

The volumes of hippocampal subfields in a group of young adults, and their relationship with pattern separation performance

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ABSTRACT

Aims: Subfields of the hippocampus have long been held responsible for the pattern separation function of episodic memory. The total neuron numbers of the entorhinal cortex (EC), which gives the major input to the hippocampus, the dentate gyrus (DG), and CA3 and their ratio to each other is thought to be important for the pattern separation process. In this study, the relationship between the volumes of the EC and hippocampal subfields and behavioral pattern separation performance was investigated.

Methods: 3D brain MRI images of 39 university students were obtained and the volumes of EC and hippocampal subfields (CA1, CA2-CA3, CA4-DG) were analyzed on the volBrain online automatic brain volumetry system. All participants were evaluated with a cognitive test for pattern separation performance. Finally, the correlation between the volume of brain areas and pattern separation performance score was statistically analyzed.

Results: Total and right CA2-CA3 volume had positive correlation with pattern separation score ($p=0.036$, $p=0.028$ respectively) and negative correlation with recognition fail ($p=0.013$, $p=0.009$ respectively). CA1 volume also had a negative correlation with recognition fail ($p=0.040$) while the ratio of EC volume to CA4-DG was positively correlated with success of pattern separation ($p=0.016$).

Conclusion: The results contribute to our understanding of memory function by indicating the relationship between EC-to-DG divergence and CA2-CA3 volume with pattern separation.

Keywords: Pattern separation, recognition, hippocampus, dentate gyrus, cornu ammonis, entorhinal cortex

INTRODUCTION

The cognitive process of pattern separation enables the brain to distinguish between similar experiences and preserve them as distinct memories.¹⁻⁵ This feature is a guarantee that overlapping memories are stored separately.⁴ It is commonly admitted that episodic memory depends on the hippocampus.⁶ However, the hippocampus is not a uniform structure, it contains different subfields serving special functions. These subfields include cornu ammonis (CA) regions (CA1, CA2, CA3, and CA4) and the dentate gyrus (DG).⁷ These subfields demonstrate differential involvement in various cognitive processes, such as memory retrieval or learning.⁸

DG has long been held responsible for pattern separation.³ This specific function has been particularly linked to adult-born neurons in the DG.² Although the role attributed to DG in pattern separation has been suggested by computer modeling, additional research have confirmed this. For instance, pattern separation is impaired in rodents with DG lesion.^{2,9} Deficit of pattern separation can result from DG malfunction, as has been seen in conditions like schizophrenia.¹⁰ Furthermore, genetic

variables that influence the likelihood of Alzheimer's disease could impact the neuronal processes involved in pattern separation in hippocampus subfields.^{11,12} The inadequacies in the pattern separation procedure may result with overgeneralization.¹³ Disrupted pattern separation is proposed to be a core mechanism underlying the overgeneralization of fear observed in anxiety disorders.¹⁴

The unique neural architecture of the hippocampus is thought to enable the separation of similar experiences. The hippocampus connects with the other brain regions through the para-hippocampal region.¹⁵ Entorhinal cortex (EC), as the major input and output region for the hippocampus, serves a crucial center in transmitting sensory information from the neocortex to the DG.¹⁵ In the hippocampus, the signal sequentially passes through DG, CA3, and CA1 (It is called as "the trisynaptic circuit"). Most obviously, the pathway begins with the EC projecting to the DG via the perforant pathway, which then projects to CA3 via the DG mossy fibers, and finally reaches CA1 via the CA3 Schaffer collaterals. It

then returns to EC back.^{7,11,15} In addition to the trisynaptic circuit, EC projects directly to both CA3 and CA1 areas via the perforant pathway.¹⁵

Studies point to the anatomical origin of behavioral pattern separation. Especially above-mentioned trisynaptic circuit of the hippocampus is the critical neural pathway for information processing within the hippocampus.³ In rats, 18 thousand inputs from approximately 200 thousand EC neurons project to 10⁶ DG cells.^{4,16,17} The DG contains five to ten times more neurons than its main input, the EC. As a result, DG inputs to the hippocampus through EC are dispersed extensively (a large divergence).^{4,16,17} Afterwards mossy fibers extend from DG to CA3, which contains approximately 300 thousand neurons. Here there is a large convergence. Similar ratios are true for the human hippocampus.¹⁷ Ultimately, according to the accepted model, the mentioned anatomical features enable the DG to facilitate pattern separation and the pattern is completed in the CA3 region.^{1,4}

In order to assess the relationality between hippocampus anatomical features and behavioral pattern separation, we performed volumetric analysis by separating hippocampal subfields. We calculated the relative ratio of the volumes of the receivers and senders of the circuit. Finally, we investigated the correlation of these volumetric data with pattern separation scores. This study aimed to investigate the association between pattern separation test performance and brain volumetric measures in healthy young individuals.

