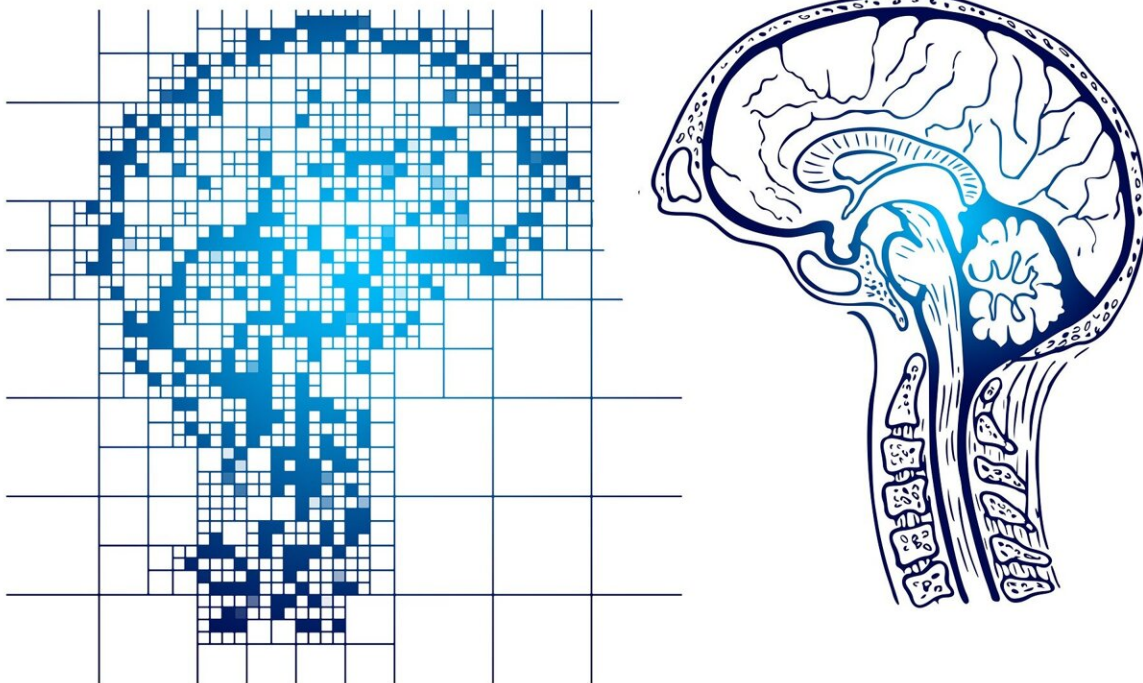


Head trauma, PTSD may increase genetic variant's impact on Alzheimer's risk

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In a study of Veterans led by Dr. Mark Logue, a statistician in the National Center for PTSD at the VA Boston Healthcare System, researchers concluded that PTSD, TBI, and the $\epsilon 4$ variant of the APOE

gene show strong associations with Alzheimer's disease and related dementias (ADRD).

The [medical community](#) has never researched the simultaneous impact of post-traumatic stress disorder (PTSD), [traumatic brain injury](#) (TBI) and [genetic risk factors](#) in a large cohort until now. They first found a greater percentage of ADRD in Veterans with PTSD and in those with TBI, relative to those without, as well as higher rates of ADRD in Veterans who had inherited the $\epsilon 4$ [variant](#). Logue and his team then looked for interactions between the $\epsilon 4$ variant, PTSD, and TBI using a [mathematical model](#).

The study found an increase in risk due to PTSD and TBI in Veterans of European ancestry who inherited the $\epsilon 4$ variant. In Veterans of African ancestry, the impact of PTSD didn't vary as a function of $\epsilon 4$, but the TBI effect and interaction with $\epsilon 4$ was even stronger. Other studies have suggested that $\epsilon 4$ may magnify the effects of a head injury and/or combat-related stress.

"These additive interactions indicate that ADRD prevalence associated with PTSD and TBI increased with the number of inherited APOE $\epsilon 4$ alleles," Logue and his colleagues wrote. "PTSD and TBI history will be an important part of interpreting the results of ADRD [genetic testing](#) and doing accurate ADRD risk assessment."

