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How Chronic Stress Increases Risk of Depression

Analysis by Dr. Joseph Mercola | November 08, 2025

STORY AT-A-GLANCE

- Chronic stress triggers a neutrophil invasion into brain-protective layers, driving depression-like behaviors through immune activation rather than just hormonal changes
- Stress-induced immune signals hijack brain reward circuits, reducing dopamine and shifting neural activity toward threat detection over pleasure-seeking behaviors
- Prolonged stress damages brain mitochondria, reducing cellular energy production while creating an inflammatory feedback loop that worsens mood and cognitive function
- Interferon pathways and inflammatory cytokines like IL-6 cross into the brain, directly altering neuron firing patterns in emotional regulation centers
- Natural interventions including healthy carbohydrates, regular exercise, positive thinking, creativity, and physical touch help counter stress-induced immune activation and protect mental health

Depression is one of the most common psychiatric conditions in America, affecting 21 million people each year.[1] While factors such as the current state of your gut health influence your mental state, chronic stress is also a key driver behind depression.

According to a new study published in Nature Communications, long-term stress repeatedly activates the body's stress-response systems, pushing the immune system into a state of chronic low-grade inflammation. As noted by Stacey Kigar, Ph.D., one of the study authors:

> *"There's a significant proportion of people for whom antidepressants don't work, possibly as many as one in three patients. If we can figure out what's happening with the immune system, we may be able to alleviate or reduce depressive symptoms."*

Following the hypothesis above, learning how the immune system works under chronic stress is key to discovering new treatments that can benefit patients experiencing this issue. Note, however, that within this field of study, animal testing is used due to ethical concerns.[2] That said, the knowledge gleaned from the analysis will still positively impact mental health care.

Immune Cells at the Brain's Border Are Driving Stress

According to the study, repeated social stress sets off a specific immune reaction that alters behavior. Researchers used a well-established model called chronic social defeat stress, which mimics the emotional toll of repeated social pressure, and tracked what happened in the protective layers around the brain — the meninges.[3]

- **Summary of the findings —** Chronic stress triggered a surge of neutrophils (the immune system's first responders) into the brain. The researchers theorized that this rush was not just a bystander effect, but a driver of the depression- and anxiety-like behaviors seen in the test subjects.

  The mice in this experiment were healthy before stress exposure, which means the changes seen were a direct result of the stressful environment. The stressed group displayed strong signs of anhedonia (the loss of pleasure), avoiding social contact and even ignoring sexual cues. They were also more anxious, exploring less and staying away from lit areas in behavior tests.

  Interestingly, about 30% of the mice were **resilient**, showing normal behavior despite exposure to stress, giving researchers a comparison group that helped separate stress-specific immune effects from random variation.

- **A closer analysis of the findings —** The researchers found a 5.6-fold increase in blood neutrophils and a 1.3 to 1.7-fold increase in meningeal neutrophils in stressed mice. This was not a random spike — the more neutrophils a mouse had, the more withdrawn and anxious it became. Mice with the highest levels of these immune cells showed the strongest reduction in social approach behavior and pleasure-seeking.

  The effect was not fleeting, too. Meningeal neutrophil levels stayed elevated for at least 24 hours after stress ended and only returned to normal after about a week, whereas blood neutrophil levels normalized much faster. This suggests that the immune footprint caused by stress lingers near the brain even after the stressful situation is over.

- **Where neutrophils came from and where they went —** Instead of traveling from distant bone marrow in the limbs, many neutrophils came directly from reservoirs in the skull bone marrow and slipped into the meninges through tiny vascular channels.

  In other words, stress triggers a very localized immune response right next to the brain, which suggests why mood and behavior are so sensitive to chronic social pressure. These skull-derived neutrophils were genetically more similar to immature bone marrow neutrophils than to circulating blood neutrophils, meaning they were fresh and primed for action.

- **Meningeal neutrophils were in a hyperactive state with a strong "interferon signature" —** They were responding to Type I interferons, immune messengers known to induce depressive symptoms even in healthy people. These neutrophils had reduced major histocompatibility complex (MHC) II expression, a molecule needed to present antigens to T cells, which means they also disrupt normal immune regulation near the brain.

The researchers even identified that some of these neutrophils were physically larger — a sign of immaturity and heightened activity — and nearly tripled in number in the stressed animals compared to controls.

- **Blocking interferon signaling with an antibody against the interferon-α/β receptor (IFNAR) reversed many of the stress effects —** Mice treated with this antibody showed restored pleasure-seeking behavior and fewer meningeal neutrophils.

Taken altogether, the findings show how the immune system leaves an imprint around the brain that keeps the nervous system in a high-alert state. Understanding this process gives you a clearer picture of why reducing chronic stress or modulating the immune system is key to preventing the spiral into depression.

