How Your Immune System Reshapes Your Cognitive Health In Midlife

5 MIN READ

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Scientists once viewed the human brain as siloed from the immune system. New research unveils how the two are intertwined, and why midlife is such a pivotal point.

There are plenty of changes you can see and feel in midlife. Those happening **inside your brain** are less obvious, but just as consequential.

Emerging research suggests that around the age of 50, the brainâ??s immune landscape begins to change. Some of its resident immune cells may decline or behave differently. Meanwhile, immune cells originating elsewhere in the body may begin contributing to the brainâ??s immune-cell population.

It turns out that your brainâ??s immune system is far more dynamic â?? and far more connected to the rest of your body â?? than scientists once thought.

How the Immune System and the Brain Interact

Historically, scientists largely believed that the brain was sheltered from immune activity elsewhere in the body. â??The brain was generally considered to be

â??immune privileged,â?? or sealed away behind the blood-brain barrier (BBB), which very tightly regulates what gets into and out of the brain,â?• says **Tommy Wood, PhD**, a neuroscientist and the author of ***The Stimulated Mind: Future-Proof Your Brain from Dementia and Stay Sharp at Any Age***.Â

We now know thatâ??s far from the case, especially when it comes to microglia, the brainâ??s resident immune cells. You can think of them as a housekeeping crew. Microgliaâ??s key role is to maintain balance in your brain, says **David Perlmutter, MD**, a board-certified neurologist, seven-time *New York Times* bestselling author, and the author of ***Brain Defenders: Harness the Power of Your Immune Cells to Protect Your Brain for Life***. They patrol for trouble, haul away cellular trash, respond to injuries and infections, and maintain healthy connections between brain cells.

How well microglia do those jobs may depend partly on how well they use energy, Dr. Perlmutter explains. Enter immunometabolism: the emerging field examining how an immune cellâ??s metabolism influences how the cell behaves in the brain and throughout the entire body.

But microglia arenâ??t the only channel through which the immune system and brain communicate. The blood-brain barrier, for example, isnâ??t an impenetrable wall. Itâ??s a selective interface that responds to hormones, inflammatory signals, metabolites, and immune cells circulating in the blood, says Dr. Perlmutter. The gut provides another line of communication: Compounds produced by the gut microbiome can influence the immune system and, in turn, impact the brain.

How Changes In the Immune System Affect the Brain In Midlife

Think about the last time you had the flu: You didnâ??t just have a fever. Your energy tanked, brain fog kicked in, and your mood probably took a nosedive. That miserable feeling is partly your immune system talking to your brain.

The concern in midlife is what happens as some of those inflammatory signals become more persistent â?? and start showing up even when youâ??re *not* under the weather.

As we get older, baseline levels of inflammatory cytokines like IL-6 and TNF-Î± often begin to creep upward, particularly as physical health worsens â?? a broader phenomenon referred to as **inflammaging**. According to Dr. Wood, these signals can â??primeâ?• microglia, making them less effective at clearing amyloid and switching off inflammation. This may contribute to a cycle in which the BBB becomes less protective, and the brain becomes less efficient at clearing waste and responding to injury. Researchers have also observed changes in microglia before the accumulation of amyloid and tau, two proteins involved in Alzheimerâ??s disease, he adds.

Metabolic health may hold another piece of the puzzle. Insulin resistance, elevated blood sugar, excess visceral fat, and chronic inflammation can all generate signals that influence the brain, says Dr. Perlmutter. As metabolic health declines, â?? mitochondria become less efficient, oxidative stress increases, and the microglia may remain in a more inflammatory state,â?• he says.

In sum, the brain doesnâ??t get a free pass from whatâ??s happening in the rest of your body.

New Research Is Rewriting the Microglia Story

For years, microglia were thought to be established early in life and remain self-sustaining inside the brain. But new studies are showing that the truth may be more dynamic.

In a ***Nature* study published in July 2026**, researchers found evidence that as we age, immune cells originating in the bone marrow can enter the brain and take on many of the characteristics of microglia. The finding challenges a long-held assumption about where the brain gets its immune cells. â??If immune cells from the

body can ultimately become part of the immune system of the brain, then the health of the body becomes even more relevant to brain health,â?• Dr. Perlmutter says. Plus, the metabolic and inflammatory environment those cells were exposed to may influence how they behave once they enter the brain.

