical and subcortical regions, which included removal of nonbrain tissue, automatic Talairach transformation, intensity normalization, segmentation of the volume of white matter and gray matter in subcortical regions, tessellation of the gray matter and white matter boundaries, automated topology correction, and surface deformation to optimally place the gray/white and gray/cerebrospinal fluid boundaries. After the above processing, the results of cortical and subcortical structural segmentation were inspected and manually corrected if necessary for each subject. Subsequently, the Bayesian inference method with the latest version of the atlas algorithm of hippocampus formations was used to subdivide the subfields [22]. A total of 13 subfields were divided for each side of the hippocampus: the alveus, parasubiculum, presubiculum, subiculum, CA1, CA2–CA3, CA4, granule cell layer of the dentate gyrus, hippocampus–amygdala transition area, fimbria, molecular layer, hippocampal fissure, and hippocampal tail (Fig. 1). Then, the total intracranial volume and whole hippocampal volume for each subject were estimated from subcortical region segmentation using FreeSurfer software. Finally, the whole cerebral gray matter volume was preprocessed and analyzed (Supplementary methods).

Statistical analysis

Statistical analyses were performed using SPSS 21.0 software (SPSS Inc. IBM). The results were considered significant at a threshold of $p < 0.05$. The chi-square test, the two-sample t test, the Mann–Whitney test, the Kruskal–Wallis test, and the Dunn multiple comparisons test were performed for demographic variables and clinical data among the MSA-MCI, PD-MCI, and healthy controls. To investigate the impact of cognitive variables and hippocampal subfield volumes, stepwise multiple regression models, using hippocampal subfield volumes as independent variables and the scores of seven different cognitive domains that extract from the MoCA as dependent variables (controlling for age, gender and total intracranial volume), were carried out among the three groups. The variance inflation factor and Durbin–Waston statistic were conducted respectively to detect the presence of the multicollinearity between variables and autocorrelation in the regression analysis.

Results

Demographic and clinical data

There were no significant differences in demographic and clinical data between groups. Both patient groups had significantly lower cognitive scores compared with the healthy controls, while no significant difference was found between

