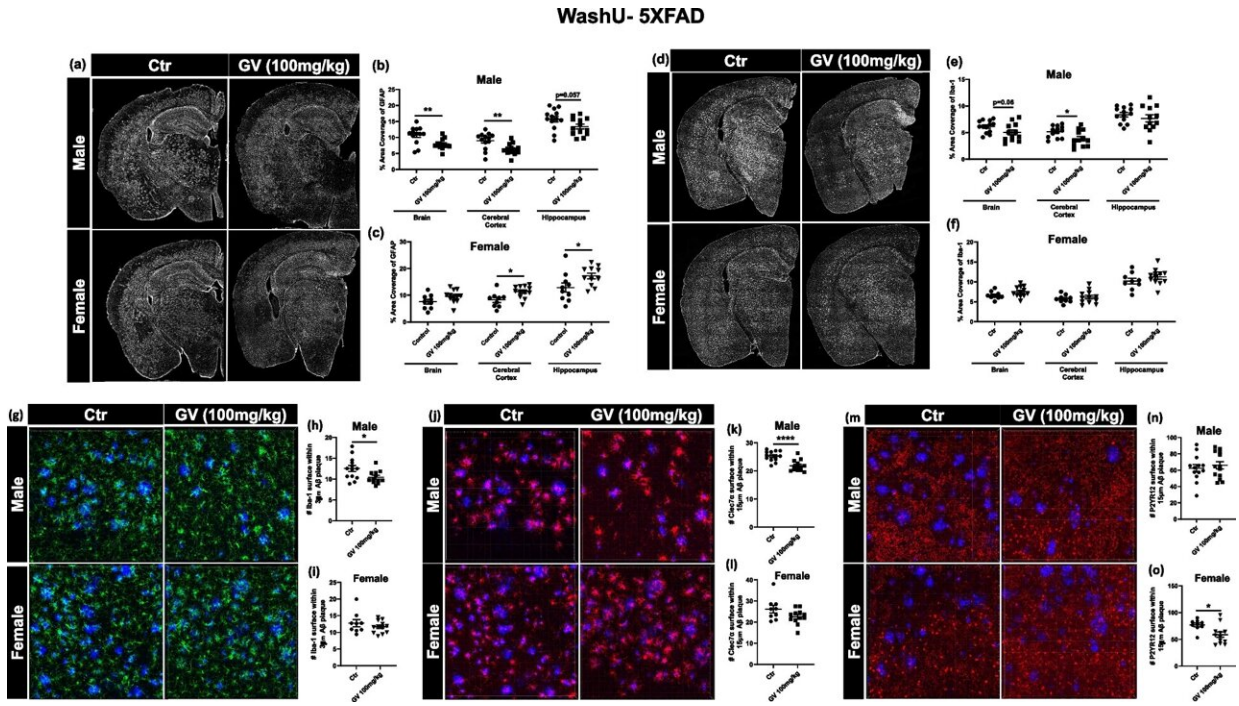
Microbiome studies explore why more women develop Alzheimer's disease

February 20 2024, by Matt Wood



GV-971 significantly reduces glial inflammation in 9 month old 5XFAD male mice. Credit: *Molecular Neurodegeneration* (2024). DOI: 10.1186/s13024-023-00700-w

According to the Alzheimer's Association, almost two-thirds of Americans with Alzheimer's dementia are women. While some of this discrepancy can be attributed to women living longer than men on average, researchers believe biological factors play a role as well.

A pair of new studies from the University of Chicago explores sex-specific differences in the development of Alzheimer's-like symptoms in mice, including the impact of estrogen, the primary female reproductive hormone, on the formation of amyloid plaques and inflammation in the brain—two hallmark symptoms of the disease. The research also strengthens evidence of the gut microbiome's role in mediating these symptoms, providing clues that could someday help develop treatments.

Clues pointing to the microbiome

Alzheimer's disease is characterized by the formation of amyloid plaques, or clumps of the protein amyloid beta (Aβ) that accumulate in the brain. The disease also activates immune cells present in the brain known as microglia, which can help remove amyloid plaques but may also exacerbate the disease by causing inflammation.

In 2019, a research team led by Sangram Sisodia, Ph.D., the Thomas A. Reynolds Sr. Family Professor of Neurobiology at UChicago, treated mouse models of Alzheimer's disease with a cocktail of antibiotics during the second week of life.

The antibiotics lessened the formation of amyloid plaques and microglia activation in males—but surprisingly, not female mice—by 3 months of age. Although this antibiotic regimen initially wipes out all gut bacteria, the gut becomes repopulated with numerous additional bacterial species over the next three months.

Sisodia reasoned that the microbiome must play a major role in these changes in amyloid deposition and neuroinflammation. To prove that the improvements in Alzheimer's symptoms were caused by alterations in the gut microbiome, they also transplanted fecal matter from untreated mice into antibiotic-treated animals.