METHODS

Selection of Participants

This study was carried out with ethical approval of Kastamonu University Clinical Researches Ethics Committee (Approval Date: 30.01.2023, Decision No: 2023-KAEK-5, Date of approval for the ethical amendment request: 06.11.2024). Thirty-nine Kastamonu University Faculty of Medicine students participated in the study (22 males, 17 females). None of the participants had color blindness. Informed written consent was obtained from all volunteers and the privacy rights of participants were observed.

Magnetic Resonance Imaging (MRI) and Volumetric Analysis

3D brain magnetic resonance (MR) images of the volunteers were taken at the Radiology Department of Kastamonu University Hospital. The same radiologist recorded in standard head position throughout the experiment. Obtained MRI images were uploaded to volBrain online web interface (<http://volbrain.upv.es>) which is a publicly available and free service of volumetric brain analysis based on multi-atlas label.

Total, left and right hippocampus,

- CA1,
- CA2-CA3,
- CA4-DG,
- EC,
- Parahippocampal gyrus volumes were obtained.

Pattern Separation Test

This test was aimed to assess the participants' pattern separation performance - their capacity to identify stimuli that are the identical, quite similar or completely different

from the stimuli that were presented to them before. The test-takers with visual impairments took part after making necessary corrections. Before the task began, a trial test was administered to ensure that the participants had received the necessary training.

The test consists of two parts: encoding and testing phase. Thirty distinct stimuli, each consisting of a scene-animal-object triplet (5 s each; inter-trial interval 0.5 s), were presented to the subjects during the encoding phase. The participants were instructed to concentrate on each stimulus by grouping items into sets of three. The encoding phase was immediately followed by the testing phase, which included 35 stimuli. During the test phase, participants classify stimuli that comprise three elements according to whether or not they saw them as a group during the encoding phase. 15 of the stimuli in the test phase were target stimuli which are identical to those in the encoding phase. "Scene traps", or stimuli that include the same animal and object but different scene, were five of the stimuli. Similarly, five stimuli were "animal traps" and five stimuli were "object traps". The remaining five stimuli were foils containing entirely new aspects of scenes, animals and objects than those presented during encoding.

On sheets of paper, participants recorded the following test events: "identical," "different scene," "different animal," "different object," or "completely new." It was ensured that every question would be answered, and there were no restrictions on response times. The stimuli and the method were adapted from the study of Ngo et al.¹⁸ The test was modified by reducing the number of stimuli.

Calculations

After completing the pattern separation test, we obtained two scores. The first was how many of the 35 stimuli did the participants respond correctly: "pattern separation score". The second was errors made by participants who believed that target stimuli were completely new: "missing target stimulus". While the first one is positive for the pattern separation function, the second one is an error score which reflects recognition deficiency.

We also computed the ratios between the volumes of the hippocampus subfields to test our hypothesis: EC to CA4-DG, CA4-DG to CA2-CA3.

Statistical Analysis

Shapiro-Wilk test was used to consider the normality of data. As the data is not normally distributed correlations were investigated through Spearman correlation coefficients. IBM SPSS Statistics 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) software was used for statistical analyzes. Statistical significance level was accepted as $p < 0.05$.

RESULTS

The mean and standard deviation of the age of the students was 21.00 ± 1.01 (minimum=19; maximum=23). The descriptive statistics of brain area volumes, relative ratios of hippocampal subfield volumes and pattern separation scores are given in **Table 1**.

Correlation analysis showed that total and specifically right CA2-CA3 volume showed a weak positive correlation with pattern separation score ($r=0.337$, $p=0.036$; $r=0.353$,

Table 1. Descriptive statistics of variables

Brain area volumes (cm ³)	Median	Minimum	Maximum
Total hippocampus	4.99	3.96	6.02
Right hippocampus	2.53	0.33	2.93
Left hippocampus	2.40	1.80	2.81
Total CA1	1.75	1.32	2.28
Right CA1	0.90	0.67	1.23
Left CA1	0.86	0.58	1.05
Total CA2-CA3	0.36	0.23	0.46
Right CA2-CA3	0.19	0.12	0.26
Left CA2-CA3	0.16	0.09	0.23
Total CA4-DG	1.25	0.93	1.51
Right CA4-DG	0.64	0.46	0.82
Left CA4-DG	0.62	0.38	0.79
Total entorhinal cortex	3.97	3.06	5.04
Right entorhinal cortex	2.00	1.53	2.80
Left entorhinal cortex	1.96	1.45	2.58
Total parahippocampal gyrus	5.89	4.88	7.63
Right parahippocampal gyrus	2.88	2.41	3.79
Left parahippocampal gyrus	3.01	2.47	3.92
Hippocampus subfields volume ratios	Median	Minimum	Maximum
Total EC to CA4-DG	3.27	2.49	4.20
Right EC to CA4-DG	3.21	2.10	4.43
Left EC to CA4-DG	3.28	2.23	4.97
Total CA4-DG to CA2-CA3	3.48	2.51	4.57
Right CA4-DG to CA2-CA3	3.25	2.24	4.46
Left CA4-DG to CA2-CA3	3.76	2.83	5.64
Total EC to CA2-CA3	11.29	8.50	15.27
Right EC to CA2-CA3	10.04	6.83	17.69
Left EC to CA2-CA3	11.47	8.06	20.27
Pattern separation test	Median	Minimum	Maximum
Pattern separation total score	22.00	10.00	29.00
Missing target stimulus	4.00	3.00	12.00