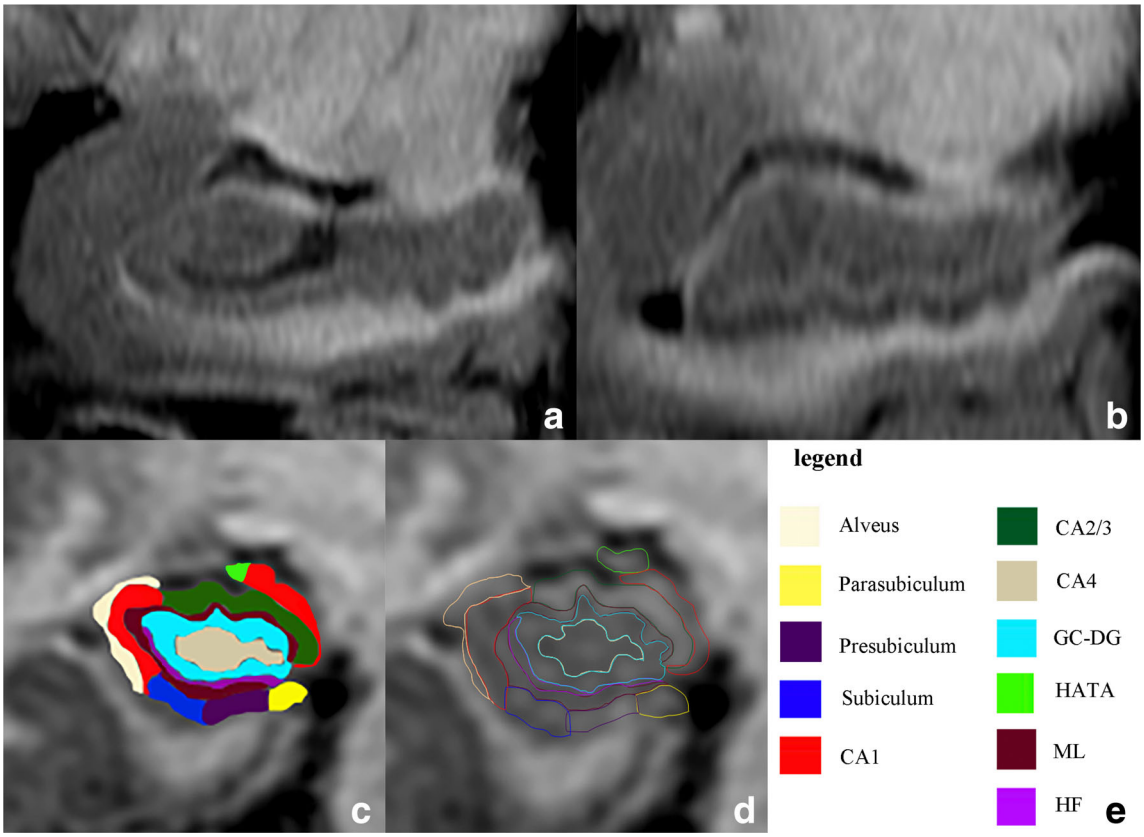

Fig. 1 Hippocampal subfields in sagittal and coronal views of a healthy control subject. **a**, **b** Different slices of the hippocampal anatomy ordered from anterior to posterior in sagittal view. **c**, **d** Hippocampal subfield full segmentation and segmentation outline in coronal view at the same slice. **e** Legend of the hippocampal subfields in **c** and **d**. CA, Cornu Ammonis; HF, hippocampal fissure; ML, molecular layer; GC-DG, granule cell layer of dentate gyrus; HATA, hippocampus–amygdala transition area

patient groups. In addition, relative to the PD-MCI patients and healthy controls, MSA-MCI patients had significantly lower scores in delayed recall and orientation function (Table 1).

Hippocampal subfield volumes of MSA-MCI and PD-MCI

Compared with healthy controls, the volume of the bilateral hippocampal fissure was increased in PD-MCI patients, while the volumes of the left CA2–CA3, bilateral molecular layer, bilateral hippocampus–amygdala transition area, right subiculum, right CA1, right presubiculum, right parasubiculum, and bilateral whole hippocampus were reduced in the MSA-MCI group. Moreover, volumetric reductions of the bilateral hippocampal tail, bilateral CA1, bilateral presubiculum, bilateral molecular layer, left CA2–CA3, left hippocampus–amygdala transition area, right parasubiculum, and bilateral whole hippocampus were found in MSA-MCI relative to the PD-MCI group (Table 2). No brain regions with significant cerebral gray matter volume differences were found among the three groups.

Association between MoCA scores and hippocampal subfield volumes

The results of multiple regression analysis showed that the volumes of the left hippocampal tail (left, $B = -33.95$, SE = 12.35, $p = 0.008$, VIF = 1.24) and left parasubiculum ($B = 4.63$, SE = 1.76, $p = 0.01$, VIF = 1.67) were correlated with abstraction function. The volumes of the left CA2–CA3 ($B = -11.34$, SE = 3.98, $p = 0.006$, VIF = 1.33) were correlated with language function. The volumes of the left fimbria ($B = 6.99$, SE = 2.22, $p = 0.002$, VIF = 1.67) and left hippocampus–amygdala transition area ($B = 2.28$, SE = 0.85, $p = 0.009$, VIF = 1.67) were correlated with visuospatial/executive function.

Discussion

The present study quantitatively compared the changes in hippocampal subfield volumes in MSA-MCI, PD-MCI, and healthy controls. Our findings showed that the extent of atrophy in the hippocampal subfield differed among the three groups: MSA-MCI > PD-MCI > healthy controls. Moreover,

