Roots of Alzheimer's disease extend beyond the brain

Hidden biological signals in the gut point to Alzheimer's as a whole-body disorder

By Richard Harth, ASU News
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For decades, Alzheimer's disease has been treated as a condition that begins and ends in the brain. Researchers have focused on the buildup of amyloid plaques, tangles of tau protein and the slow loss of neurons that erode memory and thinking.

But a growing body of research is now pointing to another player in the disease: the gut.

In a new study, Diego Mastroeni and his colleagues at Arizona State University have uncovered links between the mind-robbing progression of Alzheimer's disease and changes in the gut. The findings deepen our understanding of the gut-brain axis, suggesting new approaches for early diagnosis and treatment.

"What if Alzheimer's doesn't start in the brain at all? Gut problems aren't just coincidental in Alzheimer's disease, they appear to be biologically linked to the disease process itself, sometimes years before memory symptoms appear," Mastroeni says. "Because the brain and gut are constantly communicating through the gut-brain axis, there may be a window of opportunity for earlier diagnosis and new approaches to treatment."

Mastroeni is a researcher with the ASU-Banner Neurodegenerative Disease Research Center. The research appears in the current issue of the journal Alzheimer's & Dementia.

Wave of disaster

Over a century after the first case of Alzheimer's disease was diagnosed, the devastating illness remains without treatment or cure. But new findings are altering our picture of the disease, deepening the appreciation of its multifaceted nature and opening new doors to treatment.

New approaches are desperately needed, as the disease now afflicts around 7 million people in the U.S. alone. This number is projected to skyrocket to over 12 million by mid-century, according to the Alzheimer's Association.

The researchers analyzed colon tissue from people who had Alzheimer's disease and compared it with tissue from people without memory problems. They uncovered striking differences in gut proteins, immune activity and microbial communities. The findings suggest that the gut may play a much larger role in Alzheimer's than previously recognized.

The study was unusual because the researchers examined human colon tissue collected at autopsy. Most previous human studies have relied on fecal samples, which capture what exits the body, rather than what resides in it. This new approach allowed the team to directly measure the microbes and proteins interacting within the gut itself.

Weaker immune defenses in the gut

One of the more striking findings was that the gut's immune defenses appeared weaker in people with Alzheimer's. Key proteins that normally help the gut fight off bacteria and fungi were reduced, potentially making the gut more vulnerable to harmful microbes.

This pattern is notable because it contrasts sharply with what is seen in the brain in Alzheimer's, where immune activity is often overactive and inflammatory. The imbalance suggests that immune regulation may differ dramatically between organs during the disease.

Proteins that protect cells from stress and damage were also lower in Alzheimer's gut tissue. This could make gut cells less able to cope with inflammation and oxidative stress — processes that increase with aging and chronic disease.

The researchers also found that processes involved in energy use were more active in the Alzheimer's samples. These included activities that break down fats and proteins, as well as changes linked to how the body responds to insulin. Together, these shifts suggest that Alzheimer's may disrupt metabolism not only in the brain, but throughout the body.

A second nervous system shows signs of damage

Mammals, including humans, have two interconnected nervous systems: the central nervous system, which includes the brain and spinal cord, and the enteric nervous system — a vast network of neurons embedded throughout the digestive tract. The enteric system helps regulate digestion, movement of food through the gut and ongoing communication between the gut and the brain.

Neurons in both nervous systems communicate through connections called synapses. Alzheimer's disease is known to damage synapses between brain cells. In the new study, the researchers found that proteins involved in synaptic communication were also reduced in the gut.

This finding could help explain why many people with Alzheimer's experience gastrointestinal symptoms long before cognitive decline.

Hallmark protein appears in the gut

Another major finding was the detection of higher levels of amyloid-beta 42 (A?42), a hallmark protein of Alzheimer's, in colon tissue. People with Alzheimer's had significantly more A?42 in their gut tissue than people without memory problems.

This raises the possibility that amyloid can accumulate outside the brain or potentially move through the body. While the meaning of gut amyloid is still being investigated, the finding reinforces the idea that Alzheimer's may involve systemic processes rather than being confined to the brain.

The microbiome tells a story

The gut microbiome also looked different in people with Alzheimer's. Certain bacteria, including christensenellaceae and desulfovibrio, were more abundant, while several bacteria commonly linked to gut health, including streptococcus, blautia and lachnospiraceae, were reduced.

Several of these microbial changes were associated with disease severity, including memory test scores and the buildup of amyloid plaques and tau tangles in the brain. Together, these patterns suggest that shifts in gut microbes may mirror how far Alzheimer's has progressed.

