Precise Alterations in Hippocampal Neural Deterioration and Neural Correlates of Visual Short-Term Memory in Individuals with Amnestic Mild Cognitive Impairment

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Abstract

Purpose: Atrophy of the hippocampus is an early biomarker of Alzheimer's disease (AD) and a main contributor to the patients' mnemonic degeneration. While previous research has mostly focused on how hippocampal atrophy impaired long-term memory performance, its relation to short-term memory impairment, which was also found among patients with AD, remains largely uninvestigated. Filling this gap, the current study examined how atrophy in the hippocampus and its subfields may have influenced visual short-term memory (VSTM) in patients with amnestic mild cognitive impairment (aMCI), a common precursor of AD.

Methods: Fifty-eight aMCI patients and 69 healthy controls (HC) matched in age were included in the current study. VSTM was assessed using an adapted change detection task with a memory load of 2 or 4 items. Hippocampal subfields were automatically segmented in T1-weighted image using FreeSurfer and were manually inspected for errors. Volumes of the subfields were extracted and compared between aMCI and HC subjects using ANCOVA with age, gender and education as covariates. Furthermore, we also examined the partial correlation between VSTM performances and hippocampal subfield volumes with age, gender and education as covariates.

Results: Compared to HC subjects, aMCI subjects had lower response accuracy (ACC) and lower memory capacity under both load conditions and had longer reaction time (RT) in the 2-load condition. Left hippocampus volume was significantly smaller in aMCI and was positively correlated with ACC and capacity in HC but not in aMCI. Among the hippocampal subfields, left hippocampal tail, left molecular layer, left granule cell molecular layer of the dentate gyrus (GC-ML-DG), left CA4, right hippocampal fissure, bilateral subiculum, bilateral presubiculum, bilateral fimbria, were significantly smaller in aMCI compared to HC. Volumes of the left subiculum, left molecular layer, left GC-ML-DG and left CA4 were positively correlated with ACC and capacity in HC but not in aMCI. Bilateral fimbria volume was negatively correlated with RT under the 2-load condition in HC but not in aMCI.

Conclusion: The results of this study suggested that hippocampal atrophy, especially in subfields related to information input and output (e.g. molecular layer, GC-ML-DG, subiculum), may have contributed to VSTM impairment in aMCI by disrupting hippocampal-cortical communications. This finding adds to increasing evidence of hippocampal engagement in short-term memory processes and points to VSTM impairment as a potential neuropsychological indicator for MCI and AD.

Keywords: hippocampus, visual short-term memory, atrophy, mild cognitive impairment, subfield

Introduction

Amnestic Mild Cognitive Impairment (aMCI) is a transitional stage between normal age-related cognitive decline and more severe forms of cognitive impairment, such as Alzheimer's disease (AD) (Li et al., 2015; Petersen et al., 2006). Individuals diagnosed with aMCI often experience memory problems greater than what is expected for their age but do not meet the criteria for dementia. While aMCI can affect various cognitive domains, one of the most prominent and early signs is in the domain of visual short-term memory (VSTM), which has been recently flagged as early marker of disease (Kirova et al., 2015; Norton et al., 2020; Parra et al., 2010; Parra et al., 2011; Zokaei et al., 2020). In this introduction, we will delve into the intricate landscape of aMCI, focusing on precise alterations in hippocampal neural deterioration and exploring the neural correlates of VSTM deficits in individuals with aMCI.

Aging is an inevitable part of the human experience, and with it comes changes in cognitive function. It is well-established that as individuals grow older, they may experience subtle declines in various cognitive domains, including memory, attention, and executive function (Yang et al., 2022). These age-related cognitive changes are considered a normal part of the aging process. However, there exists a critical distinction between the typical cognitive changes associated with aging and cognitive impairment indicative of neurological disorders, such as aMCI. aMCI is a condition that lies on the continuum between healthy aging and dementia, such as Alzheimer's disease. The defining characteristic of aMCI is the presence of noticeable memory problems that are greater than expected for an individual's age but do not yet interfere significantly with daily functioning. This cognitive state represents a critical juncture because individuals with aMCI are at an increased risk of progressing to Alzheimer's disease or other forms of dementia, although not all individuals with aMCI will develop dementia. One of the intriguing aspects of aMCI is the selective impairment of specific cognitive domains, such as VSTM. VSTM plays a fundamental role in our everyday lives (A. D. Baddeley et al., 2011). It is responsible for temporarily holding and manipulating visual information, allowing us to perform a wide range of cognitive tasks, such as recognizing faces, reading, and navigating our environment. Researches have consistently shown that individuals with aMCI often exhibit deficits in VSTM tasks (Kirova et al., 2015; Parra et al., 2010; Parra et al., 2011; Zokaei et al., 2020). These deficits manifest as reduced accuracy and increased susceptibility to interference when holding visual information for brief periods. Understanding the neural underpinnings of these VSTM deficits is essential for both diagnosis and intervention.

