Data, Dogma And The Move To Early Intervention In AD Clinical Research

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Although we think of science as a method to better understand the rules by which the natural world works, scientific research usually proceeds on an uncertain path, where we believe we are making progress towards deeper understanding of biological processes, but are not always fully certain. The challenge is to stick with our ideas while at the same time comparing and contrasting them with data obtained from experiments that aim to advance these very same theories.

As case in point, the amyloid hypothesis remains the prevalent idea about the cause of Alzheimer’s disease. Genetic, molecular, pathological and advanced imaging data all point to an abnormality in amyloid biology that leads to this disease. However, clinical trials aiming to reduce amyloid in the brain, and therefore affect the progression of AD, have essentially failed. So, what is one to do when the data, seemingly, do not fit the dogma? Is the amyloid hypothesis wrong?

If there were individuals with AD who had no abnormality in amyloid in the brain, then perhaps we could start to abandon this hypothesis. However, this is not the case. In fact, the presence of abnormal amyloid is a requirement for the diagnosis of AD.

In fact, over the past 20 years, mechanisms have been identified that explain how amyloid damages the brain. In looking at recent clinical trial failures that have been aiming to treat AD by targeting amyloid, one thing is found to be in common amongst them: they required subjects to have symptoms of dementia or at least some level of cognitive impairment that indicates abnormal amyloid in the brain consistent with Alzheimer’s disease.

The limiting effect of intervening at this stage of AD cannot be overstated. By analogy, imagine waiting until a cancer reaches stage IV, which implies metastasis, before initiating treatment. In a strange but fortunate way, many cancers cause symptoms that bring patients to medical attention and therefore treatment before they metastasize, though this is not always the case. And in those patients where cancer is caught early, there is a better chance for a favorable prognosis.

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The data from the studies conducted thus far indicate that AD behaves much the same way, with one caveat. Patients come to medical attention when the disease has spread quite substantially throughout the brain, and has already caused significant brain injury. In essence, the treatments for AD need to be given earlier in the disease.

Researchers are keenly aware of this fact and there are now multiple clinical trials being organized that will aim to lower amyloid in patients who have virtually no symptoms of cognitive impairment, and certainly have no dementia, yet. These individuals will be evaluated with the most accurate tools available to identify those people who are developing amyloid in the brain, despite showing no outward symptoms. And, as part of the studies, they will be offered anti-amyloid treatments to hopefully prevent the progression to cognitive impairment and dementia.

In the next few months we will be hearing about such studies, including the ADCS A4 (Anti-amyloid in Asymptomatic AD) trial, the Alzheimer’s Prevention Initiative (API) APO4 trial and others.

Stay tuned.
Thanks for reading.
UF Researchers Find That ‘Peanut Butter’ Test Can Help Diagnose Alzheimer’s Disease

University of Florida researcher Jennifer Stamps demonstrates the peanut butter test. Researchers have found that patients in the early stages of Alzheimer’s disease have an asymmetry in their ability to detect smells, with the left nostril becoming weaker than the right.

By Marilee Griffin
University of Florida Health

A dollop of peanut butter and a ruler can be used to confirm a diagnosis of early stage Alzheimer’s disease, University of Florida Health researchers have found.

Jennifer Stamps, a graduate student in the UF McKnight Brain Institute Center for Smell and Taste, and her colleagues reported the findings of a small pilot study in the Journal of the Neurological Sciences.

Stamps came up with the idea of using peanut butter to test for smell sensitivity while she was working with Kenneth Heilman, M.D., the James E. Rooks distinguished professor of neurology and health psychology in the UF College of Medicine’s department of neurology.

She noticed while shadowing in Heilman’s clinic that patients were not tested for their sense of smell. The ability to smell is associated with the first cranial nerve and is often one of the first things to be affected in cognitive decline. Stamps also had been working in the laboratory of Linda Bartoshuk, Ph.D., the William P. Bushnell presidentially endowed professor in the College of Dentistry’s department of community dentistry and behavioral sciences and director of human research in the Center for Smell and Taste.

“Dr. Heilman said, ‘If you can come up with something quick and inexpensive, we can do it,’” Stamps said.

