ASU researchers propose unifying model of Alzheimer’s disease

Stress granules in the brain may drive massive changes in gene activity, a new theory suggests

By Richard Harth, ASU News
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In a groundbreaking theory, scientists at Arizona State University's Biodesign Institute propose a unifying explanation for the molecular chaos driving Alzheimer's disease. The condition causes widespread disruption of gene behavior, affecting every known neuropathology and clinical manifestation of the disease.

According to the analysis, the changes caused by the illness may stem from a breakdown in the transport system that shuttles vital molecules between the cell nucleus and cytoplasm, the liquid environment surrounding the nucleus where many essential processes occur. The scale of disruption, involving over 1,000 genes, underscores the complexity of Alzheimer’s.

The sabotage of cellular messaging, triggered by the formation of chronic stress granules in the brain, may be a key factor in the development of Alzheimer’s and other neurodegenerative diseases — much like a citywide power failure shutting down critical systems. Stress granules are clumps of proteins and RNA that form in response to cell stress.

The review, led by Paul Coleman and colleagues with the ASU-Banner Neurodegenerative Disease Research Center, highlights the fact that gene expression — the process by which genes produce the proteins essential for cell function — is altered on an enormous scale in Alzheimer’s.

These changes affect the proper functioning of synapses in the brain, as well as metabolism, protein processing and cell survival. The research could point the way to radically new approaches to addressing Alzheimer’s disease at its earliest stages.

“Our proposal, focusing on the breakdown of communication between the nucleus and cytoplasm leading to massive disruptions in gene expression, offers a plausible framework to comprehensively understand the mechanisms driving this complex disease," Coleman says. "Studying these early manifestations of Alzheimer's could pave the way for innovative approaches to diagnosis, treatment and prevention, addressing the disease at its roots."

Coleman is joined by Elaine Delvaux, Ashley Boehringer, Carol Huseby and center Director Jeffrey Kordower.

The research findings appear in the current issue of Alzheimer's & Dementia: The Journal of the Alzheimer's Association.

A disease's tangled web

Alzheimer's disease remains one of medical science's most devastating and mysterious ailments, often appearing like many diseases rolled into one. Its symptoms range from memory loss and cognitive decline to personality changes, all driven by complex biological disruptions.

This makes it incredibly difficult for researchers to pinpoint a single cause or develop effective treatments, leaving millions of families grappling with its devastating effects.

Despite more than a century of intense research and billions of dollars invested, there is still no treatment to halt or cure the disease. Meanwhile, the global cost of dementia care remains staggeringly high. In 2019, the worldwide cost of dementia was estimated at $1.3 trillion, a figure projected to rise to $2.8 trillion by 2030, according to Alzheimer's Disease International.

Prior research has focused on tangible symptoms of the disease, like amyloid plaques, tau tangles, inflammation and cellular dysfunction, but no single explanation has emerged to unify these phenomena.

The research suggests that these changes may be traced to a malfunction in the cell's transport system, which moves crucial molecules like RNA and proteins between the nucleus and the surrounding cytoplasm. This failure disrupts the production of essential proteins and alters the chemical switches that control gene activity.

The role of stress granules

The research highlights chronic stress granules as the primary culprits in this process. Stress granules are structures that form temporarily in response to cell stress, helping to pause nonessential processes while the cell recovers. Normally, they protect the cell during stressful conditions and dissolve once the stress subsides.

In Alzheimer’s disease, however, these granules persist abnormally and become chronic and pathological, trapping vital molecules and hampering their movements into and out of the cell nucleus. Instead of providing protection, they cause harm and contribute to the disease’s progression.

Various genetic and environmental factors — including certain gene mutations, inflammation, exposure to pesticides, viruses and air pollution — may contribute to cellular stress.

This stress response and granule formation may then trigger a cascade, leading to disruption of the nucleus-to-cytoplasm transit system. It’s like a clogged highway preventing the movement of critical goods, leaving resources stuck and causing chaos on both sides of the communication hub.

Notably, these radical changes are believed to occur at a very early stage of the disease, long before the appearance of clinical symptoms. Among the most notable of these later manifestations are amyloid plaques, which are clumps of misfolded proteins that accumulate between neurons and disrupt cell communication, and tau tangles — twisted fibers of a protein that build up inside neurons, impairing their function and ultimately leading to cell death.

The prospect of early interventions targeting stress granules offers a potentially transformative approach to combating Alzheimer’s disease. By identifying and addressing the formation of pathological stress granules at the earliest stages, it might be possible to halt or significantly delay the onset of symptoms such as amyloid plaques and tau tangles, and the devastating cognitive consequences of the disease.