The hippocampus, a seahorse-shaped structure nestled deep within the brain's medial temporal lobe, has long been recognized as a critical player in memory processes (A. Baddeley et al., 2011; von Allmen et al., 2013). It is particularly associated with episodic memory, which involves the encoding, storage, and retrieval of personal experiences and events (Aggleton et al., 2022). Research has consistently shown that

damage or dysfunction in the hippocampus can lead to profound memory deficits. Studies utilizing neuroimaging techniques, such as magnetic resonance imaging (MRI), have revealed that individuals with aMCI often exhibit structural alterations in the hippocampus (Zhang et al., 2021). These changes typically manifest as hippocampal atrophy, with the volume of the hippocampus decreasing over time. The extent and progression of atrophy can vary among individuals, but it is a hallmark feature associated with the condition. Hippocampal atrophy in aMCI is not merely a structural phenomenon; it has profound functional implications. The hippocampus is a hub for memory-related processes, and its deterioration disrupts the intricate neural networks responsible for memory encoding and retrieval. This disruption is believed to contribute significantly to the memory deficits observed in individuals with aMCI. Beyond macrostructural changes visible in MRI scans, microstructural alterations in the hippocampus have also been investigated (De Flores et al., 2015; Huang et al., 2022). These alterations involve changes at the cellular and molecular levels, including synaptic dysfunction, neuroinflammation, and the accumulation of abnormal protein aggregates. The precise mechanisms underlying these alterations are still the subject of ongoing research, but they provide valuable insights into the neural deterioration associated with aMCI.

While the hippocampus is traditionally associated with long-term episodic memory, emerging evidence suggests its involvement in short-term memory processes, including VSTM. Studies using neuroimaging techniques have demonstrated increased hippocampal activation during VSTM tasks in healthy individuals (Boran et al., 2022; Borders et al., 2022; Liu et al., 2020; Yonelinas, 2013). In contrast, individuals with aMCI may exhibit altered patterns of hippocampal activation during VSTM tasks, reflecting the specific neural changes associated with their condition.

Understanding the precise alterations in hippocampal neural deterioration and the neural correlates of VSTM deficits in individuals with aMCI is of paramount importance. It has implications for early diagnosis, intervention, and the development of targeted therapies aimed at preserving cognitive function in this vulnerable population. Additionally, this research may shed light on the broader mechanisms underlying cognitive decline in aging and neurodegenerative diseases.

In the following sections of this study, we will delve deeper into the methods employed to investigate these neural alterations, present the results of our research, and discuss the implications of our findings. By elucidating the intricate relationship between hippocampal deterioration and VSTM deficits, we aim to contribute to the growing body of knowledge surrounding aMCI and provide valuable insights into potential avenues for therapeutic intervention and cognitive rehabilitation.

Method

2.1 Diagnostic assessment

The participants in the current study were recruited from Tongji Hospital in Shanghai, China. aMCI was designated by a neurologist from the department of Neurology and the Department of Memory Clinic of Shanghai Tongji Hospital based on the 'MCI-criteria for the clinical and cognitive syndrome'(Albert et al., 2011). Specifically, the criteria included: (a) The participants and their caregiver had complaint of memory/cognitive decline; (b) Mini-Mental State Examination (MMSE) or MoCA scores met criteria adjusted by education; (c) Clinical Dementia Rating Scale (CDR) of 0.5; (d) met any of the following three criteria: (1) at least two performances within a cognitive domain fell below the established cutoff (> 1SD); (2) at least two cognitive domains were impaired (> 1SD); (3) had more than one function described in instrumental activities of daily living (IADL-14) scored of 1 or more.