She thought of peanut butter because, she said, it is a “pure odorant” that is only detected by the olfactory nerve and is easy to access.
In the study, patients who were coming to the clinic for testing also sat down with a clinician, 14 grams of peanut butter — which equals about one tablespoon — and a metric ruler. The patient closed his or her eyes and mouth and blocked one nostril. The clinician opened the peanut butter container and held the ruler next to the open nostril while the patient breathed normally. The clinician then moved the peanut butter up the ruler one centimeter at a time during the patient’s exhale until the person could detect an odor. The distance was recorded and the procedure repeated on the other nostril after a 90-second delay.

The clinicians running the test did not know the patients’ diagnoses, which were not usually confirmed until weeks after the initial clinical testing.

The scientists found that patients in the early stages of Alzheimer’s disease had a dramatic difference in detecting odor between the left and right nostril — the left nostril was impaired and did not detect the smell until it was an average of 10 centimeters closer to the nose than the right nostril had made the detection in patients with Alzheimer’s disease. This was not the case in patients with other kinds of dementia; instead, these patients had either no differences in odor detection between nostrils or the right nostril was worse at detecting odor than the left one.

Of the 24 patients tested who had mild cognitive impairment, which sometimes signals Alzheimer’s disease and sometimes turns out to be something else, about 10 patients showed a left nostril impairment and 14 patients did not. The researchers said more studies must be conducted to fully understand the implications.

“At the moment, we can use this test to confirm diagnosis,” Stamps said. “But we plan to study patients with mild cognitive impairment to see if this test might be used to predict which patients are going to get Alzheimer’s disease.”

Stamps and Heilman point out that this test could be used by clinics that don’t have access to the personnel or equipment to run other, more elaborate tests required for a specific diagnosis, which can lead to targeted treatment. At UF Health, the peanut butter test will be one more tool to add to a full suite of clinical tests for neurological function in patients with memory disorders.

One of the first places in the brain to degenerate in people with Alzheimer’s disease is the front part of the temporal lobe that evolved from the smell system, and this portion of the brain is involved in forming new memories.

“We see people with all kinds of memory disorders,” Heilman said. Many tests to confirm a diagnosis of Alzheimer’s disease or other dementias can be time-consuming, costly or invasive. “This can become an important part of the evaluation process.”

This research was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health under Clinical and Translational Science Award number UL1RR029890, and the State of Florida Memory Disorders Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.
To Sleep, Perchance To Clean

Image shows cerebral spinal fluid (in blue) entering the brain via a "plumbing system" that piggybacks on the brain's blood vessels.

By Mark Michaud
University of Rochester Medical Center

Study reveals brain ‘takes out the trash’ while we sleep

In findings that give fresh meaning to the old adage that a good night’s sleep clears the mind, a new study shows that a recently discovered system that flushes waste from the brain is primarily active during sleep. This revelation could transform scientists' understanding of the biological purpose of sleep and point to new ways to treat neurological disorders.

“This study shows that the brain has different functional states when asleep and when awake,” said Maiken Nedergaard, M.D., D.M.Sc., co-director of the University of Rochester Medical Center (URMC) Center for Translational Neuromedicine and lead author of the article. “In fact, the restorative nature of sleep appears to be the result of the active clearance of the by-products of neural activity that accumulate during wakefulness.”

The study, which was published today in the journal Science, reveals that the brain’s unique method of waste removal – dubbed the glymphatic system – is highly active during sleep, clearing away toxins responsible for Alzheimer’s disease and other neurological disorders. Furthermore, the researchers found that during sleep the brain’s cells reduce in size, allowing waste to be removed more effectively.

The purpose of sleep is a question that has captivated both philosophers and scientists since the time of the ancient Greeks. When considered from a practical standpoint, sleep is a puzzling biological state. Practically every species of animal from the fruit fly to the right whale is known to sleep in some fashion. But this period of dormancy has significant drawbacks, particularly when predators lurk about. This has led to the observation that if sleep does not perform a vital biological function then it is perhaps one of evolution’s biggest mistakes.

While recent findings have shown that sleep can help store and consolidate memories, these benefits do not appear to outweigh the accompanying vulnerability, leading scientists to speculate that there must be a more essential function to the sleep-wake cycle.

