While navigating a virtual maze, young adults at high genetic risk of Alzheimer’s disease demonstrated reduced functioning of brain cells involved in spatial navigation, causing them to navigate the maze differently than controls, a new study finds.

Identifying early biomarkers of the disease, such as abnormal grid cell functioning, could be a valuable step in the field of Alzheimer’s research since the best hope for minimizing development of the disease lies in early intervention.

Previous research reveals that Alzheimer’s begins in a region of the brain called the entorhinal cortex (EC) long before symptoms appear; abnormalities can be observed in adults under the age of 30. Lukas Kunz et al. therefore measured the functioning of grid cells, a type of cell in the EC involved in spatial navigation, in young adults navigating a virtual maze.

The researchers compared the performance of individuals with the APOE-ε4 gene, and thus at high risk of developing Alzheimer’s, against control participants. While the high-risk group had similar spatial memory performance compared to controls, functional magnetic resonance imaging (fMRI) revealed that these individuals had significantly reduced grid cell functioning. This group also showed a reduced preference to navigate in the center of the virtual arena compared to control participants.
Spatial Navigation cont’d…..

Further analysis suggests that the high-risk group may be compensating for their abnormal grid-cell functioning by harnessing the hippocampus, another brain region associated with Alzheimer’s disease, in order to maintain the same level of spatial memory performance seen in the control group.

These differences in grid cell functioning, detectable through simple fMRI, could be used to identify those susceptible to developing Alzheimer’s, although more long-term research is needed to confirm whether early reduced grid-cell functioning is directly related to disease development later in life.


Promising Phase 2 Results for Agitation Drug

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In today’s JAMA Neurology, researchers led by Jeffrey Cummings at the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas formally published the results of a 10-week Phase 2 trial of Avanir Pharmaceuticals’ AVP-923 to treat agitation in Alzheimer’s disease. As previously reported at the 2014 meeting of the American Neurological Association in Baltimore, the drug met its endpoints, dampening agitation in the majority of the patients who took it.

The drug, trade named Nuedexta, is a combination of dextromethorphan hydrobromide and quinidine sulfate. The former is the active ingredient in cough syrup and acts on several neurotransmitter systems, including glutamate, serotonin, and norepinephrine, while the latter ingredient slows the metabolism of dextromethorphan, potentiating its effects. The drug is approved to treat pseudobulbar affect, a condition present in some neurodegenerative disorders that is marked by uncontrollable bouts of laughing or crying.

In an accompanying commentary, Clive Ballard, Samantha Sharp, and Anne Corbett at King’s College London expressed cautious optimism about the drug, though they noted that longer studies will be needed to confirm the results. “The magnitude of benefit for reducing agitation/aggression observed with dextromethorphan-quinidine compares favorably with previous studies … There is a reasonably strong case to pri-oritize dextromethorphan-quinidine as an off-label treatment for agitation,” they wrote.

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Agitation Drug cont’d......

In a multi-site study of 220 patients diagnosed with probable AD according to 2011 NIA-AA criteria, treatment roughly halved the severity of agitation as measured by the Neuropsychiatric Inventory Agitation/Aggression scale. Physicians agreed that patients had improved on Clinical Global Impression of Change scales, and caregivers rated their stress as lower. About two-thirds of patients responded to the drug, compared to less than half of the placebo group. Placebo responses occur commonly in treatment of neuropsychiatric symptoms.

The drug had side effects. Dizziness, falls, diarrhea, and urinary tract infections were the most common, occurring in 5 to 8 percent of participants. These effects match the known safety profile of the drug. According to the paper, treated participants exhibited no signs of sedation, cardiac problems, or declining cognition, which have plagued other medications tested for agitation. According to Cummings, a Phase 3 study has begun enrolling.

—Madolyn Bowman Rogers

Alzheimer’s Plaques Impair Memory Formation During Sleep

By Neuroscience News
October 22, 2015

Protein deposits associated with dementia influence brain activity during sleep.

Alzheimer’s patients frequently suffer from sleep disorders, mostly even before they become forgetful. Furthermore, it is known that sleep plays a very important role in memory formation. Researchers from the Technical University of Munich (TUM) have now been able to show for the first time how the pathological changes in the brain act on the information-storing processes during sleep. Using animal models, they were able to decode the exact mechanism and alleviate the impairment with medicinal agents.

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AD is believed to occur from the toxic buildup of beta amyloid. There are many forms of AD that are genetically inherited, including Down syndrome. People with Down syndrome have an extra copy of the 21st chromosome where the production gene for the beta amyloid protein resides.

Funding support for this research came, in part, from Janssen Research and Development, LLC and the National Institutes of Health (grants AG047484 and AG01048).

The sleep slow waves, also known as slow oscillations, which our brain generates at night, have a particular role in consolidating what we have learned and in shifting memories into long-term storage. These waves are formed via a network of nerve cells in the brain’s cortex, and then spread out into other parts of the brain, such as the hippocampus.

“These waves are a kind of signal through which these areas of the brain send mutual confirmation to say ‘I am ready, the exchange of information can go ahead’. Therefore, there is a high degree of coherence between very distant nerve cell networks during sleep”, explains Dr. Marc Aurel Busche, scientist at the Department of Psychiatry and Psychotherapy at TUM University Hospital Klinikum rechts der Isar and TUM Institute of Neuroscience. Together with Dr. Arthur Konnerth from the Institute of Neurosciences, he headed the study which was published in the journal Nature Neuroscience.

