Alzheimer’s disease is a complex neurodegenerative disorder that results in a decline in cognitive functions and mental health. Recent investigations have shown specific alterations in the gut microbiome composition in individuals with Alzheimer’s disease and rodent models. In this study, the authors from Ireland, Italy, and the United Kingdom transplanted fecal materials from patients diagnosed with Alzheimer’s disease into microbiota-depleted young adult rats to investigate the involvement of gut microbiota in host physiology, behavior, and the process called adult hippocampal neurogenesis. In addition, they used an *in vitro* neurogenesis assay to examine whether serum from patients with Alzheimer’s disease modulates adult hippocampal neurogenesis.

The hippocampus, which plays a pivotal role in the learning and memory processes, is particularly susceptible to Alzheimer’s pathology and is one of the earliest brain regions to be affected. Alteration of the process called adult hippocampal neurogenesis, in which neural stem cells in the hippocampus generate new neurons, precedes neurofibrillary tangles and amyloid-β plaque formation.

Diet is a major risk factor for dementia that could be targeted to prevent the disease. A recent study investigating the association between adherence to the Mediterranean diet and the incidence of dementia showed that higher adherence to the Mediterranean diet, which induces changes in the gut microbiome and reduces fecal calprotectin concentrations, was associated with a lower risk for all-cause dementia.
https://discovermednews.com/the-mediterranean-diet-is-associated-with-a-lower-risk-of-dementia/



About the study

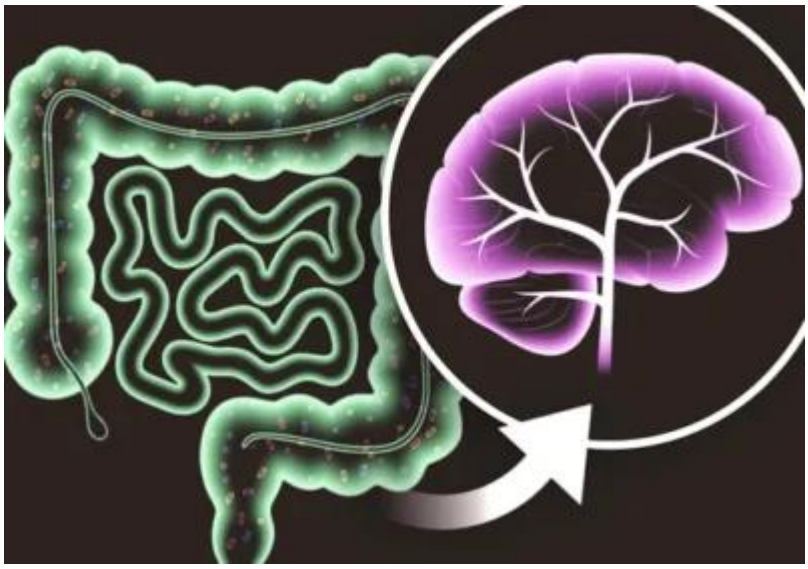
Serum and stool samples were collected from 54 participants with Alzheimer’s disease and 41 controls. The analysis of the gut microbiota composition was performed. by bacterial 16S rRNA gene sequencing. Hippocampal neurogenesis was investigated by immunohistochemistry.

The researchers transplanted fecal samples from cognitively healthy subjects or patients

diagnosed with Alzheimer's disease into microbiota-depleted young male Sprague-Dawley rats. Before fecal microbiota transplantation, the animals were treated with an antibiotic cocktail of ampicillin, vancomycin, ciprofloxacin, and imipenem for seven consecutive days. After seven days of antibiotic treatment, rats were randomly assigned to the first group that received fecal microbiota transplantation from healthy controls (n= 16), and the second group that received fecal microbiota transplantation from patients with Alzheimer's disease (n= 16).

A series of behavioral tests were performed in young adult rats colonized with fecal material: open field test, elevated plus maze test, modified spontaneous location recognition test, novel object recognition, novel location recognition, Morris water maze test, and forced swimming test.