Capitalizing on VA's Million Veteran Program

The researchers carried out the study by accessing data from VA's Million Veteran Program (MVP), one of the world's largest databases of health and [genetic information](#). MVP is aimed at learning how genes, lifestyle, and military exposures affect health and illness, with more than 900,000 Veterans enrolled in its climb to 1 million and beyond.

With more than 40% of the Veteran population above the age of 75, the number of former Service Members at risk for Alzheimer's and other forms of dementia is rising. While large cohort studies have shown that PTSD and TBI increase the risk of dementia in Veterans, Logue and his colleagues investigated further by studying these [risk factors](#) along with the APOE $\epsilon 4$ variant. Most people don't inherit that variant, but those who do inherit it from one parent (one copy) or both of their parents (two copies).

"Research has shown that if you inherit one copy of $\epsilon 4$, you're at increased risk of Alzheimer's disease," he said, "and if you inherit two copies, you are at much higher risk."

The number of $\epsilon 4$ variants a person inherits is fixed at birth, but their impact differs with age, according to Logue, who is also an Army Veteran and an associate professor at Boston University.

"The risk of Alzheimer's disease increases with age for all of the APOE genotypes," he said. "But when compared to people with two copies of the common variant, the difference in risk for those with a copy of $\epsilon 4$ appears to peak somewhere between age 65 and 70 and then decrease after that. Again, that doesn't mean that your chances of Alzheimer's decrease after that, just that the difference between the risk for those with and without $\epsilon 4$ diminishes."

The study showed that the risk associated with PTSD and head injury was larger for $\epsilon 4$ carriers. Their model led the researchers to expect that for 80-year-old Veterans of European ancestry who didn't inherit the $\epsilon 4$ variant, the percentage of ADRD would be 6% greater for those with PTSD compared to those without. But for 80-year-old Veterans of European ancestry who inherited two copies of $\epsilon 4$, the percentage of ADRD would be 11% higher for those with PTSD than those without.

Clear link between PTSD, TBI on dementia risk a surprise

Logue was most surprised to see such clear evidence of a link between PTSD and head trauma on dementia risk.

"I've worked in Alzheimer's disease genetics for over a decade now, and I was used to seeing a clear impact of APOE ϵ 4 on Alzheimer's risk," he says. "However, in this cohort, the effects of PTSD and head injury were just as clear and looked similar to the effect of inheriting ϵ 4 from one of your parents."

Next, Logue and his colleagues would like to use MVP data to research other risk factors that are relevant to Veterans, with the goal of learning how they may interact with Alzheimer's risk variants. They are also looking to do genome-wide association scans to try to find new Alzheimer's and dementia risk variants. The most recent large-scale genome-wide association study of Alzheimer's identified some 80 variants linked to the risk of Alzheimer's, Logue said, noting that those variants were rare or had a much smaller impact than ϵ 4.

MVP data can be used to boost power for this type of study, he added, but PTSD and TBI history will be an important part of interpreting the results of ADRD genetic testing and conducting accurate ADRD risk assessments.

"We know that genes play a large role in Alzheimer's risk, but they don't tell the whole story," Logue explained.

"Right now, no genetic test can tell you if you're certain to develop Alzheimer's disease. Tests can only give an estimate of your likelihood of developing Alzheimer's that may be higher or lower than average. Our

study shows that these estimates will be more accurate if they incorporate more than just age and genetics. In Veterans, a history of head injuries and PTSD can also make a large difference in dementia risk, so using that information will allow for more accurate measurement of the chances of developing dementia."

The findings appeared in the journal *Alzheimer's & Dementia*.

More information: Mark W. Logue et al, Alzheimer's disease and related dementias among aging veterans: Examining gene-by-environment interactions with post-traumatic stress disorder and traumatic brain injury, *Alzheimer's & Dementia* (2022). [DOI: 10.1002/alz.12870](https://doi.org/10.1002/alz.12870)

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