Another July 2026 study published in *Science* found evidence that, between roughly ages 50 and 75, traditional microglia in the hippocampus declined while inflammatory cells became more prominent. The finding offers a potential clue to how the brainâ??s immune environment changes with age, though the study didnâ??t establish that this shift necessarily causes neurodegeneration.

Taken together, these studies raise the possibility that the makeup â?? and even the origins â?? of the brainâ??s immune-cell population may shift as we age.

Compelling as these findings are, thereâ??s still a lot we donâ??t know. Dr. Perlmutter notes that it isnâ??t yet clear whether the influx of peripheral immune cells is helpful, harmful, or even a combination of the two. Dr. Wood also points out that the studies were relatively small and limited in scope. â??However, the fact that both studies found this similar change with age suggests that we may have to update how we think about the source of microglia in the brain,â?• he says.

Can You Keep Your Microglia Healthy?

Thereâ??s no magic solution thatâ??ll keep microglia healthy â?? at least not one that we know of yet. Still, thereâ??s good news. â??Most of the interventions that we know work for brain health almost certainly impact the microglia,â?• says Dr. Wood, â??but often as part of multiple pathways that support the health of the brain and the body.â?• Â

The major levers are all surprisingly low-tech. First on the list: exercise. **One 2022 study published in the *Journal of Neuroscience*** found that greater physical activity later in life wasÂ associated with less inflammatory microglial activity and

better cognitive function. â??This study suggests that physical activity can support microglia late in life regardless of how much wear and tear our brains have accumulated,â?• Dr. Wood shares. Remarkably, this relationship was apparent even among people who lived into their 90s.

Sleep matters, too. Skimping on it doesnâ??t just make the next morning miserable; it may also interfere with some of the maintenance work your brain does overnight.

More broadly, Dr. Perlmutter emphasizes the importance of metabolic health for keeping your brain resilient. â??Maintaining insulin sensitivity, controlling blood sugar and blood pressure, preserving muscle mass, avoiding smoking, and eating a diet built around whole foods are foundational,â?• he says. Translation: When you take care of your body, you take care of your brain.

Protecting the brain from environmental and physical insults also matters. Dr. Wood points to both air pollution and head trauma as dementia risk factors associated with changes in microglia. His practical advice: Wear a helmet for activities that put you at risk for head injury, and consider investing in a HEPA air purifier if you live in an area with poor air quality.

Then there are the interventions with more buzz than proof â?? at least for microglia.

Intermittent fasting and time-restricted eating (TRE) are two intriguing candidates. â??These are interesting because they can improve insulin signaling, cellular cleanup processes, and mitochondrial function,â?• says Dr. Perlmutter. One caveat: While lab and animal studies suggest that these pathways can influence microglia, we need stronger evidence in human populations.

A few supplements are also being studied for their potential effects on pathways relevant to microglia. Dr. Perlmutter cites curcumin, vitamin D, omega-3s, urolithin A , and spermidine as a few that may influence inflammation, mitochondria, and cellular repair.

Resveratrol has attracted interest, too: **One study** found that it altered inflammatory and metabolic activity in human microglial cells in the lab. Intriguing? Sure. But we

donâ??t have proof that taking resveratrol â?? or any of these supplements â?? will meaningfully protect your brainâ??s immune system.

And because this is longevity science, some high-tech options are in the conversation, too. Per Dr. Perlmutter, these include red and near-infrared light, 40-Hz stimulation, and hyperbaric oxygen therapy. But for now, these belong firmly in experimental territory. â??The appropriate approach is to stay open-minded without getting ahead of the evidence,â?• he says.

The Key Is to Balance, Not to Boost

When it comes to your brainâ??s immune activity, more isnâ??t necessarily better. â??The goal is not to boost brain immunity,â?• says Dr. Perlmutter. â??The goal is to balance it.â?• In other words, you want microglia that can respond to threats and jump in to repair damage â?? but also know when to stand down.

Fortunately, supporting a resilient brain doesnâ??t require overhauling your life or chasing every longevity hack that hits your feed. Keep it simple: Exercise regularly. Maintain muscle. Eat whole foods. Protect your sleep. Keep tabs on your blood pressure and blood sugar. Donâ??t smoke. Stay socially connected.

The science may be evolving, but Dr. Wood points out that the behaviors with the strongest track record for supporting brain health havenâ??t changed much. As researchers learn more about microglia and the brain-immune connection, they may be uncovering yet another reason why the boring basics work so well.

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