Fresh understanding of aging in the brain offers hope for treating neurological diseases

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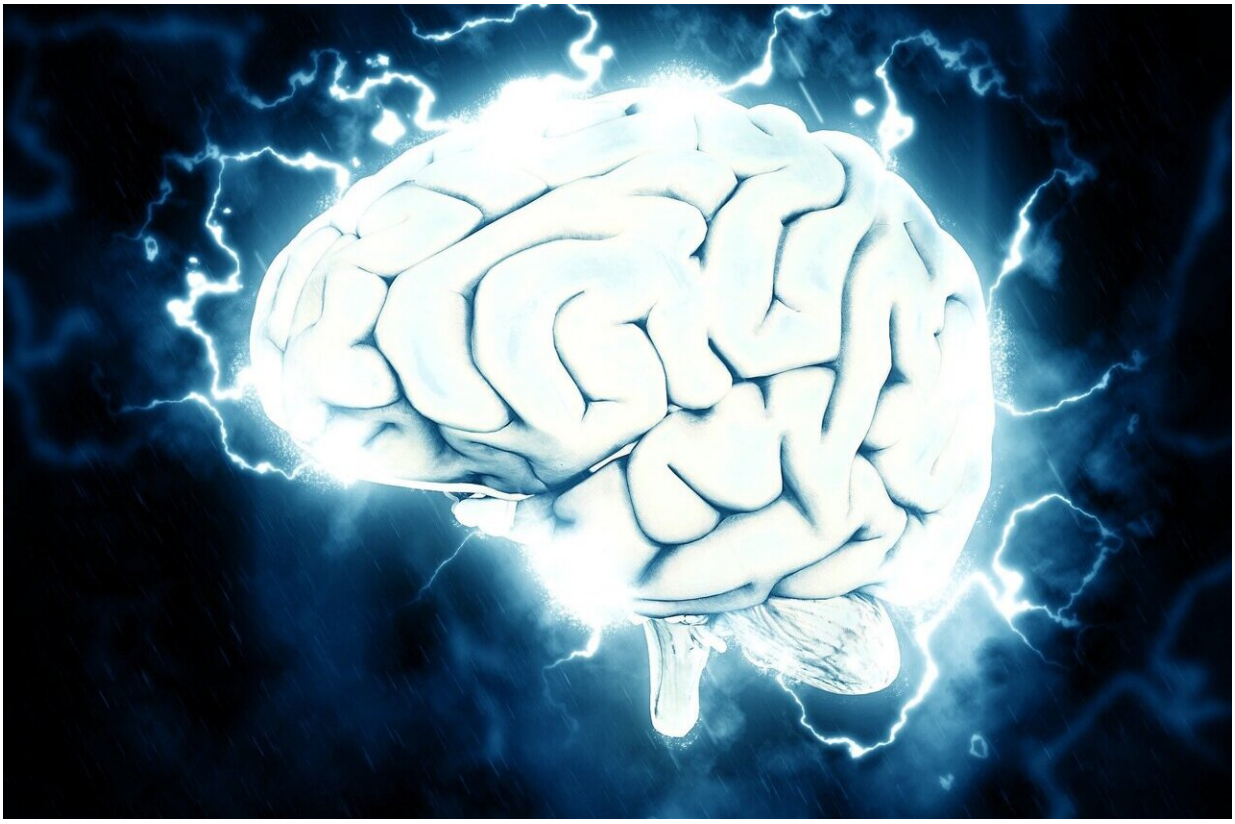

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Scientists from the Trinity Biomedical Sciences Institute (TBSI) have shed new light on aging processes in the brain. By linking the increased presence of specialized immune cells to conditions such as Alzheimer's

disease and traumatic brain injury for the first time, they have unearthed a possible new target for therapies aimed at treating age-related neurological diseases.

The research, which benefited from a collaboration with experts at the University of Maryland School of Medicine and focused on microglia in the brain and spinal cord, is published today in the journal *Science Advances*.

Microglia are a unique type of immune cell whose job it is to support nerve cells, defend against invading microbes, clear debris and remove dying nerve cells by engulfing and eating them. Emerging research indicates that microglia can have different functional responses depending on molecular and biochemical changes occurring within these specialized cells.

In fact, various subtypes of microglia can be distinguished based on a property called autofluorescence. This is the tendency of cells to emit light of one color after they have absorbed light of another, and it occurs because specific substances inside the cells absorb light. The substances stored in specialized cellular compartments include fat molecules, cholesterol crystals, metals and other misfolded proteins.

David Loane, Assistant Professor of Neuroscience in Trinity's School of Biochemistry and Immunology in TBSI is the lead author of the research. He said, "As the brain ages, these materials build up inside autofluorescent microglia, which increase their autofluorescence as a result. Unfortunately, this accumulation of cellular debris also makes it harder for the microglia to perform their essential garbage collection tasks in the brain and to prevent neurological injury and neurodegenerative disease.

"In this study we found—in aged animals—that these microglia adopt a

unique, dysfunctional state, which has a number of problematic impacts. For example, there is an increase in cellular stress and damage, an accumulation of fats and iron, alterations to metabolic processes and an increase in production of molecules that over-egg the immune response."

In addition, the scientists demonstrated that autofluorescent microglia and associated inflammation were more pronounced under pathological conditions, such as in genetic risk factor models of Alzheimer's disease, and—promisingly—were reversed by drug-assisted microglial replacement in aged animals.

Prof Loane added, "Furthermore, environmental exposure to acute traumatic brain injury in animals accelerated the age of onset and tissue-wide distribution autofluorescent microglia by increasing oxidative stress damage in the brain of injured animals.

"As a result, increasing evidence now suggests that the accumulation of autofluorescent microglia contributes to diseases of aging and neurodegeneration. If these sub-populations of microglia are highly inflammatory and damaging to the brain, then targeting them could be a new strategy for treating aging-related diseases."

More information: Rodney M. Ritzel et al, Brain injury accelerates the onset of a reversible age-related microglial phenotype associated with inflammatory neurodegeneration, *Science Advances* (2023). DOI: 10.1126/sciadv.add1101. www.science.org/doi/10.1126/sciadv.add1101

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