Table 1 Demographic and clinical characteristics

Characteristics (mean ± SD)	MSA-MCI ($n = 30$)	PD-MCI ($n = 26$)	HC ($n = 30$)	Analysis	
				$T/U/\chi^2$	p
Age (years)	63.57 ± 8.23	60.88 ± 8.33	62.67 ± 6.06	1.48	0.48
Gender (male/female)	17/13	10/16	17/13	2.41	0.30
Education	9 ± 3.5	9.85 ± 3.22	10.7 ± 2.12	5.24	0.07
Disease duration	4.07 ± 1.47	5.98 ± 3.58	–	285	0.082
UPDRS-III score	32.07 ± 15.87	38.73 ± 16.79	–	− 1.53	0.13
Hoehn and Yahr	2.3 ± 1.1	2.20 ± 0.69	–	362.5	0.83
MoCA score	20.67 ± 3.27*	21.34 ± 4.05*	26.53 ± 1.22	50.52	0.000*
Visuospatial/executive	2.89 ± 1.37*	2.85 ± 1.31*	4.53 ± 0.57	30.79	0.000*
Naming	2.76 ± 0.42*	2.69 ± 0.60*	3.00 ± 0.00	7.93	0.019*
Attention	5.26 ± 0.81*	5.06 ± 1.24*	5.73 ± 0.58	7.06	0.029*
Language	1.86 ± 0.77*	2.00 ± 0.63*	2.63 ± 0.49	17.14	0.000*
Abstraction	0.85 ± 0.77*	1.00 ± 0.97	1.43 ± 0.63	7.69	0.021*
Delayed recall	1.07 ± 1.05*/**	2.06 ± 1.69*	3.20 ± 0.99	30.91	0.000*
Orientation	5.64 ± 0.73*/**	6.00 ± 0.00	5.97 ± 0.18	7.78	0.02*

MSA multiple system atrophy, *PD* Parkinson's disease, *HC* healthy controls, *UPDRS-III* Unified Parkinson's Disease Rating Scale, *MoCA* Montreal Cognitive Assessment. *Statistically significant between patient group and HC. **Statistically significant between two patient groups

abstraction function, language function, and visuospatial/executive function were associated with the different volumes of hippocampal subfields, which may aid in better understanding of cognitive impairment.

From a whole hippocampus perspective, our findings were consistent with a previous quantitative MRI study, showing that hippocampal volume was reduced in MSA with respect to PD and healthy controls, while no volumetric difference was found between the PD and healthy controls [23]. However, the changes of the hippocampus in cognitive impairment have not been well identified in both MSA and PD. Limited studies have reported volume changes in hippocampal subfields in MSA. As a component of the limbic system, the hippocampus is one of the vulnerable regions in the pathology of MSA [24]. A number of studies have revealed that marked deposition of neuronal cytoplasmic inclusions in the limbic system is associated with cognitive impairment in MSA patients [25, 26]. Some studies suggested that the extent of accumulation of Lewy bodies and Lewy neuritis in the hippocampus was associated with the severity of cognitive impairment in PD, while others found no relationship between α-synuclein-containing inclusions and cognitive impairment [27, 28]. Previous studies also found that the volume of specific subfields within the hippocampus was associated with cognitive scores in PD patients [4, 13, 14]. Hence, the present study found that the changes of whole hippocampus volume may illustrate the importance of investigating of the hippocampus subfields between two patient groups.

The atrophy patterns of the hippocampal subfields differed between the MSA-MCI and PD-MCI groups, with more widespread impairment in MSA-MCI patients in the present study. The volume of the CA1 and CA2–CA3 were reduced in the MSA-MCI group compared with healthy controls and the PD-MCI group, while the volume of hippocampal fissure was increased in PD-MCI patients relative to healthy controls. These results were at least partially in accord with a former MSA pathological study, which showed that neuronal cytoplasmic inclusions were initially deposited in CA subfields (sectors 2, 1) in the hippocampus and then progressed to the dentate gyrus, subiculum, CA3, and CA4 [24]. A growing number of neuropathology and imaging studies have reported that the CA1 subfield is the earliest and most significantly impaired subfield in Alzheimer's disease, and it could predict cognitive impairment in healthy controls or MCI patients [29]. Thus, the CA1 sector may be the earliest volumetric reduction subfield of the hippocampus in MSA-MCI patients. The hippocampal fissure is considered a vestigial space, located between the molecular layer of CA and the dentate gyrus [22]. Consistent with previous AD and MCI research, the enlargement of the hippocampal fissure may represent the atrophy of the medial temporal lobe [30]. Therefore, we extended the existing results by demonstrating that the increased volume of the hippocampal fissure could be an indicator of atrophy of the molecular layer of CA and the dentate gyrus. A previous study also suggested that volumetric reduction in CA1 was involved in PD-MCI, and the volume of the dentate gyrus could predict the progression from PD-NCI to PD-MCI [4]. However, the comparisons lacked control subjects, which could involve the changes

