PATTERN SEPARATION ABILITY RESULTS BETWEEN YOUNG ADULT APOLIPOPROTEIN E4 ALLELE CARRIERS AND NONCARRIERS

By

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Approved by:

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Abstract

The second leading risk factor for Alzheimer's behind aging is the apolipoprotein e4 allele. This allele has been found to have slight differences in the cognitive abilities of aging populations regardless of the presence or lack of cognitive impairments. Older adult carriers tend to present better memory function than noncarriers of the e4 allele. A similar study looking at fMRI imaging in young adults reveals that neural activity in e4 noncarriers was slightly more demanding than in e4 carriers. Researchers in the current study recruited 51 graduate and undergraduate students at the University of Arizona to participate in a pattern separation task that tests the ability of working memory and recognition. Blood spot or saliva samples were collected from each participant to determine their apolipoprotein e4 status. Recognition results produced a main effect of scene condition—it was easier to recognize previously seen objects on white backgrounds than any other scene condition. Pattern separation results produced a main effect of scene condition as well—it was easier to identify objects depicted on white backgrounds than any other scene condition. Error Difference Score results produced a main effect of scene condition—repeated and novel scenes induced more errors to be made than white scene conditions. A surprising error score result of white scene condition found participants tended to incorrectly identify similar objects as "different" more often than on other scene conditions. There were no interactions between apolipoprotein status and scene condition. Further studies with more sensitive measures are needed to confirm or deny any differences in young adult apolipoprotein e4 carriers and noncarriers.

Introduction

Pattern separation is the brain's ability to distinguish between information with various overlapping features, often done automatically in the brain. To illustrate an example of memories that may have a lot of overlap with other memories, imagine describing a memory of eating breakfast: this morning's breakfast might have been eggs, toast, and orange juice; yesterday's might have been eggs, bacon, orange juice, and a piece of toast; and the day before yesterday's might have been toast, orange juice, and a hardboiled egg. This example highlights how the memories we create can have a lot of overlap with one another. What pattern separation allows one to do is differentiate one memory from another despite the reoccurrence of overlapping features such as the eggs, or the toast, or the orange juice. Pattern separation is important for researchers to study because changes in the brain associated with aging, such as the decrease in hippocampus volume and activity, are associated with changes in different types of memory, such as episodic memory, which may contribute to changes in pattern separation (Peters, 2006; Yassa & Stark, 2011). People with these types of brain changes may not be able to pattern separate very efficiently and their subsequent memory retrieval may also be difficult. Memories with many overlapping features become subjected to possible interference upon retrieval and details from different memories may be confused between one another (Ferreira et al., 2019).

An example of a pattern separation task used in experiments is the one used by Stark et al. (2013) where indoor and outdoor objects are shown to participants in an encoding phase. Following the encoding phase, participants are given a surprise memory test. Participants

determine if they are being shown objects presented earlier in the day, new objects not shown before, or similar objects to ones shown previously before.

Pattern separation tasks tend to get more difficult as people age due to the decline in perirhinal cortex functioning (Burke et al., 2018). In participants with Alzheimer's disease who were also apolipoprotein (APOE) e4 allele carriers, the ability of pattern separation was considerably more impaired than in individuals with Alzheimer's disease who were not carriers of the e4 allele (Wesnes et al., 2014). The APOE gene has three different alleles, but the e4 allele is important to study with pattern separation in the context of aging because it is the second leading risk factor of Alzheimer's disease behind age (Liu et al., 2013). Other research suggests that differences can exist among younger adult e4 carriers and noncarriers. FMRI imaging showed e4 noncarriers were found to exhibit higher demands in neural activity when completing the same task as carriers, which may suggest that carriers have better working memory than noncarriers (Christian et al., 2007). These higher levels of working memory in young e4 carriers are associated with higher levels of calcium in the brain which is thought to lead to age-related neural deficits that may contribute to the development of Alzheimer's in old age (Christian et al., 2007). In addition to calcium levels, the necessary white matter pathways connecting the entorhinal cortex, the dentate gyrus, and the CA3 cells in the brain that are required for pattern separation are degraded as aging progresses (Yassa, 2011).