Disrupted spread of sleep waves in Alzheimer models

As the researchers discovered, this coherence process is disrupted in Alzheimer’s disease. In their study, they used mouse models with which the defects in the brains of Alzheimer’s patients can be simulated. The animals form the same protein deposits, known as β-amyloid plaques, which are also visible in human patients. The scientists were now able to show that these plaques directly impair the slow wave activity. “The slow oscillations do still occur, but they are no longer able to spread properly – as a result, the signal for the information cross-check is absent in the corresponding regions of the brain,” is how Marc Aurel Busche summarizes it.

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The scientists also succeeded in decoding this defect at the molecular level: correct spread of the waves requires a precise balance to be maintained between the excitation and inhibition of nerve cells. In the Alzheimer models, this balance was disturbed by the protein deposits, so that inhibition was reduced.

**Low doses of sleep-inducing drugs as possible therapy**

Busche and his team used this knowledge to treat the defect with medication. One group of sleep-inducing drugs, the benzodiazepines, is known to boost inhibitory influences in the brain. If the scientists gave small amounts of this sleep medication to the mice (approximately one-tenth of the standard dose), the sleep slow waves were able to spread out correctly again. In subsequent behavioral experiments, they were able to demonstrate that learning performance had now improved as well.

*Image representing the slow waves in the brain, which spread out normally during sleep (left). This process is severely disrupted by the β-amyloid plaques (center). The disruption is reversed by administering a benzodiazepine (right). Credit: Marc Aurel Busche /TUM.*

For the researchers, of course, these results are just a first step on the way to a suitable treatment of Alzheimer’s disease. “But, these findings are of great interest for two reasons: firstly, mice and humans have the same sleep oscillations in the brain – the results are thus transferrable. Secondly, these waves can be recorded with a standard EEG monitor, so that any impairment may also be diagnosed at an early stage”, concludes the scientist.

**Original Research:** Abstract for “Rescue of long-range circuit dysfunction in Alzheimer’s disease models” by Marc Aurel Busche, Maja Kekuš, Helmuth Adelsberger, Takahiro Noda, Hans Förstl, Israel Nelken and Arthur Konnerth in *Nature Neuroscience*. Published online October 12 2015 [doi:10.1038/nn.4137](http://dx.doi.org/10.1038/nn.4137)
New Way to Fight Alzheimer’s

By Barbara Moran, Boston University

Amyloid beta protein—“Abeta” for short. In Alzheimer’s disease, the sticky strands clump into plaques that kill neurons. MED scientists have discovered a compound that may stop Abeta formation. Photo by Nephron via Wikimedia Commons

“In the war against Alzheimer’s disease, one of the big villains is a protein called amyloid beta—“Abeta,” for short. In a diseased brain, sticky strands of the protein clump into plaques that kill nerve cells and choke the gaps between them. Under a microscope the plaques look sinister, even to the untrained eye—scattershot black blotches, splattered across healthy tissue.

Scientists, knowing the damage Abeta can cause, have searched for therapies that clear the protein from the brains of Alzheimer’s patients. So far, all clinical trials of this approach have failed. Though two trials are still ongoing, for now Alzheimer’s remains a disease with no prevention, treatment, or cure.

Now Carmela Abraham, Boston University professor of biochemistry and medicine, and a team of scientists from the BU School of Medicine (MED) have discovered a new way to attack Abeta. Instead of clearing it from the brain, the scientists have found a compound that prevents the body from making it in the first place. They presented an unpublished preview of their discovery at the Society for Neuroscience annual meeting on October 19, 2015. The work, funded by the Alzheimer’s Association and the Cure Alzheimer’s Fund, may eventually lead to a novel treatment for this deadly disease.

“Alzheimer’s is now the number six killer of adults in the United States. Deaths from breast cancer and heart disease keep dropping, but Alzheimer’s increases every year,” says Abraham. “Caring for Alzheimer’s patients costs over $200 billion per year. The estimate for 2050 is $1.1 trillion, which means it will completely break the health care system. We have to find a drug.”

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The brain creates Abeta with enzymes that chop a larger protein, called the amyloid precursor protein (APP), into smaller bits. Sometimes, for reasons scientists don’t quite understand, two APP proteins join together in a process called dimerization, which ultimately leads to increased Abeta. Abraham wondered: if scientists could stop dimerization, would that stop Abeta in its tracks? She decided to try.

Working with Harvard’s Laboratory for Drug Discovery in Neurodegeneration, Abraham’s team screened 77,000 molecules that they thought might affect APP dimerization. They focused on small molecules because large ones don’t easily cross the blood–brain barrier. “If you want to treat brain disease, you need small molecules,” says Abraham. “If you use large molecules like antibodies, only a very small percentage get into the brain, and they can have huge effects on the rest of the body.”

The drug screen turned up one significant hit. Abraham showed the molecule to her colleague John Porco, professor of chemistry and director of BU’s Center for Molecular Discovery. Porco identified the molecule almost immediately: it was a kinase inhibitor. These block the action of enzymes called kinases, which are common in many cellular processes.

“This was the big eureka moment,” says Abraham. “Once we knew what the molecule was doing, we could search to see what kinase it inhibits and better understand the mechanism.” Further work found that the molecule was acting on a kinase in a larger cell-signaling complex. Abraham hopes that more research will find the enzyme that acts directly on APP. “That would be the target,” she says.

Her team, which includes postdoctoral fellow Ella Zeldich, research assistant professor CiDi Chen, and assistant professor of chemistry Lauren Brown, is now looking for similar molecules that may work even better, and for other molecules in the pathway that may also become drug targets. The ultimate goal, says Abraham, is an effective drug where none now exists.

“Right now there is nothing,” says Abraham. “We must find something new.”
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/clinalResearchStudy.aspx

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