Stress Signals Hijack Mood Networks in the Brain

In a report from the Brain & Behavior Research Foundation, Peter Tarr, Ph.D., explains how stress-related immune activation rewires the brain's emotional control systems and shifts behavior in ways that mimic depression. Instead of focusing only on hormones like cortisol, the researchers examined how cytokines communicate directly with brain circuits.[4]

This new angle of research is an important breakthrough because it shows depression is not just "in your head," but also rooted in immune system overactivation that pushes the brain toward a state of energy conservation and withdrawal.

- **The findings apply to both healthy individuals under chronic stress and those already struggling with mood disorders —** Elevated cytokine levels were linked with a drop in dopamine (a motivation and reward neurochemical), which explains why stressed people lose interest in activities they once enjoyed.

  In parallel, stress increased activity in brain regions like the amygdala that amplify fear and anxiety signals, creating a feedback loop where the brain prioritizes threat detection over pleasure or social engagement.

- **Your immune system rewires your brain activity —** When the immune system signals danger, the brain reallocates energy away from reward-seeking toward behaviors that favor survival. That means under long-term stress, your brain is rewiring to keep you cautious and withdrawn — a response that is protective in short bursts but harmful when it drags on for weeks or months.

  The result is your brain is more likely to interpret neutral events as threatening and to overreact emotionally, which compounds feelings of hopelessness.

- **Inflammatory biomarkers rise during stressful periods —** The findings also highlighted specific cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which spike during chronic stress and are associated with more severe symptoms. These inflammatory molecules not only float around randomly — they cross into the brain and alter the way neurons fire in regions like the prefrontal cortex, which is responsible for decision-making and emotional regulation.

- **How stress-induced immune activation disrupts connectivity in the brain's reward network —** Affected areas include the ventral striatum and nucleus accumbens. Functional magnetic resonance imaging (MRI) scans showed that people with high inflammation had lower activation in these regions when shown positive stimuli, like happy faces or rewarding cues. This blunted reward response is what makes normal activities feel joyless and effortful, a hallmark of clinical depression.

The research shows that feeling unmotivated or emotionally flat under stress is not a character flaw, but a biological process driven by immune signals. Understanding this will help change the stigma and points toward practical interventions, including reducing chronic stress exposure and exploring anti-inflammatory strategies that restore healthy brain signaling.

Stress Weakens the Brain's Power Plants and Triggers Inflammation

In another study published in Psychoneuroendocrinology, researchers explored how long-term stress affects the brain's mitochondria. The researchers used a chronic unpredictable mild stress model in rats, exposing them to a rotating series of stressors over several weeks, such as light/dark cycle changes, cold swims, and mild restraint. This type of model is designed to replicate the uncertainty and ongoing nature of stress that humans experience.[5]

- **The stressed animals developed strong signs of depression-like behavior —** They stopped drinking sweetened water, which normally indicates pleasure-seeking, and showed longer immobility times in behavioral tests that measure resignation or despair. Brain tissue from these rats showed significant reductions in mitochondrial function, meaning their brain cells were producing far less adenosine triphosphate (ATP) than normal.

  At the same time, they had elevated inflammatory biomarkers, with higher levels of cytokines such as IL-1β and TNF-α in the hippocampus and prefrontal cortex — two brain regions that are central to memory, emotional regulation, and decision-making.

- **Several key complexes in the electron transport chain were impaired in the stressed rats —** Among those affected are Complexes I and IV, which are required for the step-by-step process that extracts energy from food and converts it into usable ATP. When they were disrupted, oxidative stress levels rose sharply, leading to damage in brain cell membranes and proteins.

  In other words, the brain's energy system isn't only running slower — it's also producing more toxic byproducts that further injure neurons.

- **Treatment with antioxidants or mitochondrial-supporting compounds improved behavior and partially restored mitochondrial function —** Rats that received these interventions regained interest in sweetened water and showed more active coping behavior in stress tests.

This shows that targeting mitochondrial health could reverse some of the emotional and behavioral effects of chronic stress, which is promising for people who feel stuck in a low-energy, low-motivation state after prolonged stress exposure.

- **Mitochondrial dysfunction was not immediate —** It worsened progressively over several weeks of ongoing stress. This means that the longer the stress continues, the more deeply the brain's energy systems are disrupted, which explains why chronic stress leads to a deeper and more persistent form of depression compared to short-lived stressors.

  It also highlights the importance of early intervention — reducing stress before mitochondrial damage becomes entrenched can prevent long-term mood problems.

- **The inflammatory response and mitochondrial dysfunction amplified each other —** The more inflammation was present, the worse the mitochondrial damage became. Moreover, the weaker the mitochondria, additional inflammatory cytokines were produced. This vicious cycle created a loop that locked the brain into a state of low energy and high inflammation, making it harder for the test animals to recover naturally even after the stressors were removed.

- **Mitochondrial protection is a key therapeutic target for preventing stress-induced depression —** The researchers noted that supporting mitochondria through proper nutrition, reducing exposure to stressors, and using compounds that protect mitochondrial enzymes could offer a way to stop the downward spiral.