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The new findings hinge on the discovery last year by Nedergaard and her colleagues of a previously unknown system of waste removal that is unique to the brain. The system responsible for disposing cellular waste in the rest of the body, the lymphatic system, does not extend to the brain. This is because the brain maintains its own closed “ecosystem” and is protected by a complex system molecular gateways – called the blood-brain barrier – that tightly control what enters and exits the brain.

The brain’s process of clearing waste had long eluded scientists for the simple fact that it could only be observed in the living brain, something that was not possible before the advent of new imaging technologies, namely two-photon microscopy. Using these techniques, researchers were able to observe in mice – whose brains are remarkably similar to humans – what amounts to a plumbing system that piggybacks on the brain’s blood vessels and pumps cerebral spinal fluid (CSF) through the brain’s tissue, flushing waste back into the circulatory system where it eventually makes its way to the general blood circulation system and, ultimately, the liver.

The timely removal of waste from the brain is essential where the unchecked accumulation of toxic proteins such as amyloid-beta can lead to Alzheimer’s disease. In fact, almost every neurodegenerative disease is associated with the accumulation of cellular waste products.

One of the clues hinting that the glymphatic system may be more active during sleep was the fact that the amount of energy consumed by the brain does not decrease dramatically while we sleep. Because pumping CSF demands a great deal of energy, researchers speculated that the process of cleaning may not be compatible with the functions the brain must perform when we are awake and actively processing information.

Through a series of experiments in mice, the researchers observed that the glymphatic system was almost 10-fold more active during sleep and that the sleeping brain removed significantly more amyloid-beta.

“The brain only has limited energy at its disposal and it appears that it must choose between two different functional states – awake and aware or asleep and cleaning up,” said Nedergaard. “You can think of it like having a house party. You can either entertain the guests or clean up the house, but you can’t really do both at the same time.”

Another startling finding was that the cells in the brain “shrink” by 60 percent during sleep. This contraction creates more space between the cells and allows CSF to wash more freely through the brain tissue. In contrast, when awake the brain’s cells are closer together, restricting the flow of CSF.

The researchers observed that a hormone called noradrenaline is less active in sleep. This neurotransmitter is known to be released in bursts when brain needs to become alert, typically in response to fear or other external stimulus. The researchers speculate that noradrenaline may serve as a “master regulator” controlling the contraction and expansion of the brain’s cells during sleep-wake cycles.

“These findings have significant implications for treating ‘dirty brain’ disease like Alzheimer’s,” said Nedergaard. “Understanding precisely how and when the brain activates the glymphatic system and clears waste is a critical first step in efforts to potentially modulate this system and make it work more efficiently.”

Additional co-authors of the study include Lulu Xie, Hongyi Kang, Qiwu Xu, Michael Chen, Yonghong Liao, Thiyagarajan Meenakshisundaram, John O'Donnell, Daniel Christensen, Takahiro Takano, and Rashid Deane with URMC, Jeffrey Iliff with Oregon Health and Science University, and Charles Nicholson with New York University. The study was supported by the National Institute of Neurological Disorders and Stroke.
The green spots above are clumps of protein inside yeast cells that are deficient in both zinc and a protein that prevents clumping. Research by Colin MacDiarmid and David Eide is exploring how a shortage of zinc can contribute to diseases. Photo: Colin MacDiarmid and David Eide/Journal of Biological Chemistry

By David J Tenenbaum, University of Wisconsin-Madison

Scientists at UW-Madison have made a discovery that, if replicated in humans, suggests a shortage of zinc may contribute to diseases like Alzheimer's and Parkinson's, which have been linked to defective proteins clumping together in the brain.

With proteins, shape is everything. The correct shape allows some proteins to ferry atoms or molecules about a cell, others to provide essential cellular scaffolding or identify invading bacteria for attack. When proteins lose their shape due to high temperature or chemical damage, they stop working and can clump together — a hallmark of Parkinson’s and Alzheimer’s.

The UW researchers have discovered another stress that decreases protein stability and causes clumping: a shortage of zinc, an essential metal nutrient.

Zinc ions play a key role in creating and holding proteins in the correct shape. In a study just published in the online Journal of Biological Chemistry, Colin MacDiarmid and David Eide show that the gene Tsa1 creates "protein chaperones" that prevent clumping of proteins in cells with a zinc shortage. By holding proteins in solution, Tsa1 prevents damage that can otherwise lead to cell death.

