Investigating hyperactivation of memory circuits and Alzheimer's disease risk

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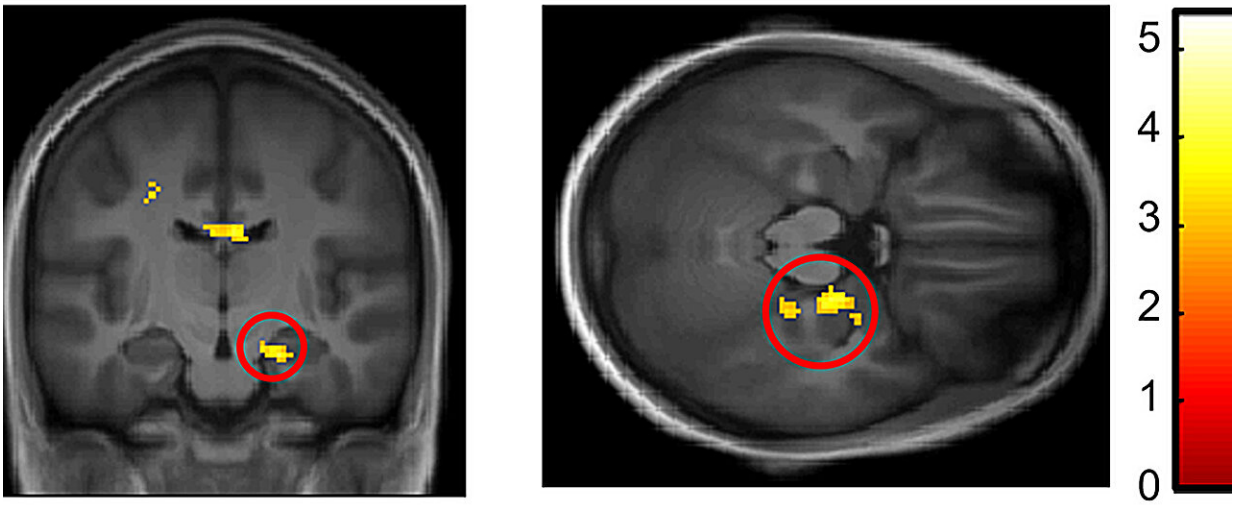

MRI visualization of hippocampal activation. Credit: UNIGE

By exploring the effects of sport on memory, scientists at UNIGE have discovered compensatory mechanisms in the brains of young individuals at genetic risk of developing Alzheimer's disease.

The benefits of physical activity on health are widely accepted, and those on cognitive capacity are increasingly well known. There may, however, be exceptions.

By studying the effects of sport on the memory of young adults with a

genetic variation that increases the risk of Alzheimer's disease, neuroscientists at the University of Geneva (UNIGE), in collaboration with the University Hospitals of Geneva (HUG) and the University of Lausanne (UNIL), have revealed that these at-risk individuals have a poorer associative memory, unlike people without this genetic mutation.

These discoveries, published in the journal *Cerebral Cortex*, also shed light on compensatory cerebral mechanisms in these young adults, who do not show any clinical symptoms of the disease.

During physical effort, the body produces small molecules called endocannabinoids, which trigger a feeling of well-being and activate the hippocampus, an area of the brain that plays a crucial role in memory and spatial navigation. Neurons in this area of the cortex are the first to degenerate during the development of Alzheimer's disease.

Dr. Kinga Igloi, a research associate in Professor Sophie Schwartz's group in the Department of Fundamental Neurosciences at the Faculty of Medicine and the Geneva Neuroscience Center at UNIGE, is studying the effects of physical exercise on memory.

In a previous study, her work showed that a 30-minute session of moderate-intensity sport improved memory capacity. In the present study, the researchers wanted to find out whether the benefits of sport on memory were also present in young, healthy individuals with an increased genetic risk of developing Alzheimer's disease.

These people, like 20% of the population, carry a variation in the APOE gene that increases the risk of Alzheimer's disease by three to twelve times and, if the disease develops, brings forward its onset by almost 15 years (to around 68 years, compared with 84 years for people who do not carry this mutation).

A significant difference in memory tests

The scientists asked 50 individuals aged between 18 and 25 with no cognitive deficits to perform a task involving their declarative memory, which corresponds to the memory of personal events (who I met yesterday) or general knowledge (what city is the capital of Switzerland), which depends on the hippocampus. The volunteers were asked to learn a series of images and then either cycle for 30 minutes at a moderate speed or rest for 30 minutes.

Finally, their memory was tested by asking them to remember the order in which they had previously seen the images. Half the volunteers were carriers of the risk variant of the APOE gene, whereas the other half formed the control group. MRI images of the brain were taken during the learning and restitution phases to visualize the intensity of hippocampal activation. Blood samples were also taken to measure endocannabinoid levels.

"To our great surprise, the at-risk group did not perform as well as the control group in this memory task, both after a cycling session and after a rest phase," explains Igloi.

Cerebral over-compensation

In individuals in the control group, post-exercise performance was accompanied by increased activation of the hippocampus—the brain region crucial for memory—and increased levels of endocannabinoids in the blood. In contrast, in at-risk individuals, MRI measurements of brain activity revealed hyperactivation of hippocampal neurons under all test conditions.

"This observation suggests the presence of physiological adaptation or

compensation mechanisms. Their brains mobilize the hippocampus more to achieve memory scores that are lower than, or similar, to those of the control group," says Sophie Schwartz.

Scientists are now continuing their behavioral and brain imaging studies to understand whether different tasks involving other memory types also require neuronal over-compensation in at-risk individuals, even when they are young.

"However, even if our results show an absence of effects of sport on memory in at-risk individuals, they should not call into question the beneficial effects of practicing sport on general synaptic plasticity. For all individuals, whether at risk of developing Alzheimer's disease or not, physical exercise remains beneficial for neuronal and cognitive health throughout life," conclude the authors.

More information: Kinga Igloi et al, Interactions between physical exercise, associative memory, and genetic risk for Alzheimer's disease, *Cerebral Cortex* (2024). DOI: 10.1093/cercor/bhae205

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