2.2 Participants

The current study included fifty-eight aMCI subjects and sixty-nine normal elderly people (NC) (For demographic characteristic, please see Supplementary Table 1). Informed consent was obtained from all participants and the study was approved by IRB board of Tongji Hospital with ethical and safety guidelines consistent with the Declaration of Helsinki.

2.3 VSTM task

VSTM was measured by an adopted change detection task (Fig. 1) (Vogel et al., 2004). Participants were asked to indentify whether the test array was either identical to the memory array or differed by one color. The presentation of test array would last until participants gave their response. Accuracy (ACC) and mean reaction time (RT) were calculated for each participants, and capacity was represented by Cowan's K coefficient (load x (hit rate -false alarm rate)) (Cowan, 2001).

<Figure 1>

2.4 MRI Acquisition

Image data were collected from two sites: East China Normal University with Siemens Prisma machine (81 participants, 38 aMCI participants and 43 NC participants) and Tongji Hospital using Siemens Verio machine (46 participants, 20 aMCI participants and 26 NC participants). To delineate the influence of machine, collecting site would be use as covariate in imaging analysis.

Collecting parameters of these two sites were same in TE (2.98ms), TR (2530ms), FOV (256mm x 256mm), and acquisition matrix (256 x 256), but different in the reconstruction voxel size (for East China Normal University: 0.5 x 0.5 x 1.0 mm^3. For Tongji Hospital: 1.0 x 1.0 x 1.0$mm^{3)}$.

Then the segmentation of hippocampal subfield was conducted based a delicate template of hippocampal subfileds with freesurfer software. We focused on the

parasubiculum, presubiculum, subiculum, CA1, CA3 (or CA2/3), CA4, granule cell molecular layer of the dentate gyrus (GC-ML-DG), hippocampal-amygdaloid transition region (HATA), fimbria, molecular layer, hippocampal fissure and hippocampal tail. After finishing the segmentation, the goodness of the segmentation was manually checked and those with bad segmentation were included from the study.

2.5 Statistical methods

Repeated measures ANOVA was used to test the ACC and the RT of the VSTM tasks ad one-way analysis of covariance (ANCOVA) was used to compared participants' capacity of VSTM. Age, gender, education and collecting site were used as covariates and Bonferroni method was applied for multiple comparison correction. One-way analyses of covariance (ANCOVAs) were also used for comparison of gray matter volumes of hippocampal subfields with age, gender, education, site and TIV as covariates, and FDR method were used for multiple comparison correction. Partial correlation was used to test the correlation between the volume of hippocampal subfields showing significant between-group difference and performance of VSTM task with age, gender, education, site and TIV as covariates.

Result

3.1 demographic characteristic of included sample

Three subjects were excluded from the analysis because of the poor segmentation of hippocampal subfields, remaining 54 aMCI and 66 NC. demographic characteristics were shown in the Table 1.

<Table 1>

3.2 VSTM performance

ANCOVA analysis showed significant main effect of group for ACC ($F(1, 114) = 15.28$, $p < 0.001$) but no interaction between group and task load ($p = 0.21$) after covarying the effect of age, gender, education and collecting site. *Post-hoc* analysis with Bonferroni correction showed that aMCI group performed significant worse than the NC group in the task of 2-item load (aMCI: 0.88±0.11; NC: 0.95±0.051; $p < 0.001$) and marginally significant worse in the task of 4-item load (aMCI: 0.73±0.095; NC: 0.78±0.091; $p = 0.051$) with age, gender, education and collecting site as covariates.

Significant main effect of group ($F(1,114) = 5.119$, $p = 0.026$) and interaction between group and task load ($F(1, 114) = 9.78$, $p = 0.002$) was found for RT after covarying the effect of age, gender, education and collecting site. *Post-hoc* analysis with Bonferroni correction showed significant longer RT in aMCI group in task of 2-

item load ($p = 0.009$), but not in the task of 4-item load with age gender, education and collecting site as covariates.

Significant between-group difference was found in capacity ($F(1, 114) = 8.46$, $p < 0.004$; aMCI: 1.93±0.11; NC: 2.40±0.089).