Natural Strategies to Address Stress and Protect Your Mental Health

If you're feeling down, the answer isn't taking an antidepressant pill. It's far better to address the source of your stress before your mood takes a nosedive. Considering this, here are several strategies to manage your stress:

1. **Add healthy carbs to your diet —** Cortisol, commonly called the "stress hormone," is strongly influenced by what you eat. When your body doesn't have enough glucose available, it compensates by producing cortisol, which then breaks down muscle, bone, and even brain tissue to create amino acids that your liver converts into glucose.

   This means that consistently eating too few healthy carbohydrates can cause cortisol levels to rise just to keep your body running smoothly. That's why I'm cautious about recommending long-term fasting or extended **time-restricted eating**. While these approaches can help with short-term weight loss, they also lead to persistently high cortisol levels over time, which can speed up aging.

   Research published in the journal Nutrients found that a carbohydrate-rich diet helped lower cortisol and improved mood after stress.[6] That said, what's a good amount to aim for every day? I recommend 250 grams a day from fruits and white rice. Then, gradually add root vegetables, non-starchy vegetables, starchy vegetables (like sweet potatoes and squash), and finally, minimally processed whole grains.

2. **Exercise regularly —** Getting your body moving is one of the most effective tools for managing stress. When you work out, your body releases endorphins — your natural "feel good" chemicals — which boost your mood and act like built-in pain relievers.[7]

   Exercise also helps keep cortisol in check. By moving regularly, you improve your sleep quality and strengthen your emotional resilience, which makes you better equipped to handle life's challenges. It also supports long-term health and longevity. By consistently lowering cortisol, you reduce your risk of stress-related conditions and give your body a buffer against chronic tension. If you aren't exercising, the perfect time to start is now.

   I recommend reading "**Nailing the Sweet Spots for Exercise Volume**" to give you an idea on how to structure your workout regimen.

3. **Think positively —** Shifting your mindset can break the stress cycle. Maintaining optimism and a hopeful outlook encourages your brain to release feel-good neurochemicals that disrupt the harmful effects of stress.[8]

   There are many ways to cultivate positivity — from practicing mindfulness and writing in a gratitude journal[9] to spending time outdoors. These habits not only reduce current stress levels but also make you less vulnerable when future challenges arise.

4. **Create art —** Working on your creativity offers a therapeutic break from stress and gives your mind space to recharge. Whether it's painting, journaling, or playing an instrument, creative activities trigger the brain's reward pathways, reduce stress hormone production, and boost feelings of joy and accomplishment.

   Thinking creatively isn't limited to hobbies. It can also help you develop fresh solutions to problems that might otherwise cause stress. Approaching challenges with innovation provides a sense of control and purpose, which can protect you from feeling overwhelmed.[10]

5. **Reach out and hug loved ones —** Physical touch is a powerful stress reliever. A simple hug can trigger the release of oxytocin — the "bonding hormone" — which lowers stress and strengthens emotional connection.

   Making touch a natural part of your daily life — along with encouraging a culture of kindness and compassion — can build healthier, more connected communities and help everyone feel less stressed.[11]

Frequently Asked Questions (FAQs) About the Link Between Stress and Depression

Q: How does chronic stress contribute to depression?

A: Chronic stress activates the body's stress-response systems repeatedly, which can push the immune system into a state of low-grade inflammation. This inflammation rewires the brain's mood and reward networks, reduces dopamine (your motivation chemical), and makes you more anxious, withdrawn, and less interested in enjoyable activities. Over time, this biological state increases the risk of developing depression.

Q: What role do immune cells play in stress-related mood changes?

A: Research shows that repeated stress triggers immune cells called neutrophils to migrate into the meninges — the protective layers around the brain. These cells enter a hyperactive state, releasing inflammatory signals that worsen anxiety and depressive behaviors. Blocking their activity with an interferon receptor antibody even restored normal behavior in animal studies, suggesting a future therapeutic target for stress-related depression.

Q: How does stress affect brain function at the cellular level?

A: Long-term stress damages mitochondria, the energy-producing structures inside brain cells. When mitochondrial function declines, the brain produces less energy and generates more oxidative stress, which harms neurons. This creates a cycle of low energy and more inflammation, leading to symptoms like brain fog, fatigue, and loss of motivation. Supporting mitochondrial health early can prevent this downward spiral.

Q: Can targeting inflammation help treat depression?

A: Yes. Measuring inflammatory markers could help doctors personalize treatment plans, combining stress reduction, immune modulation, and lifestyle changes for

better outcomes.

Q: Are there lifestyle strategies to buffer against stress and protect mental health?

A: Several natural approaches can help reduce cortisol and support brain resilience:

- Eat enough healthy carbs to avoid stress-induced cortisol spikes.
- Exercise regularly to lower cortisol, release endorphins, and improve sleep.
- Practice positive thinking with mindfulness, gratitude journaling, and time in nature.
- Engage in creative outlets like music, art, or writing to reset your mind and boost joy.
- Maintain social connection and physical touch — even simple hugs release oxytocin and reduce stress.

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