This information suggests that APOE e4 carriers have cognitive differences that can be seen when compared to noncarriers. Note that these differences are not necessarily indicative of Alzheimer's disease, but can be seen as benefits in younger adults. As seen in a previous verbal learning task between the two groups, e4 carriers were seen to have increased brain

activity in clusters when compared to noncarriers (Han et al., 2007). Based off existing information of e4, researchers now want to better understand the types of benefits young adult e4 allele carriers have compared to noncarriers. Young adult e4 carriers have already been found to have slight differences in neural activity compared to noncarriers, so will these young adults present better accuracy on the pattern separation tasks?

In this laboratory's task, objects are superimposed onto contextual backgrounds of white backgrounds, repeated scenes, or novel scenes to allow researchers to examine how difficult or easy it is for participants to pattern separate when different types of features are overlapping. Different from past pattern separation tasks, different backgrounds have been found to induce different results in participant groups. For example, in older adults, it has been seen that they will mistake similar objects for repeated objects when depicted on a repeated background (Stark et al., 2013). When looking at younger adults, they do not make the same mistake as the older adults nearly as much, but if they do make a mistake, they are more likely to mistake similar objects for novel objects when depicted on a repeated background.

Pattern separation ability in this study is described as a person's accurate recognition of a similar object as "similar." Predictions are that participants who are APOE e4 carriers will have better pattern separation ability (higher scores) when compared to noncarriers. This can indicate that e4 carriers have an easier time with pattern separation and possibly a better memory. Based on what background is being presented, different results can be hesitated: white backgrounds will yield mistakes of identifying similar objects as "same," and repeated scenes will yield similar mistakes to the white background due to both scene conditions being repeated—these mistakes are expected because the differences in similar objects are very

slight. Novel scenes will yield mistakes of identifying repeated objects as “similar,” or old, because the unfamiliar background may mislead participants to make them think this repeated object is not exactly the same as before (Hayes et al., 2007).

Methods

Thirty undergraduate participants were recruited through the SONA system through the University of Arizona. Twenty-one participants’ information and results were recruited from existing data sets in the laboratory database. The range of participant ages was 18-34 years old (mean=22). Each participant was separately asked a variety of demographic questions as well as personal health and family health questions before completing the pattern separation task practice and the pattern separation task. Participant demographic information can be found in **Table 1**. Participants had varying levels of education averaging 14.55 years of education.

The pattern separation task was a continuous recognition task. In contrast to Stark et al.’s (2013) study, there was not an encoding phase of objects before the task was administered, meaning participants had no previous interaction with the objects shown in the task. Participants were asked to identify each object as “different,” meaning not seen before in the task; “same,” meaning exactly identical to another object previously seen before in the task; or “similar,” meaning having a slight difference to an object previously seen before in the task. The backgrounds that these objects could be depicted on were blank white backgrounds, novel backgrounds not seen before in the task, and repeated backgrounds seen before in the task. The backgrounds in this task are important because they induce different types of errors in the task that show exactly how pattern separation is affected from person to person.

Participants were asked not to take the backgrounds into consideration and only identify objects in one of the three categories of “different,” “similar,” or “same.” There were nine different conditions of images shown on a computer screen that had an object depicted on a background. An example of these images and backgrounds can be seen in **Figure 3**. An example of how the task is presented to participants can be seen in **Figure 4**. The total number of images in the task was 480. There were 30 identical object pairs and 30 similar object pairs shown for each background and 120 novel objects with no identical or similar pairs. Identical and similar pairs were shown within 9-12 images of each other as to allow participants to not have to remember images for the entirety of the task.

Before the task was administered, a practice run lasting about 5 minutes was completed by the participant. They were then given feedback on their performance and could ask questions before the official task began. After the task was completed, a blood spot or saliva sample was collected to determine e4 status. Participants were then debriefed on the purpose of the study.

Performance and ability on the pattern separation task were measured in a few different ways. Recognition was measured as correctly identifying repeated objects as “same” for each background. Recognition scores were corrected for recognition false alarms. Recognition false alarms are defined as incorrectly identifying novel objects as “same.” Pattern separation performance for each background was measured as correctly identifying similar objects as “similar.” Pattern separation scores were corrected for pattern separation false alarms. Pattern separation false alarms are defined as incorrectly identifying novel objects as “similar.” When similar objects were shown, two types of errors were possible: identifying

them as “same” or “different.” Error scores were calculated by the Error Difference Score where similar objects incorrectly identified as “different” were subtracted from similar objects incorrectly identified as “same.” A higher positive score indicated a tendency to identify similar objects as “same,” rather than “different.” A lower negative score indicated a tendency to identify similar objects as “different,” rather than “same.” Carrier and noncarrier group differences were measured using a 3x2 mixed model ANOVA. The backgrounds served as a repeated measure and APOE status was the between-subjects variable.