3.2 Between-group difference in hippocampal volume and correlation to VSTM performance

Structural comparisons were conducted for bilateral hippocampus and all the subfield by ANCOVA, with age, gender, education, collecting site and TIV as covariates. The results were then corrected by FDR method. Results showed that significant smaller gray matter volume was found in the aMCI group in the left lateral hippocampus (Figure 2A), and among the hippocampal subfields, left hippocampal tail, left molecular layer, left GC-ML-DG, left CA4, right hippocampal fissure, bilateral subiculum, bilateral presubiculum, and bilateral fimbria were found significantly smaller in the aMCI group when compared to NC (Figure 2B and Table 2). No main effect of group was found for right lateral hippocampus or other subfields ($ps > 0.05$).

< Table 2 >

<Figure 2>

Partial correlation analysis with age, gender, education, collecting site and TIV as covariates showed that the gray matter volume of the left hippocampus, left subiculum, left molecular, left GC-ML-DG and left CA4 were correlated with the accuracy or capacity, and bilateral fimbria were correlated to the RT of VSTM tasks ($ps < 0.05$, Figure 2C and Table 3) in the NC group but no correlation was found in the aMCI group ($ps > 0.05$).

<Table 3>

Discussion

In the current study, we conducted structural comparison in hippocampal subfield to target precise atrophy of hippocampus in individual with aMCI and identified the association between the atrophy and VSTM deficits. The current results showed that compared to HC subjects, aMCI subjects had lower response accuracy (ACC) and lower memory capacity under both load conditions and had longer reaction time (RT) in the 2-load condition. Left hippocampus volume was significantly smaller in aMCI and was positively correlated with ACC and capacity in HC but not in aMCI. Among the hippocampal subfields, left hippocampal tail, left molecular layer, left GC-ML-DG, left CA4, right hippocampal fissure, bilateral subiculum, bilateral presubiculum and bilateral fimbria, were significantly smaller in aMCI compared to HC. Volumes of the left subiculum, left molecular layer, left GC-ML-DG and left CA4 were

positively correlated with ACC and capacity in HC but not in aMCI. Bilateral fimbria volume was negatively correlated with RT under the 2-load condition in HC but not in aMCI.

VSTM deficits has been flagged as cognitive maker for early AD recently (Alescio-Lautier et al., 2007; Kessels et al., 2015; Zokaei et al., 2019; Zokaei et al., 2020), which was also indicated by the current results. Consistent with our previous study, the gray matter volume of left hippocampus was smaller in the aMCI group than in the control group. Left lateral hippocampus has been consistently reported as the most vulnerable brain region influenced by AD pathology (Ferreira et al., 2011). The association between the gray matter volume of left hippocampus and the VSTM performance in the NC group was also add evidence to the declaration that hippocampus also play an important role in supporting visual short-term memory (Boran et al., 2022; Borders et al., 2022; Liu et al., 2020; Yonelinas, 2013).

When look into the subdivision of hippocampus, left hippocampus tail, left molecular layer, left GC-ML-DG, left CA4, right hippocampal fissure, bilateral fimbria, bilateral subiculum and bilateral presubiculum showed significant atrophy in the aMCI group when compared to the NC group. The molecular layer, hippocampal fissure, fimbria, subiculum and presubiculum were suggested to be functioned as pathway for input and output. The molecular was the input to dentate gyrus and the dentate gyrus and CA4 area has been implied as the core regions for memory and binding in hippocampus, in the current study, only the left lateral areas were atrophied, which might indicate the lateralized brain deterioration in the early stage of AD. The gray matter volume of the left molecular, the left GC-ML-DG and the left CA4 were positively correlated to the VSTM accuracy or capacity in the NC group rather than in the aMCI group, indicating that the deterioration of the areas related to the information processing would impact the VSTM in aMCI individuals.

The fimbria and the subiculum areas were suggested as the pathway for output to the thalamus and frontal area. The thalamus and prefrontal areas were also affected by AD disease in the aMCI group (Yeung et al., 2022). Among these areas, the left subiculum was correlated to the accuracy and capacity of VSTM, while bilateral fimbria were negatively correlated to the RT in the NC group, showing that these pathway played an important role in VSTM. VSTM is not solely reliant on the hippocampus; it involves a complex interplay of brain regions and networks. These networks include the prefrontal cortex, parietal cortex, and regions within the occipital lobe (von Allmen et al., 2014). In individuals with aMCI, disruptions in these networks may contribute to VSTM deficits, highlighting the need for a comprehensive understanding of the neural correlates of VSTM in this population.

