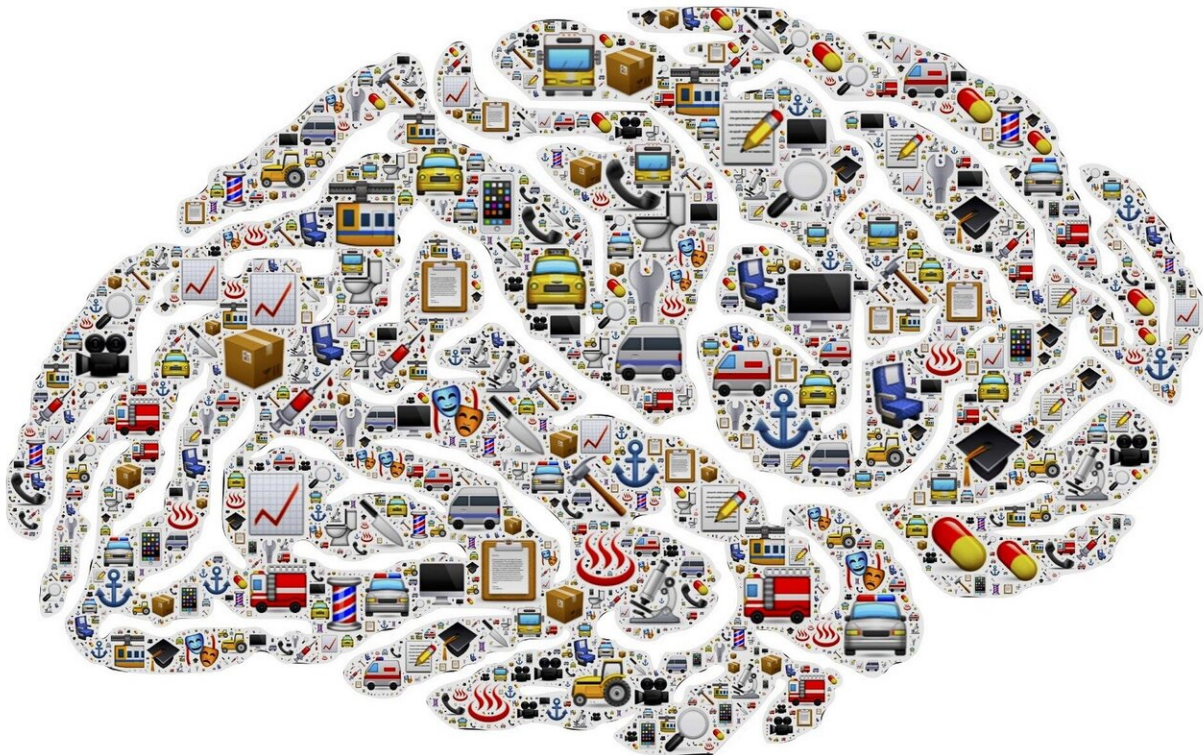


Instability of brain activity during sleep and anesthesia underlies the pathobiology of Alzheimer's disease

February 1 2022



Credit: CC0 Public Domain

A new study at Tel Aviv University revealed a pathological brain activity that precedes the onset of Alzheimer's first symptoms by many years: increased activity in the hippocampus during anesthesia and sleep, resulting from failure in the mechanism that stabilizes the neural network. The researchers believe that the discovery of this abnormal activity during specific brain states may enable early diagnosis of Alzheimer's, eventually leading to a more effective treatment of a disease that still lacks effective therapies.

The study was led by Prof. Inna Slutsky and doctoral students Daniel Zarhin and Refaela Atsmon from the Sackler Faculty of Medicine and the Sagol School of Neuroscience at Tel Aviv University. Additional participants in the study include: Dr. Antonella Ruggiero, Halit Baeloha, Shiri Shoob, Oded Scharf, Leore Heim, Nadav Buchbinder, Ortal Shinikamin, Dr. Ilana Shapira, Dr. Boaz Styr, and Dr. Gabriella Braun, all from Prof. Slutsky's laboratory. Collaborations with the laboratory teams of Prof. Yaniv Ziv of the Weizmann Institute, and Prof. Yuval Nir of TAU were essential for the project. Prof. Tamar Geiger, Dr. Michal Harel, and Dr. Anton Sheinin of Tel Aviv University, as well as researchers from Japan, also contributed to the study. The article was published in *Cell Reports*.

Prof. Slutsky says that "According to the recent study published this month in the *Lancet Public Health* journal, the number of people with dementia worldwide will increase from 50m in 2019 to more than 150m in 2050, growing by ~370% in North Africa and the Middle East. In Israel, a 145% increase is predicted, compared to ~74% in Western Europe. This huge increase in the prevalence of Alzheimer's due to the expected rise in population growth and in life expectancy will continue unless we develop effective treatments. This is clearly an alert for investing in dementia research and its most frequent form—Alzheimer's disease."

"Innovative imaging technologies developed in recent years have revealed that amyloid deposits, a hallmark of Alzheimer's disease pathology, are formed in patients' brains as early as 10-20 years before the onset of typical symptoms such as memory impairment and cognitive decline. Unfortunately, most efforts to treat Alzheimer's disease by reducing the amount of amyloid-beta proteins and their aggregation have failed. If we could detect the disease at the pre-symptomatic stage, and keep it in a dormant phase for many years, this would be a tremendous achievement in the field. We believe that identifying a signature of aberrant [brain](#) activity in the pre-symptomatic stage of Alzheimer's and understanding the mechanisms underlying its development is a key to effective treatment."