For simplicity, the researchers studied the system in yeast — a single-celled fungus. Yeast can adapt to both shortages and excesses of zinc, says MacDiarmid, an associate scientist. "Zinc is an essential nutrient but if there's too much, it's toxic. The issue for the cell is to find enough zinc to grow and support all its functions, while at the same time not accumulating so much that it kills the cell."

Cells that are low in zinc also produce proteins that counter the resulting stress, including one called Tsa1.

The researchers already knew that Tsa1 could reduce the level of harmful oxidants in cells that are short of zinc. Tsa1, MacDiarmid says, "is really a two-part protein. It can get rid of dangerous reactive oxygen species that damage proteins, but it also has this totally distinct chaperone function that protects proteins from aggregating. We found that the chaperone function was the more important of the two."

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"In yeast, if a cell is deficient in zinc, the proteins can mis-fold, and Tsa1 is needed to keep the proteins intact so they can function," says Eide, a professor of nutritional science. "If you don't have zinc, and you don't have Tsa1, the proteins will glom together into big aggregations that are either toxic by themselves, or toxic because the proteins are not doing what they are supposed to do. Either way, you end up killing the cell."

While the medical implications remain to be explored, there are clear similarities between yeast and human cells. "Zinc is needed by all cells, all organisms, it's not just for steel roofs, nails and trashcans," Eide says. "The global extent of zinc deficiency is debated, but diets that are high in whole grains and low in meat could lead to deficiency."

If low zinc supply has the same effect on human cells as on yeast, zinc deficiency might contribute to human diseases that are associated with a build-up of "junked" proteins, such as Parkinson's and Alzheimer's. Eide says a similar protective system to Tsa1 also exists in animals, and the research group plans to move ahead by studying that system in human cell culture.
Patients treated in intensive care units across the globe enter their medical care with no evidence of cognitive impairment but often leave with deficits similar to those seen in patients with traumatic brain injury (TBI) or mild Alzheimer’s disease (AD) that persist for at least a year, according to a Vanderbilt University Medical Center study published today in the *New England Journal of Medicine*.

The study, led by members of Vanderbilt’s ICU Delirium and Cognitive Impairment Group, found that 74 percent of the 821 patients studied, all adults with respiratory failure, cardiogenic shock or septic shock, developed delirium while in the hospital, which the authors found is a predictor of a dementia-like brain disease even a year after discharge from the ICU.

Delirium, a form of acute brain dysfunction common during critical illness, has consistently been shown to be associated with higher mortality, but this large study of medical and surgical ICU patients demonstrates that it is associated with long-term cognitive impairment in ICU survivors as well.

At three months, 40 percent of patients in the study had global cognition scores similar to patients with moderate TBI, and 26 percent scored similar to patients with AD.

Deficits occurred in both older and younger patients, irrespective of whether they had coexisting illness, and persisted for 12 months, with 34 percent and 24 percent still having scores similar to TBI and AD patients, respectively.

“As medical care is improving, patients are surviving their critical illness more often, but if they are surviving their critical illness with disabling forms of cognitive impairment then that is something that we will have to be aware of because just surviving is no longer good enough,” said lead author Pratik Pandharipande, M.D., MSCI, professor of Anesthesiology and Critical Care.

“Regardless of why you come in to an ICU, you have to know that, on the back end of your critical care, you are very likely to be suffering cognitively in ways similar to a TBI patient or an AD patient, except that most of the medical profession doesn’t even know that this is happening and few around you suspect anything, leaving most to suffer in silence,” said senior author Wes Ely, M.D., professor of Medicine.

“Delirium in critically ill, hospitalized adults is a serious yet understudied issue,” said Molly Wagster, Ph.D., chief of the Behavioral & Systems Neuroscience Branch in the National Institute on Aging, part of the NIH. “These new findings provide important evidence of the extent of the problem, the imperative for greater recognition and the pressing need for solutions.”
Ely said at least some component of this brain injury may be preventable through efforts to shorten the duration of delirium in the ICU by using careful delirium monitoring and management techniques, including earlier attempts at weaning from sedatives and mobility protocols that can save lives and reduce disability.