Results

A 3 (white background, repeated background, and novel scene) x2 (APOE e4 carrier and noncarrier) mixed model ANOVA was conducted.

Corrected recognition scores were calculated as correctly identified objects (correctly identifying repeated objects as “same”) subtracted by the number of false alarms (incorrectly identifying novel objects as “same”). There was a main effect of scene condition, F (2, 98) = 39.852, p<0.001. Follow up paired t-tests revealed significant differences between the Novel Scene and the other scene conditions (Repeated Scene t(50) = 7.313, p<0.001, d = 1.279; and White Background t(50) = -7.882, p<0.001, d = -1.43). These results indicate that the Novel Scene made identifying repeated objects more difficult than if presented on a White Background or a Repeated Scene. There was no main effect of APOE status F (1, 49) = 0.572, p=ns.

Corrected pattern separation scores were calculated as correctly identified similar objects as “similar” subtracted by false alarms (incorrectly identifying novel objects as “same”)

presented on each background type and a main effect of scene condition was found F (2, 98) = 4.705, p<0.001. Follow up paired t-tests revealed significant differences between the White Background and the other scene conditions (Repeated Scene t(50) = 3.994, p<0.001, d = .591; and Novel Scene t(50) = -4.276, p<0.001, d = -0.600). These results can be found in **Figure 1** below.

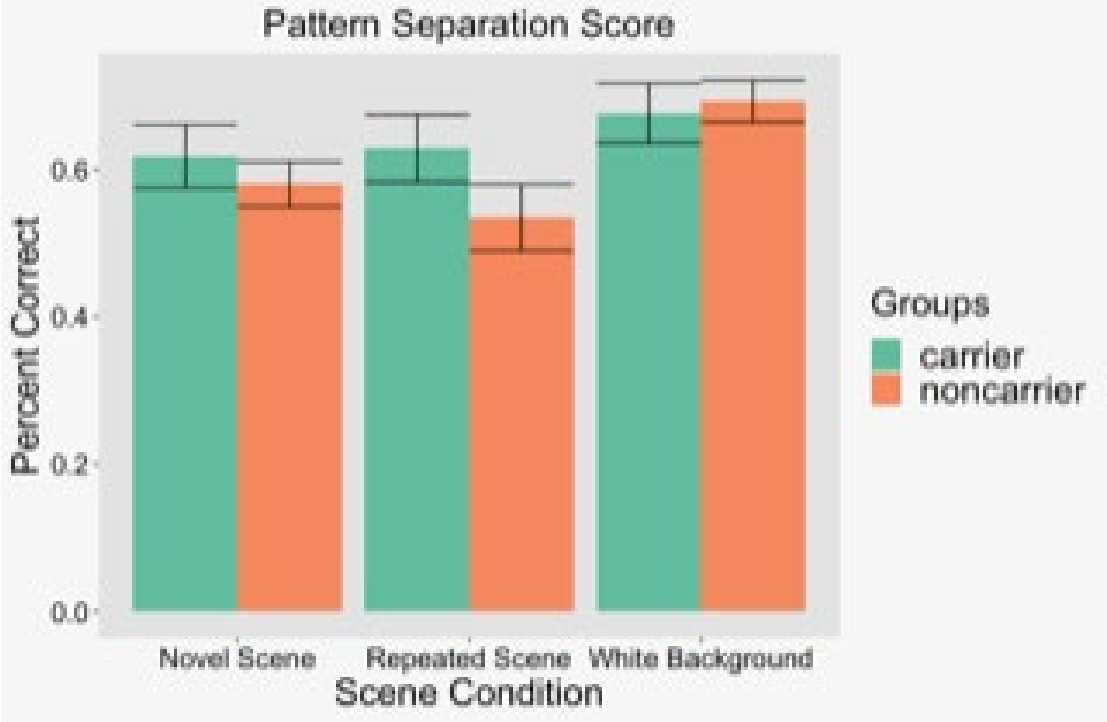

Figure 1: *Pattern separation score result graph*

These results indicate that participants were more easily able to identify similar objects on White Backgrounds rather than on Repeated or Novel Scenes. There was no main effect of APOE status F (1, 49) = 0.640, p=ns.

