# Exploring the effects of a comprehensive Mediterranean diet versus a typical American diet on spatial memory and behavior in C57BL/6J mice

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Alzheimer's disease is the most common form of dementia and affects over 6 million Americans 65 and older. In the absence of a cure, addressing modifiable risk factors could potentially reduce the risk of AD development. There is an established relationship between diet and AD risk. For example, studies in rodents found that highly processed Western diets are associated with cognitive impairment and increased amyloid-beta in the hippocampus, a brain region critical for learning and memory. Conversely, plant-based diets like the Mediterranean diet (MD) have been shown to protect against cognitive impairment. A key limitation in the scientific literature is that most animal studies have only examined the effects of extremely high-fat WD (providing over 40-60% kcal from fat), or a MD with only one or two key nutritional components. We aimed to fill a gap in the literature by designing a rodent diet that mimicked the typical American diet (TAD), rather than an exaggerated WD, and a macronutrient-matched MD. C57BL/6J mice were weaned onto one of the two diets at postnatal day 21. Following six months of diet, we conducted behavioral tests, including open field, elevated zero, and object-location memory task (OLMT). In comparison to the MD, mice consuming the TAD had decreased locomotor activity and exploratory behavior, increased anxiety-like behavior, and reduced spatial memory.

## Introduction

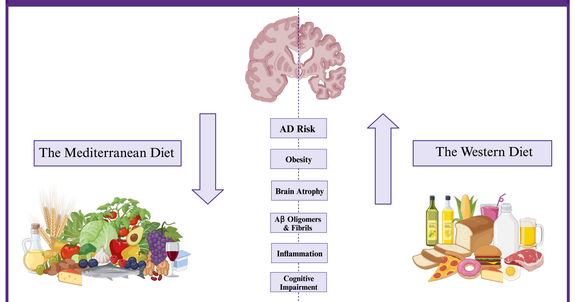
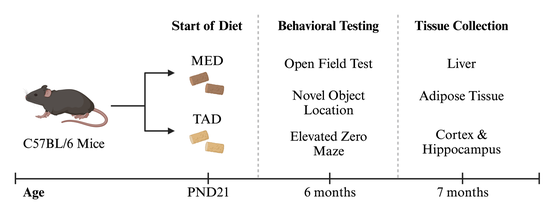



**Figure 1. The Mediterranean diet (MD) has been associated with reduced Alzheimer's-related markers.** High adherence to the traditional MD has been associated with a 72% lower risk for development of dementia in older Greek adults (Charisis et al., 2021).

## Methods

| | % kcal | MD | TAD |
|---|---|---|---|
| **Carb** | 50 | Brown rice & wheat starch | Corn starch |
| **Fat** | 35 | Olive oil, fish oil, & flaxseed oil | Safflower oil, beef fat, butter |
| **Protein** | 15 | Egg whites, soy, & fish protein | Casein (milk fat) |



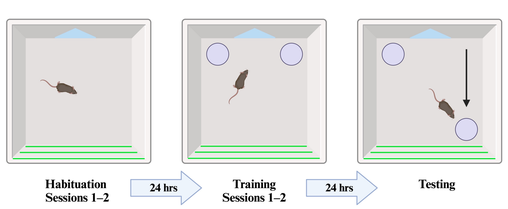
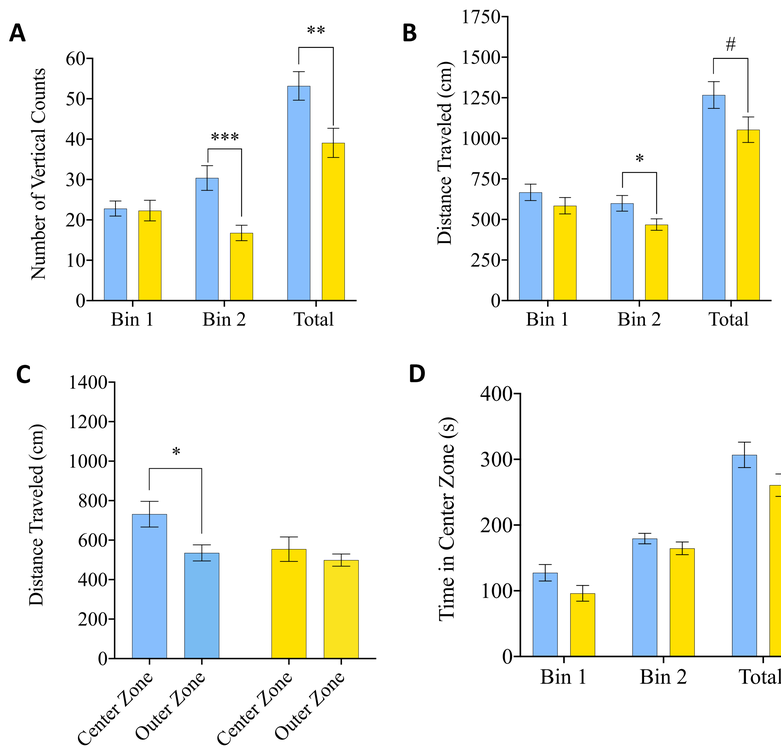




**Figure 1. Object Location Memory Task**

## Results

### Open Field Test




Mediterranean Diet (MD)
Typical American Diet (TAD)

\# $p \leq 0.08$
* $p \leq 0.05$
** $p \leq 0.01$
*** $p \leq 0.001$

**Figure 2. Open Field Test Results.** Independent samples t-tests, two-tailed, were performed to examine exploratory behavior (A) and locomotor activity (B) during the open field test. Mice on the MD exhibited (A) more vertical counts ($p \leq 0.01$) and (B) traveled a significantly farther distance ($p \leq 0.05$) during the last five minutes of testing, compared to mice on the TAD. (C) A paired samples t-test revealed that mice on the MD traveled more in the center zone of the open field compared to the outer zone, $p \leq 0.05$. (D) There was no significant difference in time (seconds) spent in the center zone between the two diet conditions, $p \geq 0.05$.