This procedure restored the gut microbiome and caused an increase in amyloid plaque formation and microglial activation. These findings have since been confirmed and reported in several labs around the country.

Sex-specific microbiome changes

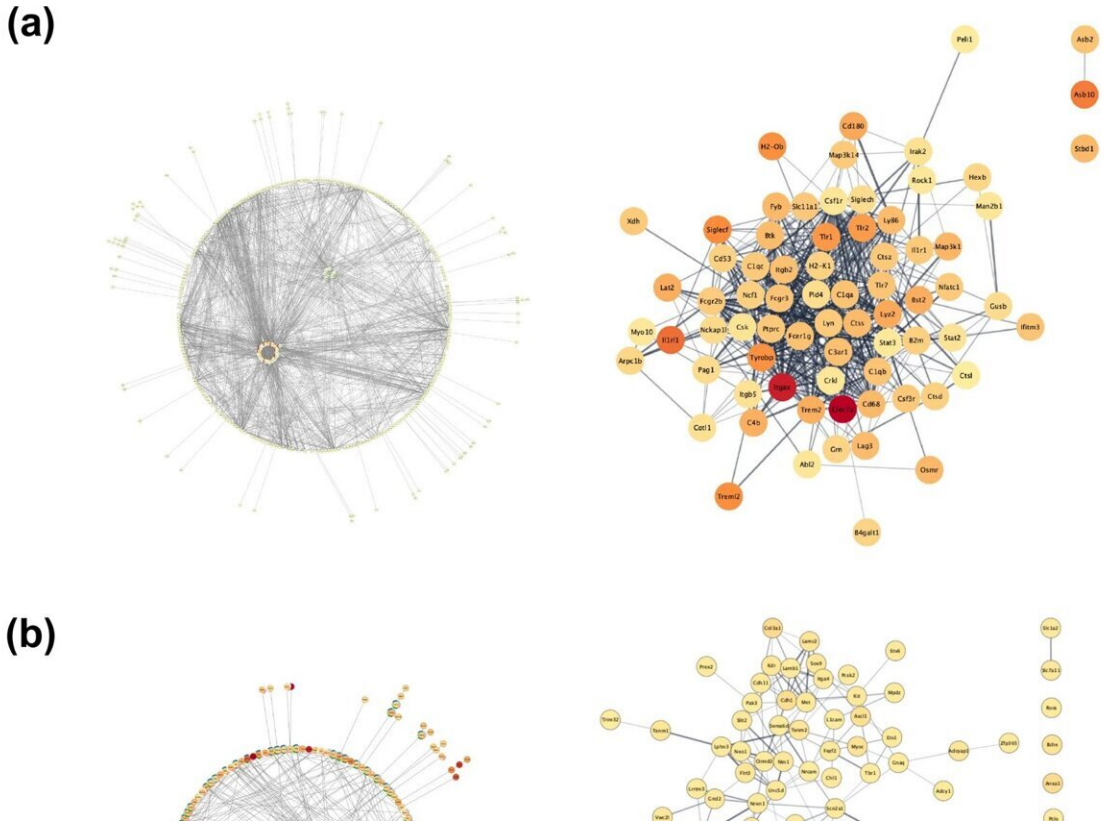
In the first of new papers, published in Molecular Neurodegeneration, Sisodia and his colleagues tested the effects of a new drug compound called sodium oligomannate, or GV-971, on the formation of amyloid deposits and neuroinflammation.

The compound was originally derived from brown seaweed by the Chinese pharmaceutical company Shanghai Green Valley Pharmaceuticals. In the company's testing, GV-971 reduced amyloid deposits and neuroinflammation in Alzheimer's mouse models. The compound has also undergone Phase III clinical trial testing in China and is now clinically approved for patients with Alzheimer's.

When Sisodia and his team tested GV-971 on a mouse model of Alzheimer's, they saw a significant drop in amyloid deposits, even at the lowest doses, and a reduction in inflammatory markers in the microglia—but again, these changes were only observed in male animals. They also noted significant changes in the composition and abundance of several types of gut bacteria in male mice but fewer changes in the microbiome of females.

Independently, and unbeknownst to Sisodia, David Holtzman, MD, the Barbara Burton and Reuben M. Morriss III Distinguished Professor of Neurology at Washington University in St. Louis and co-author of the paper, conducted a similar set of experiments with GV-971 in a different line of mice and saw similar results: The levels of amyloid deposition and neuroinflammation were significantly decreased, but only in male mice.

Moreover, a host of bacterial species that were changed by GV-971 in the studies from the Sisodia lab also appeared to be changed in Holtzman's experiments.



Cytoscape and GSEA analyses using significantly altered genes (*P*

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