“Even after the patient leaves the hospital, we think that cognitive rehabilitation might be helpful to somebody like this, and we have some early preliminary data supporting this,” he said.

This project was supported by grants from the National Institutes of Health (AG027472, AG035117, AG034257, AG031322, AG040157, HL111111, and 2 T32 HL087738-06), and the Veterans Affairs Tennessee Valley Geriatric Research, Education and Clinical Center and the VA Clinical Science Research and Development Service.
Johns Hopkins researchers say that by measuring levels of certain proteins in cerebrospinal fluid (CSF), they can predict when people will develop the cognitive impairment associated with Alzheimer’s disease years before the first symptoms of memory loss appear.

Identifying such biomarkers could provide a long-sought tool to guide earlier use of potential drug treatments to prevent or halt the progression of Alzheimer’s while people are still cognitively normal.

To date, medications designed to stop the brain damage have failed in clinical trials, possibly, many researchers say, because they are given to those who already have symptoms and too much damage to overcome.

“When we see patients with high blood pressure and high cholesterol, we don’t say we will wait to treat you until you get congestive heart failure. Early treatments keep heart disease patients from getting worse, and it’s possible the same may be true for those with pre-symptomatic Alzheimer’s,” says Marilyn Albert, Ph.D., a professor of neurology at the Johns Hopkins University School of Medicine. She is primary investigator of the study whose results are published in the Oct. 16 issue of the journal Neurology. “But it has been hard to see Alzheimer’s disease coming, even though we believe it begins developing in the brain a decade or more before the onset of symptoms,” she adds.

For the new study, the Hopkins team used CSF collected for the Biomarkers for Older Controls at Risk for Dementia (BIOCARD) project between 1995 and 2005, from 265 middle-aged healthy volunteers. Some three-quarters of the group had a close family member with Alzheimer’s disease, a factor putting them at higher than normal risk of developing the disorder. Annually during those years and again beginning in 2009, researchers gave the subjects a battery of neuropsychological tests and a physical exam.

They found that particular baseline ratios of two proteins — phosphorylated tau and beta amyloid found in CSF — were a harbinger of mild cognitive impairment (often a precursor to Alzheimer’s) more than five years before symptom onset. They also found that the rate of change over time in the ratio was also predictive. The more tau and the less beta amyloid found in the spinal fluid, the more likely the development of symptoms. And, Albert says, the more rapidly the ratio of tau to beta amyloid goes up, the more likely the eventual development of symptoms.

Researchers have known that these proteins were in the spinal fluid of patients with advanced disease. “But we wondered if we could measure something in the cerebral spinal fluid when people are cognitively normal to give us some idea of when they will develop difficulty,” Albert says. “The answer is yes.”

Alzheimer’s disease disrupts critical metabolic processes that keep neurons healthy. These disruptions cause neurons to stop working, lose connections with other nerve cells, and finally die. The brains of people with Alzheimer’s have an abundance of two abnormal structures — amyloid plaques and “tangles” made of tau.

The plaques are sticky accumulations of beta-amyloid that build up outside of the neurons, while the tangles form inside the neurons. When there are too many tangles inside the cells, the cells start to die. In a normal brain, tau helps the skeleton of the nerve cell maintain itself. When too many phosphate groups attach themselves to tau, too much of the protein develops and tangles form.

Albert says researchers believe that the relative amount of beta-amyloid in the spinal fluid decreases as Alzheimer’s progresses because it is getting trapped in the plaques and therefore isn’t entering the fluid.
Though the BIOCARD study has been going on for nearly two decades, this is some of the first predictive data to come out of it, Albert says, owing to the length of time it takes for even high-risk middle-aged people to progress to dementia. Only 53 of the original patients have progressed to mild cognitive impairment or dementia, giving a sample size just large enough to draw some preliminary conclusions. These first symptoms include memory disruptions such as repeating oneself, forgetting appointments, and forgetting what others have said.

Albert cautions that the biomarker ratio at this point is not accurate enough to precisely predict whether a particular individual is progressing to dementia, and further analysis of information about the group over time is needed.