Table 2 Hippocampal subfield volumes of MSA-MCI, PD-MCI, and HC

Subfields	MSA-MCI ($n = 30$)	PD-MCI ($n = 26$)	HC-MCI ($n = 30$)	D-W	F	p	MSA-MCI vs HC				IPD-MCI vs HC				MSA-MCI vs IPD-MCI			
							B	SE	*p*	VIF	*B*	SE	*p*	VIF	*B*	SE	*p*	VIF
Left																		
HT	489.13 ± 74.84	536.74 ± 96.80	512.61 ± 64.45	1.84	4.36	0.03*	− 44.8	21.1	NS	1.37	25.3	24.5	NS	1.27	− 70.1	24.29	0.00**	1.81
Sub	405.71 ± 57.99	443.38 ± 51.26	422.58 ± 46.28	1.99	6.99	0.00*	− 22.4	12.9	NS	1.27	8.17	15.5	NS	1.24	− 30.6	15.34	NS	1.77
CA1	560.85 ± 81.27	618.74 ± 80.47	486.91 ± 56.60	2.15	7.82	0.00*	− 39.2	17.8	NS	1.29	13.4	21.1	NS	1.24	− 52.6	21.1	0.015**	1.81
HF	158.34 ± 32.15	169.19 ± 33.72	147.10 ± 19.38	2.48	6.89	0.00*	8.98	6.24	NS	1.19	24.3	7.57	0.00**	1.21	− 15.4	7.67	NS	1.79
Pre	300.29 ± 46.90	336.32 ± 58.15	325.53 ± 27.15	1.47	12.4	0.00*	− 19.1	11.5	NS	1.85	10.7	12.9	NS	1.61	− 29.8	11.2	0.01**	1.77
Para	64.50 ± 15.69	69.69 ± 18.37	68.70 ± 6.71	1.71	9.37	0.00*	− 4.44	3.21	NS	1.47	− 1.11	3.63	NS	1.29	− 3.33	3.54	NS	1.79
ML	505.52 ± 71.31	556.62 ± 68.98	536.50 ± 47.48	1.96	10.8	0.00*	− 40.7	14.9	0.00**	1.27	4.29	17.8	NS	1.24	− 45.0	17.7	0.013**	1.77
GC-DG	262.84 ± 43.77	287.73 ± 39.50	278.62 ± 29.46	2.11	8.76	0.00*	− 20.1	9.24	NS	1.27	− 0.58	10.9	NS	1.24	− 19.5	10.9	NS	1.77
CA2–CA3	177.37 ± 30.29	192.87 ± 22.84	186.67 ± 21.82	2.21	7.74	0.00*	− 23.9	6.9	0.00**	1.65	− 5.8	7.69	NS	1.42	− 18.1	7.17	0.014**	1.78
CA4	228.75 ± 36.43	248.99 ± 31.80	240.84 ± 23.82	2.21	7.74	0.00*	− 15.9	7.66	NS	1.27	0.54	9.12	NS	1.24	− 16.5	9.05	NS	1.77
Fimbria	66.73 ± 27.59	85.21 ± 24.08	81.10 ± 13.40	1.83	6.85	0.00*	− 7.12	6.61	NS	1.91	4.02	7.29	NS	1.61	− 11.1	6.38	NS	1.78
HATA	51.64 ± 10.48	60.89 ± 11.18	57.79 ± 5.57	2.29	11.4	0.00*	− 7.95	2.62	0.00**	2.05	2.75	2.86	NS	1.69	− 10.7	2.45	0.00**	1.78