(n=39) CA: Cornu ammonis, DG: Dentate gyrus, EC: Entorhinal cortex

p=0.028 respectively). In addition to this again both total and specifically right CA2-CA3 volume showed a negative correlation with “missing target stimulus” score (r=-0.396, p=0.013; r=-0.411, p=0.009 respectively) (Table 2).

Apart from these, the right CA1 volume also had a weak negative correlation with “missing target stimulus” score (r=-0.330 p=0.040) (Table 2).

Finally left EC to CA4-DG volume ratio had a moderate positive correlation with pattern separation score (r=-0.382, p=0.016) (Table 3).

DISCUSSION

Impairment in episodic memory significantly affects quality of life and functionality. If pattern separation, a critical process of episodic memory, fails, new information can be overwritten on existing memories, causing interference, potentially leading to memory errors. The responsibilities, appointments, and daily tasks of such a person will suffer. Additionally, spatial memory may be affected and the person may have difficulty with navigating in familiar environments. Furthermore, impairments in pattern separation can affect

Table 2. Correlations of brain area volumes and pattern separation scores

		Pattern separation total score	Missing target stimulus
Total hippocampus volume	r	0.211	-0.284
	p	0.196	0.080
Right hippocampus volume	r	0.128	-0.291
	p	0.437	0.072
Left hippocampus volume	r	0.182	-0.162
	p	0.269	0.324
Total CA1 volume	r	0.139	-0.205
	p	0.400	0.212
Right CA1 volume	r	0.188	-0.330
	p	0.251	0.060
Left CA1 volume	r	0.072	-0.085
	p	0.665	0.607
Total CA2-CA3 volume	r	0.337*	-0.396*
	p	0.036	0.013
Right CA2-CA3 volume	r	0.353*	-0.411**
	p	0.028	0.009
Left CA2-CA3 volume	r	0.287	-0.295
	p	0.077	0.069
Total CA4-DG volume	r	0.289	-0.288
	p	0.074	0.076
Right CA4-DG volume	r	0.187	-0.217
	p	0.254	0.185
Left CA4-DG volume	r	0.239	-0.236
	p	0.143	0.147
Total entorhinal cortex volume	r	-0.088	-0.016
	p	0.594	0.925
Right entorhinal cortex volume	r	-0.038	0.049
	p	0.820	0.768
Left entorhinal cortex volume	r	-0.152	-0.088
	p	0.354	0.595
Total parahippocampal gyrus volume	r	-0.141	0.109
	p	0.392	0.510
Right parahippocampal gyrus volume	r	-0.140	0.173
	p	0.395	0.293
Left parahippocampal gyrus volume	r	-0.136	0.006
	p	0.409	0.969

r: Correlation coefficient, *Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level, (n=39), CA: Cornu ammonis, DG: Dentate gyrus

Table 3. Correlations of hippocampal subfield volume ratios and pattern separation scores

		Pattern separation total score	Missing target stimulus
Right EC to CA4-DG	r	0.207	-0.259
	p	0.207	0.111
Left EC to CA4-DG	r	0.382*	-0.229
	p	0.016	0.161
Right CA4-DG to CA2-CA3	r	-0.305	0.342
	p	0.059	0.063
Left CA4-DG to CA2-CA3	r	-0.150	0.131
	p	0.361	0.425

r: Correlation coefficient, *Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level, (n=39), EC: Entorhinal cortex, CA: Cornu ammonis, DG: Dentate gyrus

emotional memory processing, potentially leading to mood disorders. As a matter of fact, impaired pattern separation has been associated with major depressive disorder.¹⁹ Additionally, it has been reported in various studies that pattern separation is impaired in Alzheimer's disease.^{11,12} Therefore, understanding the mechanisms underlying pattern separation not only sheds light on fundamental aspects of memory but also provides implications for neurological and psychiatric disorders. One of the theories in hippocampal information processing suggests that a divergent projection pattern from the EC to DG plays a critical role in enabling pattern separation. Supporting this theoretical framework, one of the most striking findings of our study was the positive correlation between the relative volume of the left EC to CA4-DG region and behavioral pattern separation performance.