However, she says, if the findings prove valid, they not only could guide the use of early treatments with drugs that become available, but also may also help test new drugs by seeing if they alter the rate at which the proteins change over time.

The research was supported by grants from the National Institutes of Health’s National Institute on Aging (U01-AG03365 and P50-AG005146). Other Johns Hopkins researchers involved in the study include Abhay Moghekar, M.B.B.S.; Shan-shan Li; Yi Lu; Ming Li; Mei-Cheng Wang, Ph.D.; and Richard O’Brien, M.D., Ph.D.

Albert reports that she serves on scientific advisory boards for Eli Lilly, Eisai, Genentech, Biogen and AgeneBio, and receives research support from GE Healthcare.
Older adults with hardening of the arteries are more likely to have beta-amyloid plaques in their brain even if they have no signs of dementia, according to a University of Pittsburgh study published online today in the journal *Neurology*.

While researchers still do not know whether amyloid plaques in the brain are the cause or a byproduct of dementia, their presence is associated with and considered the hallmark of Alzheimer’s disease. Arterial stiffness, also known as arteriosclerosis or hardening of the arteries, indicates how hard the heart has to work to pump blood through the body, and is associated with a higher risk of cardiovascular diseases such as stroke and hypertension. Arterial stiffness also affects cerebral blood flow, leading to increased and possibly damaging blood flow in areas of the brain while leaving other areas without enough.

“This research shows more evidence that vascular health and brain health are closely connected,” said study author Timothy M. Hughes, Ph.D., who conducted the research while at the University of Pittsburgh Graduate School of Public Health and is now a senior postdoctoral fellow at Wake Forest School of Medicine. “The findings show that measures of vascular disease, independent of blood pressure, are associated with amyloid deposition in the brain of dementia-free older adults.”

Researchers scanned the brains of 91 individuals aged 83 to 96 who did not have dementia to measure plaque levels in the brain. Two years later, researchers examined the amount of stiffness in the participants’ arteries.

Approximately half of the participants had beta-amyloid plaques in their brains, and were more likely to have high blood pressure and higher arterial stiffness. Furthermore, arterial stiffness was highest in people who had both amyloid plaques and white matter or cerebrovascular lesions, both types of brain lesions.

Each unit of increase in arterial stiffness was associated with a two- to four-fold increase in the odds of having both amyloid plaques and a high amount of brain lesions. According to the authors, individuals with both conditions may therefore be at significantly greater risk of developing dementia. Amyloid imaging studies, using compounds like the Pittsburgh Compound B, also show beta-amyloid deposition is more common than expected in elderly adults.

Previous studies have demonstrated that arterial stiffness is associated with cerebrovascular disease, impaired cognitive function and dementia in the elderly. Recent studies suggest that elevated blood pressure is associated with amyloid deposits in the brain, and that arterial stiffness may be the driving factor. This study is the first to associate arterial stiffness and beta-amyloid deposits in the brain.

“We don’t yet know why amyloid occurs or what the risk factors are. This study adds to the growing research suggesting that arterial stiffness may be more important than current hypertension and both are important potential targets for the prevention of age-related amyloid deposition. Future research will have to tell us if successfully treating hypertension will reduce the beta-amyloid burden in the brains of older adults,” added Hughes.

Co-authors on this paper include Lewis H. Kuller, M.D., Emma J.M. Barinas-Mitchell, Ph.D., Rachel H. Mackey, Ph.D., Eric M. McDade, D.O., William E. Klunk, M.D., Howard J. Aizenstein, M.D., Ph.D., Ann D. Cohen, Ph.D., Beth E. Snitz, Ph.D., Chester A. Mathis, Ph.D., and Oscar L. Lopez, M.D., all of the University of Pittsburgh; and Steven T. DeKosky, M.D., of the University of Virginia.

This study was supported by National Institutes of Health grants AG005133, AG025516, AG025204 and AG000181.
Although problems with memory become increasingly common as people age, in some persons, memories last long time, even a lifetime. On the other hand, some people experience milder to substantial memory problems even at an earlier age.

Although there are several risk factors of dementia, abnormal fat metabolism has been known to pose a risk for memory and learning. People with high amounts of abdominal fat in their middle age are 3.6 times as likely to develop memory loss and dementia later in their life.