When participants saw similar objects, they can make one of two different kinds of errors. Error difference scores were calculated as incorrectly identified similar images as “same” subtracted by incorrectly identified similar images as “different.” A main effect of scene

condition was found, F (2, 98) = 9.714, p<0.001. Follow up paired t-tests revealed significant differences between the White Background and the other scene conditions (Repeated Scene t(50) = -7.392, p<0.001, d = -1.033; and Novel Scene t(50) = 3.350, p<0.01, d = 0.4739). These results can be found in **Figure 2** below.

***Figure 2**: Error difference score result graph*

A negative error difference score means participants tended to say "different" more than "same" and a positive error difference score means participants tended to say "same" more than "different." The results represented in **Figure 2** above indicate that participants tended to make the mistake of incorrectly identifying similar objects as "same" on both Repeated Scenes and Novel Scenes. It was also found that similar objects shown on White Backgrounds tended to be incorrectly identified more as "different" than on the other scene conditions. There was no main effect of APOE status F (1, 49) = 0.129, p=ns.

Discussion

The white scene condition made an impact in the pattern separation and error analyses. The white and repeated scene conditions benefitted younger adults in corrected pattern separation and recognition scores, as it made correct identification of objects easier. The white scene condition also happened to influence the types of errors that were made, as it influenced participants to incorrectly identify similar objects as “different” more than on the repeated or novel scene conditions.

For corrected recognition scores, there was a main effect of scene. This means that it was easier for participants to recognize certain objects on certain scenes. T-tests revealed that participants were collectively worse at identifying repeated objects when they were depicted on novel scenes. This could be due to the fact that the unfamiliarity of scene condition induced the participant to believe they had not seen the repeated object before.

For pattern separation scores, there was a main effect of scene and t-tests revealed that participants were collectively better at identifying objects when they were depicted on white backgrounds. This could be due to the fact that the white scene condition did not have any additional distractions and the participants only had one feature of overlap (the objects) to differentiate between.

For error scores, there was a main effect of scene condition and t-tests revealed that participants tended to make the same types of errors on repeated scenes and novel scenes of incorrectly identifying similar objects as “same.” However, the white scene condition was different from the other scene conditions, such that participants tended to identify similar objects as “different.” It appears that the white scene condition had fewer familiar components, so participants were able to direct their cognitive resources to just looking at the object they needed to identify.

APOE e4 carriers and noncarriers did not differ in scores or error types throughout the task. Cognitive differences in e4 carriers and noncarriers are subtle, especially in younger adults, and it may not be noticeable in such a task as this. More sensitive measures may be needed to detect whether or not there are differences between young adult carriers and noncarriers of the e4 allele.

It was expected that the repeated and white scene conditions would have helped participants to identify repeated objects and these results would be similar for recognition. However, this repeated scene condition may have served more as a distraction from the object, whereas the white scene condition required participants to only focus on the object without the overlapping features of scene condition.

It was also expected that all objects depicted on white backgrounds would be easier to identify and little to no errors would be made on these scene conditions. While this was true, a surprising result was observed that similar objects tended to be identified as novel more than on the other scene conditions. Because the white condition is not providing any other

information besides object, it is less likely to make the error of subtle details that the repeated and novel scenes provide. Research has provided evidence to suggest that the context objects are viewed in are always taken into consideration, even if it is not an intentional effort (Burke et al., 2018). It could be that participants were focusing more on scene condition than predicted, and their responses relied heavily on these scenes, so without detailed scene context, such as in the white backgrounds, it was difficult to differentiate between objects.

Conclusion

Although no differences were found in relation to APOE status, scene conditions had an effect on participant scores. As stated before, context of the object and of surrounding elements is always taken into consideration when identifying and recognizing objects (Burke et al., 2018). This has impacts on day to day function in younger and older adults alike. There is a question of how brain activation in carriers and noncarriers differs in pattern separation and other tasks like it and how the results are indicative of aging effects.