The positive correlation between the left EC to CA4-DG ratio and pattern separation score is an intriguing finding. According to the recommended models DG receives its main input from EC, which has five times fewer neurons than itself. During this projection, the information flowing from EC neurons spreads to different neurons in the DG. This divergence enables pattern separation.¹⁷ In this study, higher EC to CA4-DG ratio may reflect the higher divergence. So, the above-mentioned correlation between the volume ratio and test score may suggest that as the divergence from EC to DG increases, more success is achieved in distinguishing similarities. Apparently, the architecture of the hippocampus contributes to the behavioral performance.

Actually, smaller hippocampus and entorhinal cortex volumes were linked to spatial pattern separation impairment before.¹² DG has also shown to be closely linked to pattern separation. For instance, a group found that aging is associated with a reduction in DG volume and this correlates with impairments in pattern separation.²⁰ Furthermore, in a study DG volume was found to be the best predictive factor for pattern separation performance among at other hippocampal subfields.²¹ While that study included patients with encephalitis and they showed an overall memory deficit, our study included cognitively active, healthy young adults because the ability to perform pattern separation efficiently decrease with age.²² In our investigation, statistical analysis showed the relationship between CA2-CA3 volume and pattern separation. The first significant positive relationship is seen between the total & right CA2-CA3 volume and the pattern separation score. This is possibly showing the role of these regions in pattern separation process. These regions also have a negative correlation with "missing target score" of pattern separation test. The "missing target score", indicates that the stimulus in the test phase was exactly the same as the previously encountered in the encoding phase but the participant did not recognize it, in other words missed the target. The negative correlation between this recognition error and the mentioned volumes indicates that higher volume is linked with lower error. So, we are linking these regions with recognition performance.

Previously proximal CA3 have been suggested to involve in pattern separation.²³ It is suggested that, when the similarity between items is high, DG makes pattern separation and CA3 performs pattern completion, which means is the cognitive process where the brain fills in missing parts of an incomplete sensory input.³ According to the generally

accepted theory, CA3 also participates in pattern separation when the similarity between elements is low.³ CA3 neurons also show marked synaptic plasticity and are fundamental for recording new information.⁹ Besides, as CA2 receives projections from both EC and CA3, and projects to CA1 Martig and Mizumori²⁴ suggested the CA2 as a possible "mismatch detector" and is accepted to be essential for social recognition.²⁵ The unique properties of CA2 neurons, such as their sensitivity to oxytocin, strengthen their role in recognition.²⁶ Overall, considering the literature and the significances in our study, we think that CA2-CA3 involves in separating similar memories from each other correctly and in recognition of familiar. In fact, CA2 and CA3 together were the hippocampal regions most associated with pattern separation performance in our young adult group.

The diverse role of CA1 as a junction for integrating, encoding, and relaying hippocampal information makes it a focus of interest in studies of memory. CA1 neurons are suggested to be critical for memory retrieval as they are particularly active during retrieval tasks.²⁷ Dong et al.²⁸ demonstrated that long-term depression in CA1 is critical for novelty exploration. In our study, the right CA1 volume has negative correlation with missing the target. Thus, the bigger volume of CA1 reduces the errors in recognition of familiar. This is consistent with the role of CA1 as a novelty detector. The studies suggest that CA1 neurons exhibit heightened activity in response to familiar stimuli.²⁹ This activity is believed to be essential for recognizing previously encountered objects.

Limitations

This study has several limitations that should be acknowledged. First, although we were not able to separate hippocampal subfields at higher resolution, we believe our findings still provide valuable evidence, particularly given the impossibility of histological analysis in living humans. Second, our relatively small sample size may limit how broadly the results can be generalized. Third, since the study was carried out at a single center and involved a specific participant group-medical students-there is a risk of selection bias. Lastly, although automated volumetric analysis offers efficiency, it is not free from potential segmentation errors.

CONCLUSION

Certainly, pattern separation may not be limited to the hippocampus alone; extrahippocampal regions are also involved in this process, including sensory and prefrontal cortex.³⁰ Any study in this area will contribute to the basic knowledge of how memory works and will allow us to develop a more accurate understanding. Considering the relationship between pattern separation impairment and fear anxiety, and depression, and even considering that pattern separation impairments may be useful for early diagnosis of Alzheimer's, we need to understand which features of the hippocampus or extrahippocampal areas should be focused on.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Kastamonu University Clinical Researches Ethics Committee (Approval Date: 30.01.2023, Decision No: 2023-KAEK-5, Date of approval for the ethical amendment request: 06.11.2024).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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