“Our paper contributes to the ongoing debate about when Alzheimer’s truly begins — an evolving concept shaped by advances in technology and research,” Coleman says.

“The key questions are when it can first be detected and when intervention should begin, both of which have profound implications for society and future medical approaches.”

Such an approach could shift the focus of Alzheimer’s treatment from managing later-stage symptoms to preventing the disease from advancing altogether. While these interventions are still in the research phase, they highlight a promising avenue for understanding and mitigating the disease’s underlying mechanisms.

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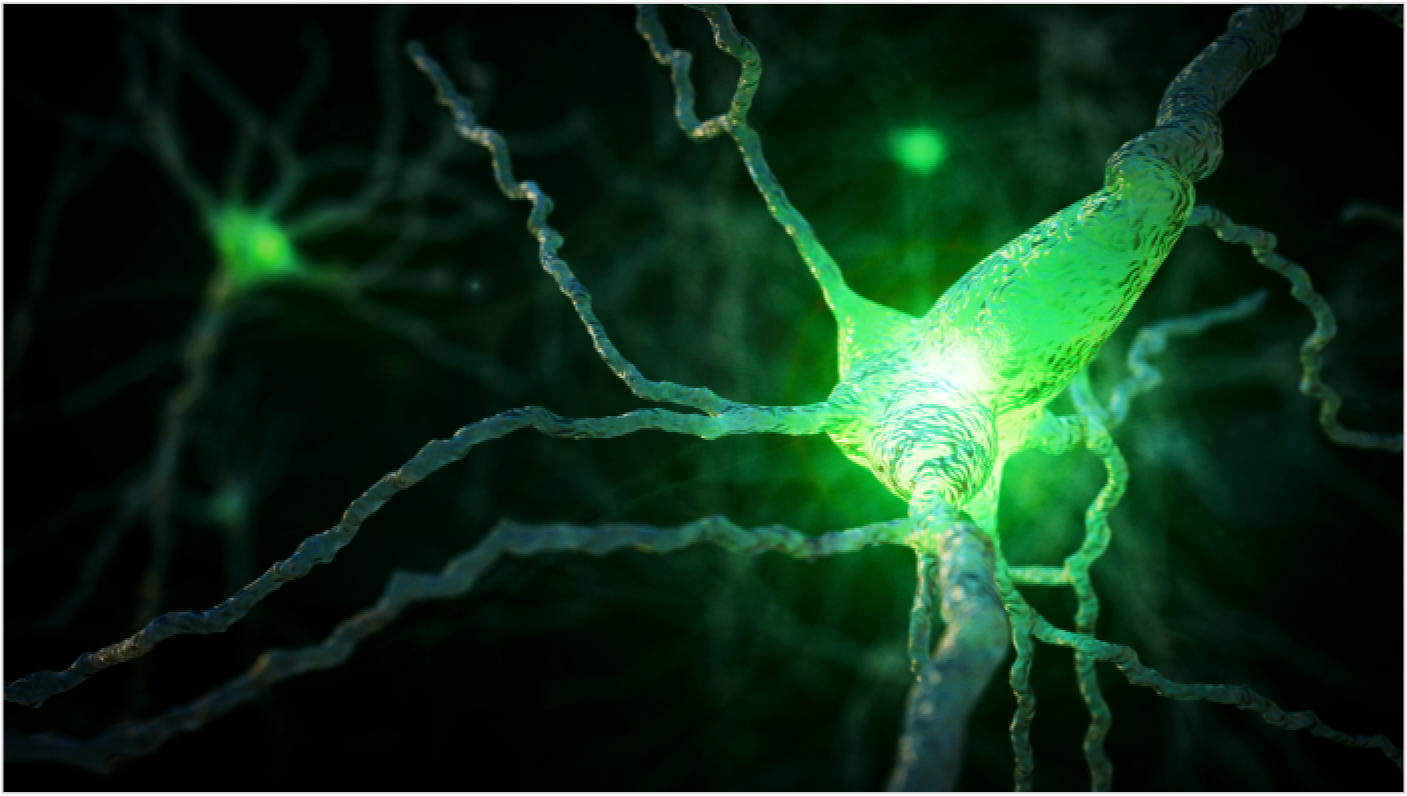
Main image



The disruption of cellular communication, caused by the formation of chronic stress granules in the brain, may play a pivotal role in the onset of Alzheimer’s and other neurodegenerative disorders — similar to a traffic jam clogging key highways and halting the flow of critical resources. Stress granules are clusters of proteins and RNA that assemble in response to cellular stress. Graphic by Jason Drees/ASU

Text image(s)

Paul Coleman

Learn more about how the Biodesign Institute's research is advancing the fight against neurodegenerative diseases.