The researchers used animal models for Alzheimer's, focusing on the hippocampal region of the brain, which plays a key role in memory processes, and is known to be impaired in Alzheimer's patients. At first, they measured cell activity in the hippocampus when the model animal was awake, active, and exploring its surroundings. For this they used advanced methods that measure brain activity at a resolution of single neurons.

Daniel Zarhin says that "previous studies have examined cell activity in the brains of anesthetized animals in a model for Alzheimer's and found overactivity in the hippocampus and cortex. To my surprise, when I examined the model animals, I found no difference between the activity of neurons and synapses in their hippocampus and corresponding activity in the control group of healthy animals."

In light of these findings, the researchers decided to examine activity in the hippocampus in other states of consciousness—under anesthesia and during natural sleep. Refaela Atsmon says that "it is known that neuronal activity of the hippocampus decreases during sleep in healthy animals. But when I examined model animals in early stages of Alzheimer's, I

found that their hippocampal activity remained high even during sleep. This is due to a failure in the physiological regulation, never before observed in the context of Alzheimer's disease." Daniel Zarhin found similar dysregulation in model animals under anesthesia: neuronal activity does not decline, the neurons operate in a manner that is too synchronized, and a pathological electrical pattern is formed, similar to 'quiet' seizures in epileptic patients. Halit Baeloha, who is researching sleep problems related to Alzheimer's disease, emphasizes that the discovered disruption begins before the onset of the typical sleep disturbances observed in Alzheimer's patients.

Prof. Slutsky explains that they "found that brain states that block responses to the environment—such as sleep and anesthesia—expose abnormal activity which remains hidden when the animal is awake, and this happens before the symptoms of Alzheimer's disease are observed. Even though this abnormal activity can be detected during sleep, it is much more frequent under anesthesia. Therefore, it would be important to test whether short anesthesia can be used for early diagnosis of Alzheimer's."

At the next stage of the study, the researchers asked what causes the abnormality. To this end, they relied on findings from previous studies from Prof. Slutsky's laboratory and other researchers on homeostasis of neural networks: each neural circuit has a set point of activity, maintained by numerous stabilizing mechanisms. These mechanisms are activated when the balance is disturbed, restoring neuronal activity to its original set point.

Is a disruption of these homeostatic mechanisms the main cause of aberrant brain activity during sleep and anesthesia in Alzheimer's disease animal models? To test this, Dr. Antonella Ruggiero examined the effect of various anesthetics on neurons grown on a chip and found that they lower the set point of neuronal activity. In healthy neural networks,

activity remained low over time, but in neural networks expressing familial Alzheimer's mutations, the lowered set point recovers quickly, despite the presence of anesthetics. In another experiment, Dr. Ruggiero increased neuronal activity, and once again she found a failure in the mechanisms responsible for restoring activity to its normal set point in neurons expressing Alzheimer's mutations.

The researchers now sought to examine a potential drug for the impaired regulatory mechanism. Prof. Slutsky says that "the instability in neuronal activity which we found in this study is known from epilepsy. In a previous study we discovered that an existing drug for multiple sclerosis may help epilepsy patients by activating a homeostatic mechanism that lowers the set point of neural activity. Doctoral student Shiri Shoob examined the effect of the drug on hippocampal activity in the [animal model](#) for Alzheimer's and found that in this case also the drug stabilizes activity and reduces pathological activity observed during anesthesia."

Prof. Slutsky concludes that "the results of our study may help early diagnosis of Alzheimer's, and even provide a solution for instability of neuronal activity in Alzheimer's disease. Firstly, we discovered that anesthesia and sleep states expose pathological brain activity in the early stages of Alzheimer's disease, before the onset of cognitive decline. We also proposed the cause of the pathological activity—failure of a very basic homeostatic mechanism that stabilizes electrical activity in brain circuits. Lastly, we showed that a known medication for multiple sclerosis suppresses this type of anesthesia-induced aberrant brain [activity](#)."

The researchers now plan to collaborate with medical centers in Israel and worldwide to test whether the mechanisms discovered in animal models can also be identified in patients with early-stage Alzheimer's [disease](#). For this purpose, they propose to incorporate EEG monitoring into surgical procedures, to measure [brain activity](#) of patients under

anesthesia. They hope that their findings will promote early diagnosis and drug development for the most common form of late-onset dementia.

More information: Daniel Zarhin et al, Disrupted neural correlates of anesthesia and sleep reveal early circuit dysfunctions in Alzheimer models, *Cell Reports* (2022). [DOI: 10.1016/j.celrep.2021.110268](https://doi.org/10.1016/j.celrep.2021.110268)

Provided by Tel-Aviv University

Citation: Instability of brain activity during sleep and anesthesia underlies the pathobiology of Alzheimer's disease (2022, February 1) retrieved 24 June 2024 from <https://medicalxpress.com/news/2022-02-instability-brain-anesthesia-underlies-pathobiology.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.