Neurological scientists at the Rush University Medical Center in collaboration with the National Institutes of Health have discovered that same protein that controls fat metabolism in the liver resides in the memory center of the brain (hippocampus) and controls memory and learning.

Results from the study funded by the Alzheimer’s Association and the National Institutes of Health were recently published in *Cell Reports*.

“We need to better understand how fat is connected to memory and learning so that we can develop effective approach to protect memory and learning,” said Kalipada Pahan, PhD, the Floyd A. Davis professor of neurology at Rush University Medical Center.

The liver is the body’s major fat metabolizing organ. Peroxisome proliferator-activated receptor alpha (PPARalpha) is known to control fat metabolism in the liver. Accordingly, PPARalpha is highly expressed in the liver.

“We are surprised to find high level of PPARalpha in the hippocampus of animal models,” said Pahan.

While PPARalpha deficient mice are poor in learning and memory, injection of PPARα to the hippocampus of PPARalpha deficient mice improves learning and memory,” said Pahan.

Since PPARalpha directly controls fat metabolism, people with abdominal fat levels have depleted PPARalpha in the liver and abnormal lipid metabolism. At first, these individuals lose PPARalpha from the liver and then eventually from the whole body including the brain. Therefore, abdominal fat is an early indication of some kind of dementia later in life, according to Pahan.

By bone marrow chimera technique, researchers were able to create some mice having normal PPARalpha in the liver and depleted PPARalpha in the brain. These mice were poor in memory and learning. On the other hand, mice that have normal PPARalpha in the brain and depleted PPARalpha in the liver showed normal memory.

“Our study indicates that people may suffer from memory-related problems only when they lose PPARalpha in the hippocampus”, said Pahan.

CREB (cyclic AMP response element-binding protein) is called the master regulator of memory as it controls different memory-related proteins. “Our study shows that PPARalpha directly stimulates CREB and thereby increases memory-related proteins”, said Pahan.

“Further research must be conducted to see how we could potentially maintain normal PPARalpha in the brain in order to be resistant to memory loss”, said Pahan.

Other Rush researchers involved in this study include Avik Roy, PhD, research assistant professor; Malabendu Jana, PhD assistant professor; Grant Corbett, neuroscience graduate student; Shilpa Ramaswamy, instructor; and Jeffrey H. Kordower, PhD, the Jean Schwppe Armour professor of neurological sciences.
By Kelly Lawman
Beth Israel Deaconess Medical Center

Whether you’re nervous about the consequences of your teenager’s concussion, you’re worried about your aging parents and the anxieties associated with the threat of dementia, or your own bouts of forgetfulness, many of us are rightfully concerned about our brain health. Using the neighborhood gym as a model, Beth Israel Deaconess Medical Center’s new Brain Fit Club offers members a way to support brain health by devising personalized workout routines designed to keep each member’s brain limber and active.

An individual Brain Fit Club workout routine might involve a combination of scientifically-validated computerized cognitive training, brain stimulation, nutritional coaching, mindfulness training, sleep and lifestyle education, gait and balance evaluation and treatment, and group classes in meditation, tai chi and gentle yoga designed to target a full range of cognitive struggles or decline.

“At BIDMC we have nearly 40 years of experience in expertly diagnosing and treating disorders of cognition,” says Albert Galaburda, MD, Chief of Cognitive Neurology. “Through research here and elsewhere we know that there’s a lot to be gained from pairing traditional treatments like medication with special kinds of exercises, and we’re very excited to offer this comprehensive approach to our patients.”

The concept underlying the Brain Fit Club relies on the science of neuroplasticity, or the brain’s ability to change or adapt in the presence of new experiences or obstacles. Until recently, it was thought that after the first few years of life, our brains stopped creating new cells and that once our neural connections were laid down in childhood, those brain networks were fixed for life. But research in the past two decades has shown that the brain actually never stops producing new cells, that new connections are constantly made and that there is lifelong potential for development and adaptation.

“We know that a healthy brain is better able to cope with challenges that come with injury, disease and the natural aging process,” says Alvaro Pascual-Leone, MD, PhD, Director of the Berenson-Allen Center for Noninvasive Brain Stimulation. “Fundamentally there are things we could all do better for better brain health, things like making sure we get enough sleep, eating a healthy, balanced diet, participating in heart pumping exercise, and then we need to challenge our brain outside of its comfort zone in an environment like the Brain Fit Club.”