W-H	3223.3 ± 434.7	3437.2 ± 416.5	3297.8 ± 263.3	1.97	9.99	0.00*	− 251.8	91.5	0.01**	1.27	59.1	108.9	NS	1.24	− 310.9	108.1	0.00**	1.77
Right																		
HT	546.82 ± 63.03	594.79 ± 93.61	561.89 ± 62.60	1.54	5.12	0.01*	− 46.2	19.4	NS	1.46	19.5	21.9	NS	1.29	− 65.7	21.5	0.00**	1.79
Sub	413.96 ± 54.26	452.27 ± 59.05	437.21 ± 38.73	1.46	7.26	0.00*	− 46.7	14.0	0.00**	1.65	2.19	15.7	NS	1.42	− 48.9	14.6	0.00**	1.78
CA1	582.10 ± 80.46	644.96 ± 79.71	622.60 ± 53.70	2.18	10.5	0.00*	− 61.9	17.8	0.00**	1.27	16.1	21.1	NS	1.24	− 78.1	20.9	0.00**	1.77
HF	167.46 ± 39.68	184.98 ± 44.71	157.38 ± 25.83	2.26	7.49	0.00*	5.61	8.6	NS	1.19	41.3	10.4	0.00**	1.19	− 35.7	10.5	NS	1.77
Pre	290.86 ± 40.26	327.96 ± 60.03	317.03 ± 33.39	2.13	11.7	0.00*	− 36.8	10.1	0.00**	1.27	4.54	12.1	NS	1.24	− 41.4	11.9	0.00**	1.77
Para	55.83 ± 10.02	64.62 ± 16.03	61.21 ± 9.98	2.24	8.45	0.00*	− 7.67	3.01	0.01**	1.27	3.08	3.58	NS	1.24	− 10.8	3.56	0.00**	1.77
ML	521.94 ± 70.50	570.27 ± 68.14	559.19 ± 39.92	1.68	7.97	0.00*	− 67.6	16.8	0.00**	1.65	− 12.4	18.7	NS	1.42	− 55.2	17.4	0.00**	1.78
GC-DG	274.96 ± 44.32	292.67 ± 35.23	284.36 ± 22.12	1.86	4.76	0.01*	− 25.6	10.3	NS	1.65	− 8.34	11.5	NS	1.42	− 16.8	10.7	NS	1.78
CA2–CA3	195.28 ± 37.74	201.99 ± 25.47	201.74 ± 22.73	1.99	2.55	0.05	− 20.69	9.05	NS	1.65	− 10.7	10.1	NS	1.42	− 10.6	9.39	NS	1.78
CA4	232.95 ± 59.14	254.27 ± 30.28	245.79 ± 19.27	1.85	3.33	0.025*	− 20.9	11.2	NS	1.27	1.06	13.34	NS	1.24	− 21.9	13.2	NS	1.78
Fimbria	62.16 ± 22.93	75.85 ± 19.79	72.32 ± 17.53	1.72	5.93	0.01*	− 8.68	5.2	NS	1.19	− 0.25	6.26	NS	1.19	− 8.43	6.34	NS	1.77
HATA	50.95 ± 10.41	58.08 ± 9.83	56.93 ± 6.60	1.78	6.38	0.00*	− 6.16	2.42	0.01**	1.39	0.12	2.75	NS	1.24	− 6.29	2.83	NS	1.91
W-H	3235.5 ± 418.3	3537.7 ± 418.3	3420.3 ± 232.4	1.58	8.65	0.00*	− 377.2	98.6	0.00**	1.65	− 20.7	109.9	NS	1.42	− 356.5	102.4	0.001**	1.78