The gut-brain connection is a rapidly expanding area of research. This study strengthens the idea that changes in gut immunity, metabolism, microbial communities and nerve signaling could contribute to the inflammation, protein buildup and neural dysfunction seen in Alzheimer's.

Understanding these gut changes may eventually open doors to new diagnostic tools, such as gut-based biomarkers in tissue or possibly even in stool. The work also points toward potential treatment strategies, including targeting the microbiome through diet, probiotics or other interventions.

"While more research is needed to understand how these changes begin and whether they can be targeted, the field is clearly moving beyond a brain-only view toward a broader, systems-level understanding of the disease," Mastroeni says.

The research was made possible through critical support from the Arizona Alzheimer's Consortium, whose investment in local scientific teams enabled the generation of early-stage data needed to compete for major national funding. The researchers emphasize that these relatively small state investments play an outsized role in launching innovative biomedical discoveries.

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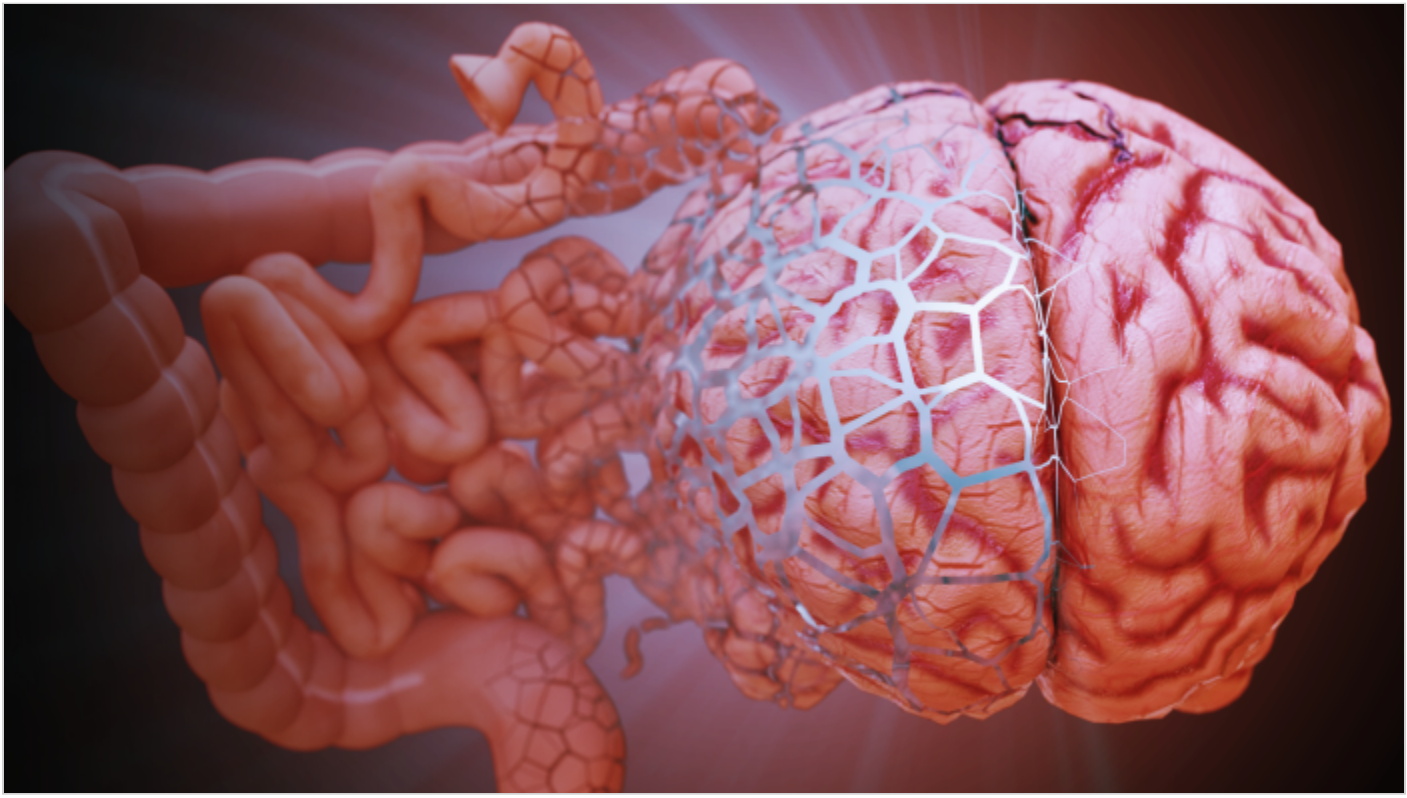

New research is reshaping how scientists think about Alzheimer’s by revealing unexpected connections between the gut and the brain. Graphic by Jason Drees/ASU

Text image(s)

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