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Do brains have a freshness date?

the effect of aging on the human brain

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As humans age, many bodily functions and abilities change. Scientists have long been interested in discovering how aging produces a decline in brain function and contributes to the development of certain diseases. To investigate the molecular shifts that occur in the brain during aging, some recent studies have focused on changes in gene expression patterns, both in humans and in other animals.

A recent study by Lu et al. (1) compared the levels of gene expression in postmortem brain samples from young and old human subjects. The gene expression profiles were clustered into three broad groups: young (below 40 years), intermediate (40-70 years), and old (70+ years) (see data at the Gene Expression Omnibus) (2). Whereas the young and old subjects were relatively homogeneous in their gene expression profiles, the intermediate group was much more heterogeneous, with vastly different rates of progression through the transition from the young gene expression profile to the old profile.

In older brains, the expression of genes involved in learning and memory, neuronal survival, and maintenance was decreased. Among these were the genes coding for microtubule-associated protein MAP1B, which stabilizes microtubules and promotes axonal growth (3,4) (see Entrez Gene entry, GEO data); MEF2C (see Entrez Gene entry, GEO data), which promotes the survival of neurons (1); subunit 2A of the glutamate receptor NMDAR (see Entrez Gene entry, GEO data), which is centrally involved in synaptic plasticity, the brain-restructuring process used in learning and memory; and calmodulin 1 (see Entrez Gene entry, GEO data), which is a central regulator of calcium-mediated signaling and plays an important role in memory. In contrast, the expression of genes coding for proteins involved in sensing and responding to cellular stresses increased, suggesting that older brains are exposed to higher levels of damaging stressors than are young brains (1). For example, one of the genes more highly expressed in older brains was the DNA repair enzyme OGG1 (see Entrez Gene entry, GEO data), which targets oxidatively damaged DNA.

Similar studies have been performed with a range of other animals, including *Caenorhabditis elegans*, *Drosophila melogaster* (5), and mice (6,7). Although the affected genes were not the same among all of the systems, the functional systems of the cells were affected in similar ways across species. For example, in the brains of both mice and humans, the expression of genes involved in synaptic function was decreased, whereas those involved in stress responses increased.

Further investigation of the genes whose expression was decreased in older human subjects showed that the promoters of these genes were more susceptible to oxidative damage than other genes tested (1), suggesting a mechanism for the observed decreased gene expression. Oxidative damage is caused by oxidants such as superoxide and hydrogen peroxide, which are produced as natural by-products of cell metabolism (8). The cell has response systems specifically dedicated to sensing and destroying such oxidants, as well as systems to repair any damage caused by those oxidants. It has long been hypothesized that oxidants play a role in aging processes, but this has proved difficult to demonstrate directly (9). The variable gene expression profiles (1) of the

intermediate-age group suggest that oxidative damage may accumulate over a long period of time, with the effects occurring long after the initial oxidative damage is inflicted.

Perhaps some of the effects of aging can be slowed or lessened by controlling the level of oxidative stress in the cell; many methods are currently under investigation for reducing the creation of oxidants during metabolism. These include calorie restriction (currently being tested in clinical trials, see news coverage) (10), the use of antioxidant supplements, and a wide range of methods designed to target various cellular and molecular processes to safely and effectively reduce the production of oxidants during metabolism (10). Another potentially fruitful therapeutic strategy is to enhance DNA repair in cells to slow the accumulation of oxidative damage in the DNA. Because the results outlined by Lu et al. (10) show that after the age of about 40 years, humans may begin to exhibit age-related changes in gene expression, some treatments might be more effective in young patients than in those already experiencing the effects of aging. The challenge for future scientific investigation will be to find effective treatments for increasing life expectancy while ensuring high quality of life.

This Coffee Break was contributed by Victoria Sutton, PhD, while on rotation at the National Center for Biotechnology Information as a part of the Emerging Leaders Program from the Department of Health and Human Services (DHSS).
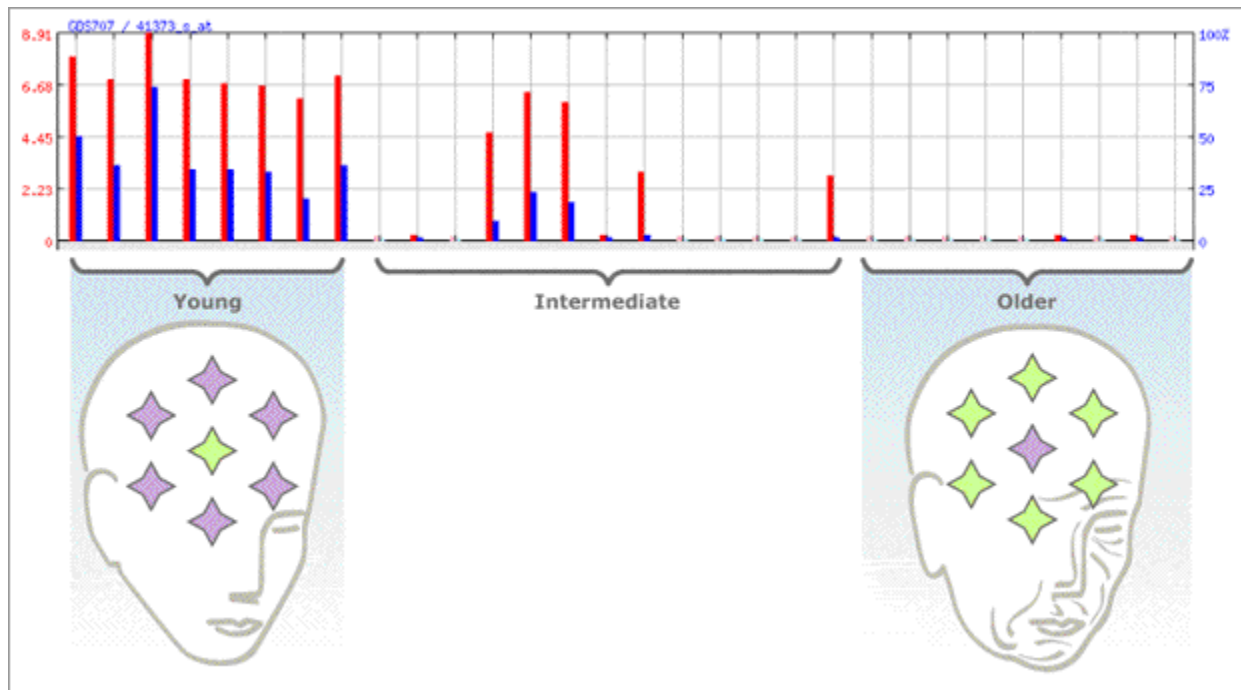

Aging and the Human Brain.

The changes in gene expression that underlie the effects of aging in humans

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The gene expression in human brains changes with age, with some genes decreasing expression while others increase. This is illustrated by a chart of the expression of the gene MAP1B, which shows high levels expression in the young, variable levels of expression at intermediate ages, and greatly reduced expression in older people. For more information about the chart, please visit the tutorial on "Aging and the Human Brain".

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