Loneliness triggers cellular changes that can cause illness, study shows

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Loneliness is more than a feeling: For older adults, perceived social

isolation is a major health risk that can increase the risk of premature death by 14 percent.

Researchers have long known the dangers of loneliness, but the cellular mechanisms by which loneliness causes adverse health outcomes have not been well understood. Now a team of researchers, including UChicago psychologist and leading loneliness expert John Cacioppo, has released a study shedding new light on how loneliness triggers physiological responses that can ultimately make us sick.

The paper, which appears Nov. 23 in the *Proceedings of the National Academy of Sciences*, shows that loneliness leads to fight-or-flight stress signaling, which can ultimately affect the production of white blood cells .

Along with Cacioppo, the research team includes Steven W. Cole of UCLA and John P. Capitanio of the California National Primate Research Center at the University of California, Davis. The study examined loneliness in both humans and rhesus macaques, a highly social primate species.

Previous research from this group had identified a link between loneliness and a phenomenon they called "conserved transcriptional response to adversity" or CTRA. This response is characterized by an increased expression of genes involved in inflammation and a decreased expression of genes involved in antiviral responses. Essentially, lonely people had a less effective immune response and more inflammation than non-lonely people.

For the current study, the team examined gene expression in leukocytes, cells of the immune system that are involved in protecting the body against bacteria and viruses.

As expected, the leukocytes of lonely humans and macaques showed the effects of CTRA—an increased expression of genes involved in inflammation and a decreased expression of genes involved in antiviral responses. But the study also revealed several important new pieces of information about loneliness' effect on the body.

First, the researchers found that loneliness predicted future CTRA gene expression measured a year or more later. Interestingly, CTRA gene expression also predicted loneliness measured a year or more later. Leukocyte gene expression and loneliness appear to have a reciprocal relationship, suggesting that each can help propagate the other over time. These results were specific to loneliness and could not be explained by depression, stress or social support.

Next, the team investigated the cellular processes linking social experience to CTRA gene expression in rhesus macaque monkeys at the California National Primate Research Center, which had been behaviorally classified as high in perceived social isolation. Like the lonely humans, the "lonely like" monkeys showed higher CTRA activity. They also showed higher levels of the fight-or-flight neurotransmitter, norepinephrine.

Previous research has found that norepinephrine can stimulate blood stem cells in bone marrow to make more of a particular kind of immune cell—an immature monocyte that shows high levels of inflammatory gene expression and low levels of antiviral gene expression. Both lonely humans and "lonely like" monkeys showed higher levels of monocytes in their blood.

More detailed studies of the monkey white blood cells found that this difference stemmed from expansion of the pool of immature monocytes. In an additional study, monkeys repeatedly exposed to mildly stressful social conditions (unfamiliar cage-mates) also showed increases in

immature monocyte levels. These analyses have finally identified one reason why CTRA gene expression is amplified in the white blood cell pool: increased output of immature monocytes.

Finally, the researchers determined that this monocyte-related CTRA shift had real consequences for health. In a monkey model of viral infection, the impaired antiviral gene expression in "lonely like" monkeys allowed simian immunodeficiency virus (the monkey version of HIV) to grow faster in both blood and brain.

Taken together, these findings support a mechanistic model in which loneliness results in fight-or-flight stress signaling, which increases the production of immature monocytes, leading to up-regulation of inflammatory genes and impaired anti-viral responses. The "danger signals" activated in the brain by loneliness ultimately affect the production of white blood cells. The resulting shift in monocyte output may both propagate loneliness and contribute to its associated health risks.

The team plans to continue research on how loneliness leads to poor health outcomes and how these effects can be prevented in older adults.

More information: Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1514249112

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