Values expressed as mean ± SD. *MSA-MCI* multiple system atrophy with mild cognitive impairment, *PD-MCI* Parkinson's disease with cognitive impairment, *HC* healthy controls, *HT*, hippocampal tail, *Sub* subiculum, *CA* Cornu Ammonis, *HF* hippocampal fissure, *Pre* presubiculum, *Para* parasubiculum, *ML* molecular layer, *GC-DG* granule cell layer of dentate gyrus, *HATA* hippocampus–amygdala transition area, *W-H*, whole hippocampus, *D-W* Durbin-Waston, *VIF* variance inflation factor, *Statistical significance, $p < 0.05$; **Statistical significance, $p < 0.017$ (Bonferroni correction), *NS* non-significant

in physiological aging. In addition, other pathological studies demonstrated that Lewy body densities in the entorhinal and cingulate cortex could predict PD-MCI, while greater deposits of α-synuclein-containing inclusions in hippocampal subfields, including the CA and dentate gyrus, were only observed in PDD patients [25, 31]. Thus, the volumetric reductions of the CA sector may be more severe and earlier in MSA-MCI, which could occur in PD patients progressively. The CA1 sector sends projections to many brain regions, including the subiculum, entorhinal cortex, Papez circuit, and medial septum, which is a major hippocampal output avenue in the trisynaptic path and the most essential component of temporal and memory processing and encoding of spatial information [32]. The CA2–CA3 subfield is pivotal in the formation of new memories and may responsible for higher level cognitive functions [33–35]. The molecular layer consists of two parts, one from the subiculum and the other from the CA sectors, which is a new segmentation subfield in FreeSurfer 6.0 [22]. A previous nonhuman primate study indicated that the molecular layer is involved in visuospatial function [36]. The molecular layer sector may correspond well with the CA and subiculum sectors in pathological results. The present study found that the left CA2–CA3 was correlated with language function, i.e., a verbal memory task. Considering its role in memory function, the volumetric changes of CA and molecular layer may provide a better understanding of more severe cognitive impairment in MSA patients.

In addition, the volumes of the subiculum, presubiculum, parasubiculum, and hippocampus–amygdala transition area were reduced in the MSA-MCI group compared with HC and PD-MCI group in our study. The subicular complex is composed of the subiculum, presubiculum, and parasubiculum, which is responsible for the regulation of information about space, movement, and memory as a relay station between the hippocampus and the cortical and subcortical areas [32, 36]. The hippocampus–amygdala transition area is closely connected with the amygdala, which lies in the medial region of the hippocampus and is superior to the other subfields [22]. The fimbria, a white matter structure, forms part of the fornix and projects to the amygdala [22]. Previous studies indicated that these two subfields are related to visuospatial function and object discrimination though the mediation of amygdala–hippocampus interactions [4]. Therefore, we speculated that the atrophy pattern of the MSA-MCI mainly involved the output component of the hippocampus, including the trisynaptic loop and amygdala–hippocampus interactions. Moreover, the volumes of the left parasubiculum were correlated with abstraction function, while the volumes of the left fimbria and left hippocampus–amygdala transition area were correlated with visuospatial/executive function, which suggests that hippocampal subfields may contribute to the MCI and could be a key target to detect MCI in the MSA-MCI patients.

In recent studies, the results regarding specific hippocampal subfield atrophy patterns were heterogeneous. A previous study showed that the volumes of the fimbria and the hippocampus–amygdala transition area were prominently decreased in PD-MCI patients compared with PD patients [4]. Several subfields involved in the pathology in that study, including the dentate gyrus, subiculum, CA3, and CA4, did not show differences in the patient groups in our study [13, 14, 24, 37]. The above controversial results may be attributed to several reasons. First, variability of hippocampus segmentation approaches could account for the conflicting results. Second, in contrast to the participants in other studies, the duration was relatively short in the present study, which may be too early to involve pathological alternation in several subfields. Moreover, the volume of the hippocampal tail was decreased in MSA-MCI relative to the PD-MCI group, which was also correlated with abstraction function in the present study. The hippocampal tail, labeled as "umbrella," was identified the first coronal slice (anterior to posterior) where the fornix is fully connected to the hippocampus, which may share the function with the fimbria and deserve more investigation [22].

There are several limitations to our study. First, although the segmentation package of hippocampal subfields has been applied in many MRI studies, the accuracy of the new FreeSurfer still needs more validation. Second, it is imperative to note a well-known problem in hippocampal subfield segmentation, namely that MPRAGE sequences (a 1-mm voxel size) other than the high-resolution T2 data were used in the present study, which lack precise subfield boundaries and are processed purely inferentially [4, 22]. Thus, the volumetric changes should be interpreted with caution. Nevertheless, highly useful information on hippocampal subfields as well as the whole structure was obtained. The distinct atrophy pattern may allow us to interpret the differences in MCI underlying the two patient groups. Third, the present exploratory study had a relatively small sample, which needs further research to replicate the results. Finally, the memory functions that are classically related to hippocampal atrophy and more declarative memory tests need to be assessed.

In conclusion, hippocampal subfields may play a critical role i1n MCI in both MSA and PD patients. The MSA-MCI group showed more widespread and severe impairment than the PD-MCI group, involving trisynaptic loop and amygdala–hippocampus interactions, which may help to improve our understanding of the differences of cognitive impairment in MSA and PD. In addition, the CA1 sector may be the earliest-impaired subfield in the hippocampus of MSA-MCI patients. The alteration of hippocampal subfields still requires further comparison between the two patient groups.

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Methodology
- cross-sectional study
- performed at one institution

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