

Title

New horizons in Alzheimer's disease prevention research

A project funded by the European Commission will study vagus nerve stimulation as a strategy for preventing Alzheimer's disease.

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Abstract

Alzheimer's disease is associated with brain changes that begin at a young age in a brain area called the locus coeruleus, which is important for attention and memory. The locus coeruleus is therefore an area of interest in Alzheimer's disease prevention research. An innovative way to target this structure is through electrical stimulation of the vagus nerve, one of the nerves that enables body-brain communication. Many studies have been carried out to understand the effects of vagus nerve stimulation on the locus coeruleus, but these have focused on young adults. Given the lack of studies in older adults, a project funded by the European Commission will study for the first time whether electrical stimulation of the vagus nerve can increase the activity of the locus coeruleus in this age group of the population. This project will be a fundamental starting point for the study of vagus nerve stimulation as a strategy for the prevention of Alzheimer's disease.

Article

It is a commonly held belief that Alzheimer's disease (AD) begins in old age. Just the opposite, a biological hallmark of AD, "tau pathology", is evident even in young people. Tau proteins help neurons in the brain function. But when these proteins malfunction, they form protein deposits that lead to neuron death. These deposits constitute tau pathology. Surprisingly, a German study has shown that, in most people, tau proteins begin to malfunction between the ages of 20 and 30 in some neurons. These findings offer an encouraging perspective since they suggest there may be a long period in which we can intervene to prevent or slow the onset of AD.

The same German study showed that tau pathology begins in a small area of the brain called the locus coeruleus, or blue spot. The locus coeruleus is a structure at the base of the brain about a centimeter long and dark blue in color. This part of the brain allows us to be alert, memorize new information, and remember what we have learned. As we age, the locus coeruleus changes both in its structure and in its functioning, which makes it more difficult to be attentive and memorize. Older adults with a less intact locus coeruleus tend to have worse memory. Therefore, this area plays a fundamental role in cognitive aging and is of interest in Alzheimer's disease prevention research.

Canadian researchers have studied how to prevent AD by acting on the locus coeruleus in rodents. They showed that it is possible to prevent cognitive aging in rodents by increasing a specific kind of activity of the locus coeruleus called "phasic activity" during a time window of a few weeks. This activity consists of a rapid and temporary increase in the activity of the locus coeruleus, and it occurs whenever a stimulus captures our attention. These results suggest that increasing phasic locus coeruleus activity may be the key to preventing AD. One promising strategy to increase this activity in humans is electrical stimulation of the vagus nerve.

The vagus nerve is the tenth of twelve cranial nerves, which are nerves that originate in structures of the brain and allow body-brain communication. It regulates the activity of many organs, such as the heart, lungs, and stomach. For example, when we relax, this nerve is responsible for slowing our heart rate. Moreover, eighty percent of its fibers transmit information from the body to the brain, and in particular, the vagus nerve "communicates" with the locus coeruleus. Studies in animals have repeatedly shown that electrical stimulation of the vagus nerve increases phasic activity in the locus coeruleus.

In humans, we can safely electrically stimulate the vagus nerve by placing a small metal object, called an electrode, on the skin of the left ear in an area communicating only with the vagus nerve. This electrode is connected to a special device that allows low-intensity electrical pulses to be sent repeatedly for 3 to 5 seconds. The resulting sensation is similar to a tingling vibration, but it is not painful. Studying the effects of electrical vagus nerve stimulation on the locus coeruleus in humans involves measuring pupil sizes because the locus coeruleus causes the pupils to dilate. There are currently several studies showing that electrical stimulation of the vagus nerve increases pupil size in individuals between the ages of 18 and 35. These results are encouraging because they confirm that stimulating the vagus nerve increases phasic activity of the locus coeruleus in young adults. However, we do not know whether such stimulation has the same effects in older people, the primary group of interest for an intervention to prevent AD.

Starting in February 2025, a project funded by the European Commission will study whether electrical stimulation of the vagus nerve affects the locus coeruleus in older adults. The researcher working on this project, Martina D'Agostini, will carry out this research for three years at KU Leuven (Belgium) and the University of Southern California (USA) in collaboration with Ilse Van Diest (KU Leuven) and Mara Mather (University of Southern California), two professors specialized in the field. The project will compare the effects of electrical stimulation of the vagus nerve in young and older adults. We know that the locus coeruleus changes in its functioning and structure with age, and it is likely that the effects of the stimulation are stronger in young people. To improve the effects of vagus nerve stimulation in older adults, the project aims to:

- understand which stimulation parameters maximize the effects of vagus nerve stimulation on pupil size in the two age groups;
- understand when it is best to administer the stimulation, as it may be more effective to stimulate the vagus nerve when one is in a calm state rather than stressed.

The third objective of the project is to demonstrate that electrical stimulation of the vagus nerve can improve cognitive processes such as memory or attention that deteriorate with age. This information is fundamental to use this technique as a strategy to prevent cognitive aging.

In conclusion, electrical stimulation of the vagus nerve offers interesting new horizons in Alzheimer's research. However, we are only at the beginning of a long path of intense research on the prevention of AD. Researchers will have the fundamental role of testing whether electrical stimulation of the vagus nerve prevents cognitive aging before it can be used as a strategy for the prevention of AD. Researchers will have to understand at what age it is best to start using such stimulation and for how long. They will also have to test which individuals may benefit the most from electrical vagus nerve stimulation as a strategy to prevent Alzheimer's disease. Likely, such stimulation is not equally effective in all people. Finding answers to these questions is essential to create guidelines for the use of electrical stimulation of the vagus nerve as a strategy for the prevention of Alzheimer's disease.

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