Tables and Figures

	Carriers (n=14)	Noncarriers (n=37)
Mean Age (sd)	23 (5.0)	21 (4.3)
Mean Education (sd)	14.9 (3.1)	14.2 (2.7)
High school	42.80%	48.60%
Some college	21.40%	18.90%
Undergraduate degree	14.30%	13.50%
Postgraduate degree	21.40%	18.90%
Ethnicity		
White	85.70%	73%
Hispanic	7%	2.70%
Asian	7%	2.70%
Gender		
male	21.40%	27%
female	78.50%	73%

Table 1: *Demographic information of participants*

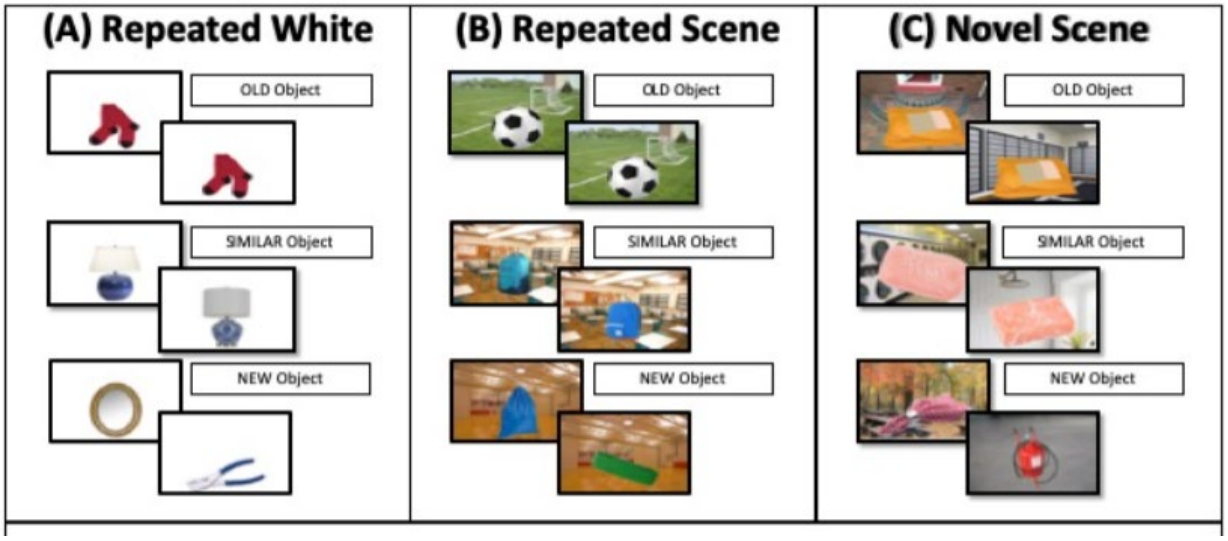

Figure 3: *Example background and object combinations*

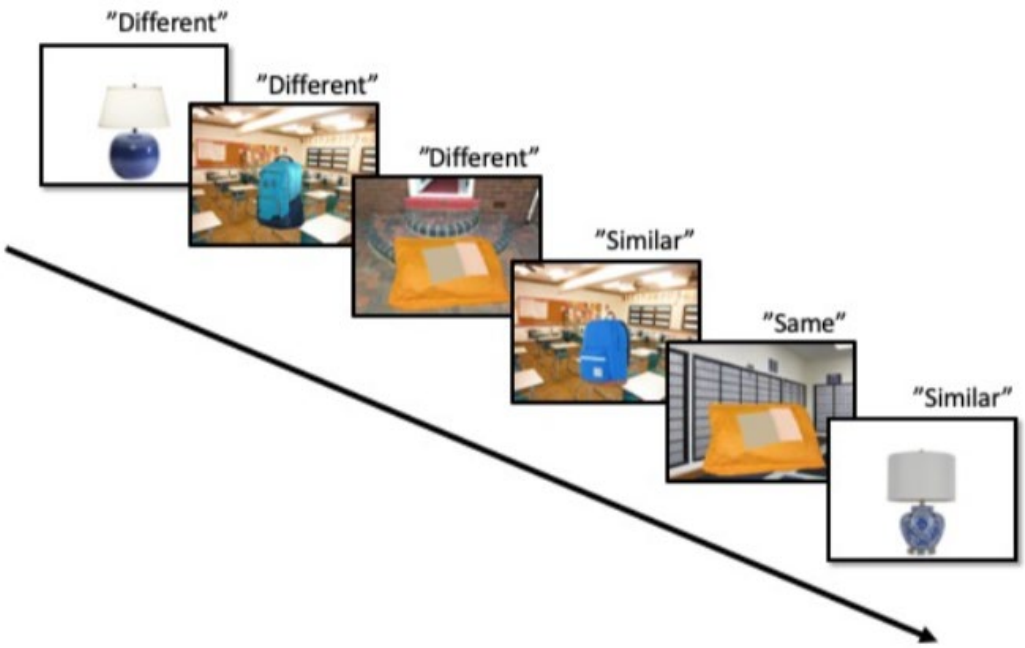

Figure 4: *Task example pictures*

References

Burke, S. N., Gaynor, L. S., Barnes, C. A., Bauer, R. M., Bizon, J. L., Roberson, E. D., & Ryan, L. (2018). Shared Functions of Perirhinal and Parahippocampal Cortices: Implications for Cognitive Aging. *Trends in neurosciences*, *41*(6), 349–359. https://doi.org/10.1016/j.tins.2018.03.001

Christian R. A. Mondadori, Dominique J. -F. de Quervain, Andreas Buchmann, Henrietta Mustovic, M. Axel Wollmer, Conny F. Schmidt, Peter Boesiger, Christoph Hock, Roger M. Nitsch, Andreas Papassotiropoulos, Katharina Henke (2007). Better Memory and Neural Efficiency in Young Apolipoprotein E *ε4* Carriers. *Cerebral Cortex*, *17*(8), 1934–1947. https://doi.org/10.1093/cercor/bhl103

Ferreira, Catarina S, Maraver, Maria J, Hanslmayr, Simon, & Bajo, Teresa. (2019). Theta oscillations show impaired interference detection in older adults during selective memory retrieval. *Scientific Reports, 9(1),* 9977-11. https://doi.org/10.1038/s41598-019-46214-8