Previous study has suggested the thalamus-hippocampus-prefrontal mechanism supported the memory (Aggleton et al., 2022). Frontal areas were also critical in VSTM (Prabhakaran et al., 2000; Ranganath et al., 2004; Rissman et al., 2008). Besides, previous research has proposed a compensatory role of the prefrontal area in

helping to sustain cognitive function in aMCI when hippocampus-related function is impaired (Bokde et al., 2010; Garcia-Alvarez et al., 2019).The current results highlighted the critical role of this thalamus-hippocampus-prefrontal mechanism in the AD pathology.

Conclusion

The present study suggested that hippocampal atrophy, especially in subfields related to information input and output (e.g., molecular layer, GC-ML-DG, subiculum), may have contributed to VSTM impairment in aMCI by disrupting hippocampal-cortical communications. The pathway between hippocampus-thalamus-frontal cortical was highlighted. This finding adds to increasing evidence of hippocampal engagement in short-term memory processes and points to VSTM impairment as a potential neuropsychological indicator for MCI and AD.

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Table 1. demographic characteristics.

	aMCI (n = 54)	NC (n = 66)	Between-group differences
Age (years)	72.42 (6.75)	70.35 (6.12)	t(118) = 1.77, p = 0.080 [a]
Gender (male: female)	23:31	43:23	χ^2 = 6.11, p = 0.013[b]
Education (years)	11.37 (2.66)	12.42 (2.80)	t(118) = -2.1, p = 0.038 [a]
MMSE	24.93 (2.49)	27.49 (2.51)	W = 621.00, p < 0.001[c]
MoCA	17.17 (3.50)	24.24 (2.51)	W = 183.00, p < 0.001[c]

Values are mean (standard deviation). Abbreviation: aMCI, amnestic mild cognitive impairment; NC, normal controls; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

[a] independent two-sample t-test, [b] chi-square test, [c] Mann-Whitney U test.

Table 2. Subfields showing significant between-group difference.

subfield	group	mean (SD)	ANCOVA
L hippocampus tail	aMCI	450.73(12.02)	$F(1,113) = 5.71$ $p = 0.039$
	NC	509.16(8.9)	
L subiculum	aMCI	380.81(8.34)	$F(1,113) = 6.56$ $p = 0.039$
	NC	425.33(6.24)	
L presubiculum	aMCI	254.06(6.52)	$F(1,113) = 5.94$ $p = 0.039$
	NC	287.15(5.48)	
l molecular	aMCI	463.06(10.13)	$F(1,113) = 8.79$ $p = 0.026$
	NC	519.28(6.68)	
L GC-ML-DG	aMCI	240.31(5.31)	$F(1,113) = 9.93$ $p = 0.026$
	NC	272.5(3.9)	
L CA4	aMCI	212.27(4.44)	$F(1,113) = 7.06$ $p = 0.037$
	NC	237.28(3.36)	
L fimbria	aMCI	64.86(3.61)	$F(1,113) = 6.78$ $p = 0.037$
	NC	84.56(2.88)	
R subiculum	aMCI	391.17(8.87)	$F(1,113) = 6.11$ $p = 0.039$
	NC	434.38(6.1)	
R hippocampus fissure	aMCI	184.88(5.49)	$F(1,113) = 5.81$ $p = 0.039$
	NC	178.79(5.74)	
R presubiculum	aMCI	242.96(5.89)	$F(1,113) = 8.55$ $p = 0.026$
	NC	274.97(5.17)	
R fimbria	aMCI	59.77(3.2)	$F(1,113) = 7.09$ $p = 0.037$
	NC	73.09(2.87)	

L hippocampus	aMCI	2888.41(61.09)	$F(1,113) = 9.70$ $p = 0.026$
	NC	3244.81(40.96)	

P values were FDR corrected.