Brain Fit Club members start with an evaluation by a neuropsychologist who assesses each person’s cognitive abilities using objective measures. “Based on that cognitive profile, we then identify targeted interventions to address each individual’s area of weakness. The ‘workout’ regimen will be different for a person dealing with an attention issue, say, than for a person having trouble with memory,” says Bonnie Wong, a neuropsychologist and the Director of the Brain Fit Club. “Not only do we develop a program that’s tailored to that particular person’s needs, but we can also track their progress and adjust their program as time goes on.”

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In essence, it’s like a personal trainer for your brain who assesses you, follows you and challenges you,” says Pascual-Leone. “And that trainer pushes you to work hard in the hopes of achieving the best benefit for your brain.”

The coaching aspect is an important component of the Brain Fit Club to ensure that members stay motivated and get the workout dosage right. “We want to help people understand that it’s not just about continuing to lift the same two pound weight, we want to make sure each person is working for the right amount of time at the right level and not falling back on what feels comfortable or routine,” says Wong.

And while the hope is that many of the exercises can ultimately be done in the home, Pascual-Leone says that the social aspects of coming into the gym are often just as important as the actual training. “Humans are social beings, our brains are responsive to both the number of social interactions that we have as well as our own belief of how supportive our social environment is,” says Pascual-Leone. “These are very powerful mechanisms that are important factors for brain health, for brain plasticity.”

Many Brain Fit Club members are already reporting benefits. They say they feel better and are able to function better.

“I have one patient who has told me she felt as though she was ‘back to where she was’ before she had her concussion,” says Wong. “She was having a lot of difficulty at work, finding the right words, organizing thoughts, and although she hasn’t been retested, she feels as though after going through this very rigorous computerized training program, she’s back to where she should have been.”

“We think the Brain Fit Club will be able to help a lot of people, and as we move forward, we’ll be able to collect data and refine our programming to be able to help even more people with brain injury and cognitive deficits in the future,” adds Pascual-Leone. “And even though we know we’re not going to, for example, prevent a disease like Alzheimer’s, we should hopefully be able to make it easier for the patients who are unfortunate enough to have the disease to have less symptoms of it and cope with it better.”

For more information visit the Brain Fit Club web site: http://www.brainfitclub.org/
Alzheimer’s disease is recognized as a public health crisis worldwide. As public and private funding agencies around the world enhance and expand their support of Alzheimer’s disease research, there is an urgent need to coordinate funding strategies and leverage resources in order to maximize the impact on public health and avoid duplication of effort and inefficiency. Such coordination requires a comprehensive assessment of the current landscape of Alzheimer’s disease research in the US and internationally. To capture and compare their existing investments in AD research and research-related resources, funding organizations need to use a common language and a common classification system. To this end, the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer’s Association (ALZ) developed the Common Alzheimer’s Disease Research Ontology. NIA and ALZ hope to expand the use of the CADRO to other federal and non-federal organizations supporting AD research in the US and internationally and their portfolio information to this publicly available International Alzheimer’s Disease Research Portfolio. To date, the US federal and non-federal organizations listed below have contributed their AD research portfolios for inclusion in the IADRP.

Participating US Federal Agencies:
National Institutes of Health http://www.nih.gov/
Administration on Aging http://www.aoa.gov/
Agency for Healthcare Research and Quality http://www.ahrq.gov/
Centers for Disease Control and Prevention http://www.cdc.gov/
United States Army Medical Research and Materiel Command (Department of Defense) https://mrmc.amedd.army.mil/index.cfm
United States Department of Veteran Affairs http://www.va.gov/

Participating US Non-Federal Agencies:
Alzheimer's Association http://www.alz.org/
Alzheimer's Drug Discovery Foundation http://www.alzdiscovery.org/

Participating International Agencies:
Alzheimer's Research UK http://www.alzheimersresearchuk.org/
Studies That Will Be Open for Enrollment Soon

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

A4 – Anti Amyloid in Aysymptomatic Alzheimer’s Disease

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer’s disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.