Amnesia caused by sleep deprivation could be reversed with existing drugs

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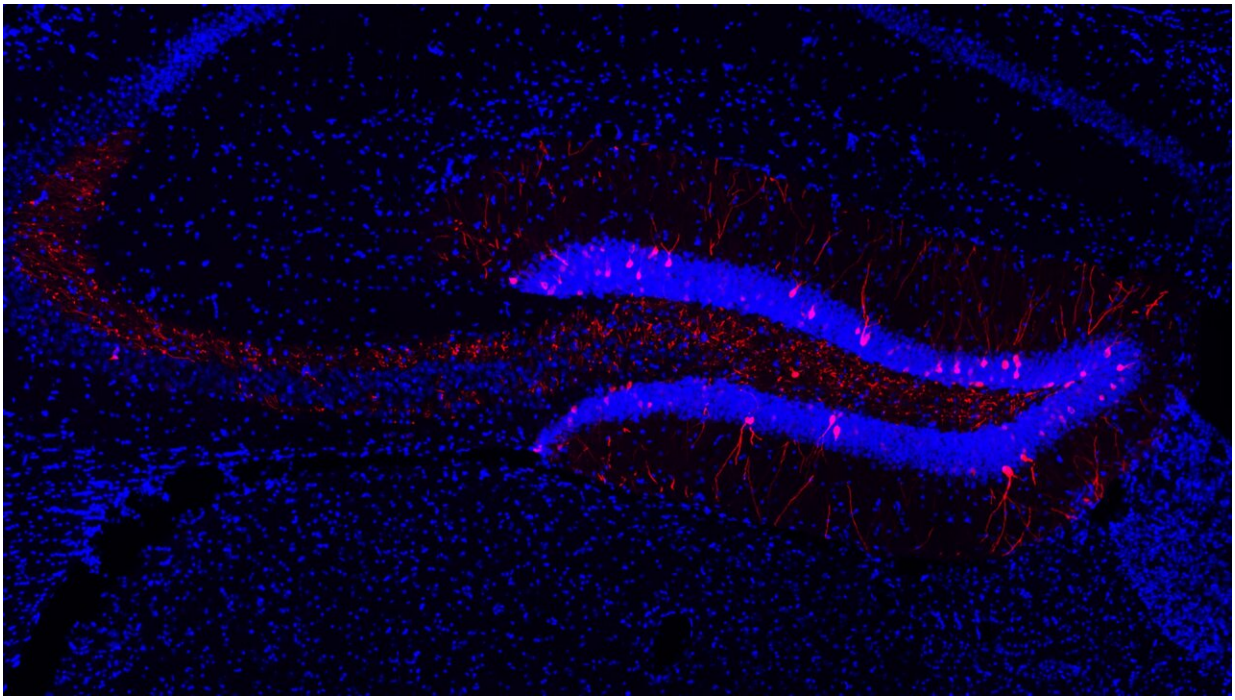

Image of memory engram cells visualized in the brain. Credit: FENS Forum / Robbert Havekes

The loss of social memories caused by sleep deprivation could potentially be reversed using currently available drugs, according to a study in mice presented at the Federation of European Neuroscience Societies (FENS) Forum 2024.

Lack of sleep is known to affect the brain, including memory, in mice and in humans, but research is beginning to show that these memories are not lost, they are just "hidden" in the brain and difficult to retrieve.

The new research shows that access to these otherwise hidden social memories can be restored in mice with a drug currently used to treat asthma and chronic obstructive pulmonary disease. The team of researchers have also shown that another drug currently used to treat erectile dysfunction can restore access to spatial memories. Researchers say these spatial memories in mice are akin to humans remembering where they put their keys the night before, whereas the social memories could be compared with remembering a new person you met.

The research was presented by Dr. Robbert Havekes from the University of Groningen in the Netherlands. He said, "Ever since starting as a Ph.D. student, many years ago, I have been intrigued by the observation that even a single period of sleep deprivation can have a major impact on memory processes and the brain as a whole. The early work published years ago helped us identify some of the molecular mechanisms that mediate amnesia.

"By manipulating these pathways specifically in the hippocampus, we have been able to make memory processes resilient to the negative impact of sleep deprivation. In our new studies, we have examined whether we could reverse amnesia even days after the initial learning event and period of sleep deprivation."

The new studies were conducted by Dr. Havekes's Ph.D. students Adithya Sarma and Camilla Paraciani, who will also be presenting their work as poster presentations.

To study social memories in the lab, the researchers gave mice the opportunity to choose between interacting with a mouse they had never

encountered before or a sibling from their own cage. Under normal circumstances, the mice preferred interacting with the new mouse over their littermate that they already knew. Given the same choice the next day, mice would interact to a similar extent with both their littermate and the mouse they had met the day before, as both mice would now be considered familiar.

However, if the mice were sleep-deprived after their first encounter, then the next day they would still prefer to interact with the new mouse as if they had never met it before. These findings suggest that they simply could not recall their previous encounter.

The team found they were able to permanently restore these hidden social memories, first using a technique called optogenetic engram technology. This technique allows them to identify neurons in the brain that together form a memory (known as a memory engram) for a specific experience and alter those neurons so they can be reactivated by light. Researchers can then use light to reactivate this specific group of neurons resulting in the recall of the specific experience (in this case a social memory).

They were also able to restore the mice's social memories by treating them with roflumilast, a type of anti-inflammatory drug, approved by the US Food and Drug Administration, that is used to treat chronic obstructive pulmonary disease. Dr. Havekes says this finding is particularly interesting as it provides a stepping stone towards studies of sleep deprivation and memory in humans, and he is now collaborating with another research group that is embarking on human studies.

In parallel, the same researchers have investigated the loss of spatial memory caused by sleep deprivation, by studying mice's abilities to learn and remember the location of individual objects. A brief period of sleep deprivation following training meant the mice could not recall the

original locations of the object, and so they did not notice when an object was moved to a new location during a test.

As with social memories, access to these spatial memories could be restored by treating the mice with another drug, vardenafil, that is currently used to treat erectile dysfunction. This is a second drug that is approved by the US Food and Drug Administration that the researchers have successfully used to reverse amnesia in mice.

Dr. Havekes said, "We have been able to show that sleep deprivation leads to amnesia in the case of specific spatial and social recognition memories. This amnesia can be reversed days later after the initial learning experience and sleep deprivation episode, using drugs already approved for human consumption. We now want to focus on understanding what processes are at the core of these accessible and inaccessible memories. In the long term, we hope that these fundamental studies will help pave the way for studies in humans aimed at reversing forgetfulness by restoring access to otherwise inaccessible information in the brain."

Professor Richard Roche is chair of the FENS Forum communication committee and Deputy Head of the Department of Psychology at Maynooth University, Maynooth, County Kildare, Ireland, and was not involved in the research. He said, "This research shows that social and spatial memories seemingly lost through sleep deprivation can be recovered. Although these studies were carried out in mice, they suggest that it may be possible to recover people's lost social and spatial memories using certain drug treatments that are already approved for human use.

"There are many situations where people cannot get the amount of sleep they need, so this area of research has obvious potential. However, it will take time and a lot more work to move this research from mice into

humans."

More information: "Restoring access to memories thought-to-be lost in the sleep-deprived brain", by Robbert Havekes, Part of Scientific Symposia: S48 Brain plasticity during sleep between homeostasis and memory consolidation 16:53 – 17:11 hrs, Friday, 28 June, Hall H, fens2024.abstractserver.com/pr … ls/presentations/112

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