Lastly, researchers used an *in vitro* neurogenesis assay to study how serum from patients with Alzheimer's disease modifies hippocampal neurogenesis. Human embryonic hippocampal progenitor cells were exposed to serum derived from Alzheimer's patients or healthy control subjects. The percentage of cells expressing markers for neural stem cell proliferation (Ki67), differentiation (MAP2, DCX), and programmed cell death (CC3) was determined.



Results

Patients diagnosed with Alzheimer's disease had increased serum levels of interleukin (IL)-1β, IL-10, inflammasome marker NLRP3, and macrophage migration inhibitory factor (MIF). They had decreased serum levels of IL-4 compared to healthy controls. The stool samples of patients with Alzheimer's disease had higher levels of fecal calprotectin, which directly measures intestinal inflammation, than healthy controls.

The analysis of the gut microbiota composition demonstrated that alpha and beta diversities did not differ between patients with Alzheimer's disease and healthy controls. At the phylum level, Alzheimer's patients exhibited a higher abundance of Bacteroidetes and a lower abundance of Firmicutes and Verruocomicrobiota. At the genus level, Alzheimer's patients

had a reduced relative abundance of Clostridium sensu stricto 1 and the genera Coprococcusm, and an increased relative abundance of the pathobiont genera Desulfovibrio.

Fecal microbiota transfer from cognitively healthy subjects into microbiota-depleted young male Sprague-Dawley rats resulted in relatively stable taxa diversity in rats. In contrast, rats colonized with fecal material from Alzheimer's patients showed greater changes in microbial genera between 10 and 59 days after transfer. *Desulfovibrio*, a genus enriched in participants with Alzheimer's disease, increased significantly in rats on day 59, compared to day 10.

Behavioral tests performed in young adult rats colonized with fecal materials demonstrated that rats colonized with fecal material from patients with Alzheimer's disease exhibited reduced discrimination between familiar and novel locations, with impairments in their long-term spatial and recognition memory. There was no change in locomotor parameters and anxiety-related behavior.

Immunohistochemistry showed reduced hippocampal neurogenesis in the dentate gyrus of rats colonized with fecal material from Alzheimer's patients. A 3D reconstruction of cells expressing neural stem cell differentiation (DCX) markers demonstrated a reduction in total dendritic length and dendritic complexity in DCX cells. According to these results, gut microbiota from patients diagnosed with Alzheimer's disease negatively affected the survival and dendritic arborization of neurons. There were no significant differences in microglia density in the dentate gyrus, suggesting that neuroinflammatory processes in this brain region play a minimal role in the cognitive dysfunction observed in rats.

Ii vitro neurogenesis assay demonstrated decreased expression of Ki67-positive cells and reduced proliferative capacity of differentiating embryonic hippocampal progenitor cells in the presence of serum from patients with Alzheimer's disease, indicating a decreased proliferative capacity of differentiating embryonic hippocampal progenitor cells. The percentage of Map2-positive immature neurons and DCX-positive neuroblasts also decreased, indicating impaired neurogenesis.

These *in vitro* findings are consistent with those found *in vivo,* showing that serum from patients with Alzheimer's disease had a direct and negative effect on neuron proliferation and differentiation.

Conclusion

This study showed that fecal material transfer from Alzheimer's patients to healthy young adult rats resulted in cognitive deficits and impaired hippocampal neurogenesis. These results confirmed the significance of gut microbiota in Alzheimer's disease. The researchers suggested that future studies should explore the underlying mechanisms by which the gut microbiota affect hippocampal neurogenesis and pathogenesis of Alzheimer's disease, potentially opening avenues for new therapeutic approaches.

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Journal Reference

Grabrucker, S, Marizzoni, M, Silajdžić E, et al. Microbiota from Alzheimer's patients induce

deficits in cognition and hippocampal neurogenesis. BRAIN 2023: 00; 1–19. https://doi.org/10.1093/brain/awad303