Han, S. Duke, Houston, Wes S., Jak, Amy J., Eyler, Lisa T., Nagel, Bonnie J., Fleisher, Adam S., Brown, Gregory G., Corey-Bloom, Cody, Salmon, David P., Thal, Leon J., Bondi, Mark W. (2007). Verbal paired-associate learning by APOE genotype in non-demented older adults: fMRI evidence of a right hemispheric compensatory response. *Neurobiology of Aging, 28*(2), 238-247. https://doi.org/10.1016/j.neurobiolaging.2005.12.013.

Hayes, S.M., Nadel, L., & Ryan, L. (2007). The effect of scene context on episodic object recognition: Parahippocampal cortex mediates memory encoding and retrieval success. *Hippocampus,* 17, 873-889.

Liu, C. C., Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature reviews. Neurology*, *9*(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

Peters, R. (2006). Ageing and the brain. *Postgraduate medical journal*, *82*(964), 84–88. https://doi.org/10.1136/pgmj.2005.036665

Sheppard, D. P., Graves, L. V., Holden, H. M., Delano-Wood, L., Bondi, M. W., & Gilbert, P. E. (2016). Spatial pattern separation differences in older adult carriers and non-carriers for the apolipoprotein e epsilon 4 allele. *Neurobiology of Learning and Memory*, *129*, 113–119. https://doi-org.ezproxy4.library.arizona.edu/10.1016/j.nlm.2015.04.011

Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. (2013). A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia*, *51*(12), 2442–2449. https://doi.org/10.1016/j.neuropsychologia.2012.12.014

Wesnes, K.A., Annas, P., Basun, H. *et al.* Performance on a pattern separation task by Alzheimer's patients shows possible links between disrupted dentate gyrus activity and apolipoprotein E ∈4 status and cerebrospinal fluid amyloid-β42 levels. (2014). *Alzheimer's Research Therapy*, *6*(20). https://doi.org/10.1186/alzrt250

Yassa, M. A., & Stark, C. E. (2011). Pattern separation in the hippocampus. *Trends in neurosciences*, *34*(10), 515–525. https://doi.org/10.1016/j.tins.2011.06.006