Table 3. Brain-behavioral association between hippocampal subfield and VSTM performance.

subfield	Group	ACC_2T	RT_2T	Capacity _2T	ACC_4T	RT_ 4T	Capacity_4T
L subiculum	aMCI	\	\	\	\	\	\
	NC	r = 0.297, *p* = 0.020	\	\	r = 0.317, *p* = 0.013	\	r = 0.301, *p* = 0.018
L molecular layer	aMCI	\	\	\	\	\	\
	NC	r = 0.328, *p* = 0.010	\	\	r = 0.280, *p* = 0.029	\	r = 0.309, *p* = 0.015
L GC-ML-DG	aMCI	\	\	\	\	\	\
	NC	r = 0.270, p = 0.035	\	\	\	\	\
L CA4	aMCI	\	\	\	\	\	\
	NC	r = 0.294, *p* = 0.022	\	\	\	\	\
L fmbria	aMCI	\	\	\	\	\	\
	NC	\	r = -0.288, *p* =0.024	\	\	\	\
r fimbria	aMCI	\	\	\	\	\	\
	NC	\	r = -0.283, *p* = 0.027	\	\	\	\
L hippocampus	aMCI	\	\	\	\	\	\
	NC	r = 0.282, *p* = 0.027	\	\	r = 0.294, *p* = 0.021	\	r = 0.323, *p* = 0.011

\ represents unsignificant correlation.

Figure legend

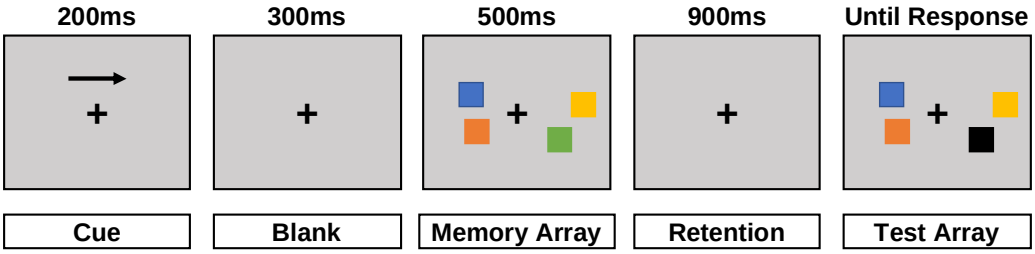

Figure 1. Stimuli and trail procedure of visual change detection task.

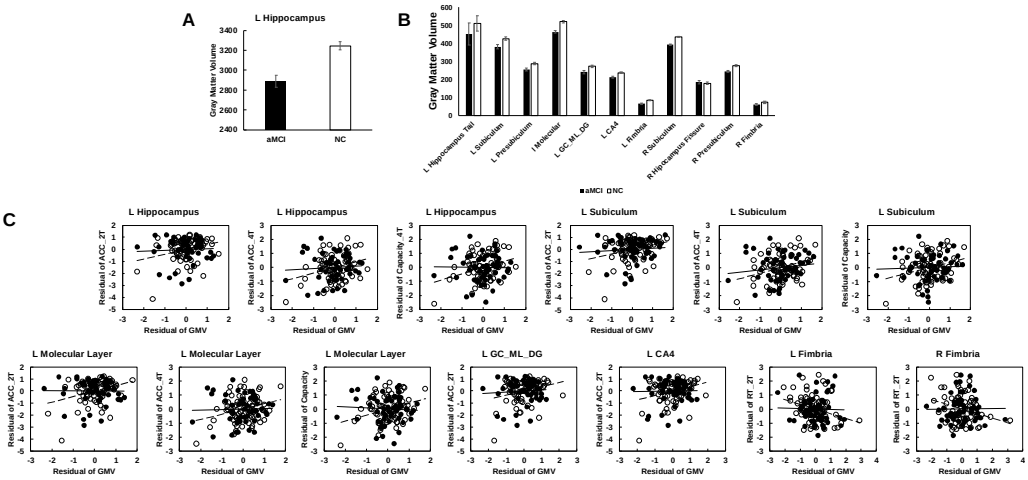

Figure 2. Significant between-group difference in unilateral hippocampus (A) and hippocampal subfields (B). Correlation between gray matter volume (GMV) and VSTM performance (C) were conducted by partial correlation analysis. Analyses were conducted with age, gender, education, TIV and collecting site as covariates.