# Gene variation predicts rate of age-related decline in mental performance

October 25 2011

A tiny difference in the coding pattern of a single gene significantly affects the rate at which men's intellectual function drops with advancing age, investigators at the Stanford University School of Medicine and the Veterans Affairs Palo Alto Health Care System have learned.

In a study to be published online Oct. 25 in *Translational Psychiatry,* the researchers tested the skills of experienced airplane pilots and found that having one version of the gene versus the other version doubled the rate at which the participants' performance declined over time.

The particular genetic variation, or polymorphism, implicated in the study has been linked in previous studies to several psychiatric disorders. But this is the first demonstration of its impact on skilled task performance in the healthy, aging brain, said the study's senior author, Ahmad Salehi, MD, PhD, clinical associate professor of psychiatry and behavioral sciences at Stanford.

The study also showed a significant age-related decline in the size of a key brain region called the hippocampus, which is crucial to memory and spatial reasoning, in pilots carrying this polymorphism.

"This gene-associated difference may apply not only to pilots but also to the general public, for example in the ability to operate complex machinery," said Salehi, who is also a health-science specialist at the VA-Palo Alto.

The gene in question codes for a well-studied protein called brain-derived neurotropic factor, or BDNF, which is critical to the development and maintenance of the central nervous system. BDNF levels decline gradually with age even in healthy individuals; researchers such as Salehi have suspected that this decline may be linked with age-related losses of mental function.

Genes, which are blueprints for proteins, are linear sequences of DNA composed of four different chemical units all connected like beads on a string. The most common version of the BDNF gene dictates that a particular building block for proteins, called valine, be present at a particular place on the protein. A less common - though far from rare - variation of the BDNF gene results in the substitution of another building block, methionine, in that same spot on the protein. That so-called "val/met" substitution occurs in about one in three Asians, roughly one in four Europeans and Americans, and about one in 200 sub-Saharan Africans. Such a change can affect a protein's shape, activity, level of production, or distribution within or secretion by cells in which it is made.

It appears that the alternative "met" version of BDNF doesn't work as well as the "val" version. This variant has been linked to higher likelihood of depression, stroke, anorexia nervosa, anxiety-related disorders, suicidal behavior and schizophrenia.

So Salehi and his colleagues decided to look at whether this polymorphism actually affected human cognitive function. To do this, they turned to an ongoing Stanford study of airplane pilots being conducted by two of the paper's co-authors - Joy Taylor, PhD, clinical associate professor of psychiatry and behavioral sciences, and Jerome Yesavage, MD, professor of psychiatry and behavioral sciences -examining a wide array of neurological and psychiatric questions.

For this new research, Salehi and his colleagues followed 144 pilots, all healthy Caucasian males over the age of 40, who showed up for three visits, spaced a year apart, spanning a two-year period. During each visit, participants - recreational pilots, certified flight instructors or civilian air-transport pilots - underwent an exam called the Standard Flight Simulator Score, a Federal Aviation Administration-approved flight simulator for pilots.

This test session employs a setup that simulates flying a small, single-engine aircraft. Each participant went through a half-dozen practice sessions and a three-week break before his first visit. Each annual visit consisted of morning and afternoon 75-minute "flights," during which pilots confronted flight scenarios with emergency situations, such as engine malfunctions and/or incoming air traffic. Resulting test scores pooled several variables, such as pilots' reaction times and their virtual planes' deviations from ideal altitudes, directions and speed. A pilot's score represented the overall skill with which he executed air-traffic control commands, avoided airborne traffic, detected engine emergencies and approached landing strips.

Blood and saliva samples collected on the pilots' first visits allowed the Stanford investigators to genotype all 144 pilots, of whom 55 (38.2 percent) turned out to have at least one copy of a BDNF gene that contained the "met" variant. In their analysis, the researchers also corrected for pilots' degree of experience and the presence of certain other confounding genetic influences.

Inevitably, performance dropped in both groups. But the rate of decline in the "met" group was much steeper.

"We saw a doubling of the rate of decline in performance on the exam among met carriers during the first two years of follow-up," said Salehi.

About one-third of the pilots also underwent at least one round of magnetic resonance imaging over the course of a few years, allowing the scientists to measure the size of their hippocampi. "Although we found no significant correlation between age and hippocampal size in the non-met carriers, we did detect a significant inverse relationship between age and hippocampal size in the met carriers," Salehi said.

Salehi cautioned that the research covered only two years and that the findings need to be confirmed by following participants over a multiyear period. This is now being done, he added.

No known drugs exist that mimic BDNF's action in the brain, but there is one well-established way to get around that: Stay active. "The one clearly established way to ensure increased BDNF levels in your brain is physical activity," Salehi said.

Provided by Stanford University Medical Center