'Tangles' trigger early-stage Alzheimer's abnormalities in neocortical networks

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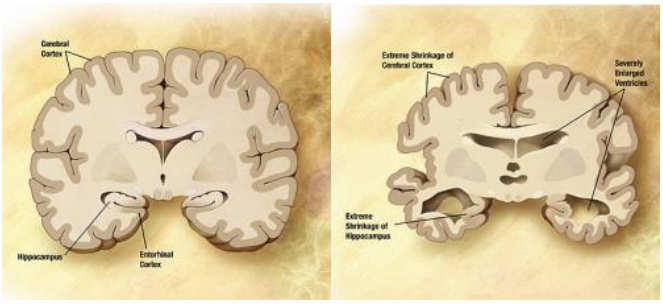

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

Alzheimer's disease (AD) is a neurodegenerative condition that strikes at the heart of what makes us human: the ability to think, to feel, to remember and to communicate with those around us. The tragedy is compounded by the fact that there is currently no cure, no treatment, and no diagnostic method capable of identifying Alzheimer's at its early stages.

A ground-breaking study has now, for the first time anywhere, characterized early-stage changes that occur inside individual, Alzheimer's-affected cells in the intact brain. Remarkably, the study indicates that even if only a small number of cells is affected, the result is a reduction of electrical activity throughout the cerebral cortex - the area of the brain that serves as the center of higher mental function and cognition.

The researchers - Drs. Edward Stern and Dana Cohen of Bar-Ilan University and Dr. Tara Spires-Jones of the University of Edinburgh - published their findings in the academic journal *Neuron* on February 19th, 2015.

A Tangled Web

Dr. Edward Stern, the lead author of the study, is a member of Bar-Ilan University's Gonda (Goldschmied) Multidisciplinary Brain Research Center, and also holds an appointment at the MassGeneral Institute for Neurodegenerative Disease at Massachusetts General Hospital in the United States. He explains that the study's dramatic results are due, in part, to the scientists' decision to focus on a seldom-studied brain cell pathology known as "tangles".

"Alzheimer's disease is associated with three pathologies: cell death, extra-cellular build-up of amyloid plaques, and tangles - the abnormal twisting of the cellular filaments which hold the neuron in its proper shape," Stern says, adding that tangles are caused by an aberrant form of a protein known as tau.

"While it was already known that pathological tau is associated with dementia, ours is the first study to reveal the tau-linked changes in cell- and network-based activity that underlies neurodegeneration. Significantly, we found that if even a small number of cells have tangles, this amplifies into a devastating effect across the entire network, characterized by long latencies between spikes of inter-neuron communication, as well as a reduction in the overall level of synaptic activity."

Recording Network-Based "Conversations" in the Intact Brain

The researcher's observations were made possible through the use of a technique that allowed them to position electrodes inside individual cells in the intact anaesthetized brains of transgenic mice. Studying these mice - genetically altered to produce the tangle-triggering abnormal tau protein - the scientists measured spontaneous sub-threshold fluctuation of electrical activity. They also observed how neuronal activity patterns change in response to stimulation.

Experiments performed by Dr. Noa Menkes-Caspi,

at the time a doctoral candidate in Stern's lab, demonstrated that pathological tau disrupts the activity of single cells as well as intra-cellular communication in the neocortex. This phenomenon was observed prior to any significant cell death, at a time when only a small fraction of the neurons displayed fully-developed tangles.

According to Stern, these results indicate that Alzheimer's symptoms - long suspected to be caused by the extra-cellular build-up of amyloid-beta, are also caused by the abnormal accumulation of tau that afflicts individual cells. By reducing the rate at which individual neurons fire, tangles act to suppress synaptic activity in the wider neocortical network, leading to reduced cognitive function. Stern suggests that the two pathologies combine with devastating effect to change the neuronal activity patterns in the brain, causing Alzheimer's disease symptoms.

A Timely Message with Medical Potential

Stern points out that this study represents the first time that an abnormality in neural physiology has been causally linked to changes in brain behavior on the network level. He states that this data may eventually point the way toward an elusive goal of clinical medicine: a method for positively identifying Alzheimer's onset, before it's too late.

"Now that we have characterized patterns of neocortical electrical activity in the presence of tangle-afflicted cells and amyloid-beta affected brains, it may be possible to screen for these patterns with EEG," he says, referring to electroencephalogram, a non-invasive technique commonly used to identify epilepsy and other brain disorders. "This could someday form the basis of early AD diagnosis."

Stern also sees these findings as an important step toward the longer-term goal of effective Alzheimer's treatment.

"The key is to compare pathological to normal neurons, and identify ways in which abnormal neural activity might be reversed," he says. "Since a change in brain cell activity is what causes disease symptoms, a clearer understanding of abnormal neural physiology may bring us closer to what we all want, and what the world needs - a treatment for Alzheimer's disease."

More information: Pathological Tau Disrupts Ongoing Network Activity, DOI: dx.doi.org/10.1016/j.neuron.2015.01.025

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