### Elevated Zero Maze

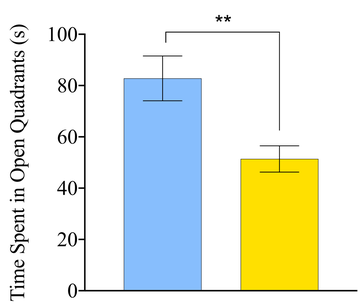



**Figure 3. Elevated Zero Results**. Mice on the MD spent significantly more time in the open quadrants of the elevated zero maze in comparison to mice on the TAD, $p \leq 0.01$.

### Object Location Memory Task

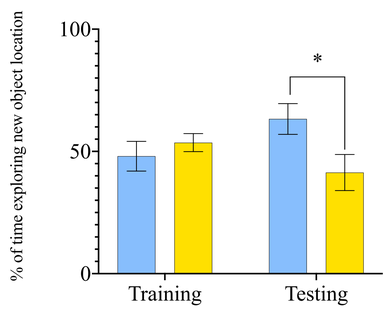



**Figure 4.Object-Location Memory Task Results.** Mice on the MD spent significantly more time exploring the object in the novel location during testing, $p \leq 0.05$. Bars represent mean ± SEM.

## Conclusions

- The TAD decreased exploratory behavior and locomotor activity, and increased anxiety-like behavior compared to the MD.
- The MD protected against *cortical* $A\beta_{1-42}$ & spatial memory impairment compared to the TAD

## Future Directions

- Investigate molecular markers related to learning and memory in the hippocampus and frontal cortex.
- Further explore the specific type of memory deficits through additional behavior testing, such as the Barnes Maze.

## References

1. Charisis, S., Ntanasi, E., Yannakoulia, M., Anastasiou, C. A., Kosmidis, M. H., Dardiotis, E., Hadjigeorgiou, G., Sakka, P., & Scarmeas, N. (2021). Mediterranean diet and risk for dementia and cognitive decline in a Mediterranean population. *J Am Geriatr Soc*, *69*(6), 1548-1559. https://doi.org/10.1111/jgs.17072
2. Farr, S. A., Price, T. O., Dominguez, L. J., Motisi, A., Saiano, F., Niehoff, M. L., Morley, J. E., Banks, W. A., Ercal, N., & Barbagallo, M. (2012). Extra virgin olive oil improves learning and memory in SAMP8 mice. *J Alzheimers Dis*, *28*(1), 81-92. https://doi.org/10.3233/jad-2011-110662
3. Grossi, C., Rigacci, S., Ambrosini, S., Ed Dami, T., Luccarini, I., Traini, C., Failli, P., Berti, A., Casamenti, F., & Stefani, M. (2013). The polyphenol oleuropein aglycone protects TgCRND8 mice against Aß plaque pathology. *PLoS One*, *8*(8), e71702. https://doi.org/10.1371/journal.pone.0071702
4. Lauretti, E., Iuliano, L., & Praticò, D. (2017). Extra-virgin olive oil ameliorates cognition and neuropathology of the 3xTg mice: role of autophagy. *Ann Clin Transl Neurol*, *4*(8), 564-574. https://doi.org/10.1002/acn3.431
5. Li, X. Y., Liu, Y. H., Wang, B., Chen, C. Y., Zhang, H. M., & Kang, J. X. (2018). Identification of a sustainable two-plant diet that effectively prevents age-related metabolic syndrome and extends lifespan in aged mice. *J Nutr Biochem*, *51*, 16-26. https://doi.org/10.1016/j.jnutbio.2017.09.003
6. Nakajima, S., Fukasawa, K., Gotoh, M., Murakami-Murofushi, K., & Kunugi, H. (2020). Saturated fatty acid is a principal cause of anxiety-like behavior in diet-induced obese rats in relation to serum lysophosphatidyl choline level. *Int J Obes (Lond)*, *44*(3), 727-738. https://doi.org/10.1038/s41366-019-0468-z
7. Nardiello, P., Pantano, D., Lapucci, A., Stefani, M., & Casamenti, F. (2018). Diet Supplementation with Hydroxytyrosol Ameliorates Brain Pathology and Restores Cognitive Functions in a Mouse Model of Amyloid-β Deposition. *J Alzheimers Dis*, *63*(3), 1161-1172. https://doi.org/10.3233/jad-171124
8. Walker, J. M., Dixit, S., Saulsberry, A. C., May, J. M., & Harrison, F. E. (2017). Reversal of high fat diet-induced obesity improves glucose tolerance, inflammatory response, β-amyloid accumulation and cognitive decline in the APP/PSEN1 mouse model of Alzheimer's disease. *Neurobiol Dis*, *100*, 87-98. https://doi.org/10.1016/j.nbd.2017.01.004
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