Is a Cure for Alzheimer’s on the Horizon?

The public often wonders when a cure will become available for Alzheimer’s disease (AD). Not a day goes by that AD researchers and clinicians don’t hear the question from patients, their family members, the media and others interested in when the public can expect a solution to this brain-robbing disease that affects over five million people in the U.S. alone. But if you ask leading AD researchers they will tell you that there isn’t going to be a cure, at least not as the public uses the term. What they will tell you is that improved treatments are imminent.

Paul Aisen, M.D., Director of the Alzheimer’s Disease Cooperative Study, says the term “cure” is problematic. “For someone with AD dementia, there will never be a cure in the sense of a return to normal cognition and function,” he says.

Pierre Tariot, M.D., Director of the Banner Alzheimer’s Institute in Phoenix, Arizona, agrees and says the term is misconstrued. “I think more in terms of major advances for treatment of AD, whether this means improving cognition or functional ability, slowing decline, relieving distressing psychological symptoms or possibly delaying the emergence of impaired memory and thinking.”

The problem with the term “cure” is that extensive damage has already occurred in the brain by the time a person receives an AD diagnosis, damage that cannot be repaired. It is not dissimilar to heart disease. By the time a person suffers a heart attack the damage has been done to the heart and short of a heart transplant, that damage cannot be reversed.

Dave Morgan, Ph.D., CEO of the Byrd Alzheimer’s Institute, admits that “taking someone with severe dementia and restoring normal cognition will require some major breakthroughs. There is very little spontaneous restoration of neurons after such damage, and bringing someone back will require new capacities to regenerate neurons and get them to functionally integrate with the remaining nervous system. While ideas exist, to date none have been meaningfully implemented even in animal models.”

Instead of thinking of a cure, Aisen says that researchers are focusing on stabilizing the disease by slowing or halting the progression.

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“It is possible to improve cognition,” he adds, “but not reasonable to think we can restore normal function to a brain that has been so severely damaged.”

Michael Rafii, M.D., Ph.D., Director of the UCSD Memory Disorders Clinic, concurs adding that a treatment that will slow AD progression is on the horizon, but is not imminent. “I don’t think that we will have a cure, as it is rare in medicine, expect for antibiotics and surgery, to have any curative treatments.”

Where does that leave the millions already suffering from AD and those with mild cognitive impairment who are transitioning into full-blown AD?

Douglas Galasko, M.D, Director of the UCSD Shiley-Marcos Alzheimer’s Disease Research Center, says “Our best hope is to slow down further progression. Prevention may be easier than trying to restore brain circuits and connections; therefore early intervention makes sense.”

Galasko adds that if amyloid is found to be the instigator of AD and simply lowering its production or removal from the brain will slow or halt the next series of downstream changes in the brain, that researchers have the tools and some drugs they can use to test that hypothesis in the next 10 years. “In the next decade we will be able to evaluate whether we can reduce amyloid build up in the brain, and how much that helps to preserve cognitive abilities.”

Aisen points directly to the Lilly investigational drug, solanezumab, as one promising chance for a disease-slowing therapy. Solanezumab had been used in several studies and was chosen as the drug to be tested in cognitively normal, amyloid-positive subjects in the upcoming A4 study. He thinks that if found effective in this at-risk population it could lead to approval as a prevention treatment in about four years. He notes that secondary prevention is more plausible. “Most likely we will achieve a risk reduction (disease slowing), rather than prevention.”

Rafii is more cautious in discussing prevention. He considers the results coming in from genome-wide association studies that look at genetic risk factors. “We also have new data on the dietary effects on AD risk, including some studies of omega-3 fatty acids and cholesterol intake. Pairing all of these into longitudinal studies of brain aging, that incorporates amyloid imaging, will undoubtedly shed light on prevention strategies.” Rafii is anxious to learn the results of the current clinical trials examining immunotherapy against beta-amyloid in the prodromal stage of AD, as well as studies examining the asymptomatic stage of AD, such as A4, API, and the DIAN-TU studies.

Circling back to an earlier correlation, the analogy to heart disease gives focus to what can be expected for AD. Morgan points out that the age-adjusted risk of dying from cardiovascular disease has decreased by 50% in the last half century. “It was not a single item that turned this around,” he says, “but recognition of risk factors and consistent improvements in our ability to mitigate these risks with lifestyle changes and medicine. We have not cured heart disease, but still had major impact. We are poised to have similar success in attacking AD.”

Alan Lerner, M.D., Director of the Brain Healthy and Memory Center at University Hospitals – Case Medical Center, agrees that we are moving towards the cardiovascular model where multiple medications may target different aspects of the disease, much like anti-hypertensives, cholesterol lowering, and diuretic medications treat cardiovascular disease before irreversible damage is done to the heart. He sees a combination of pharmacological and non-pharmacological interventions as treatments for the spectrum of the preliminary stages of AD.

Josh Grill, Ph.D., Director of the Katherine and Benjamin Kagan Alzheimer’s Disease Treatment Development Program at UCLA believes that society, national governments, and the general public will endorse the need to support research to allow the pace to not only continue, but to accelerate
in the coming years. He points to the necessity of finding causes of AD, such as which lifestyle interventions can delay its onset, as well as identifying targets for new therapies that can better treat/delay onset and decline.

The researchers are realistically hopeful, all believing that within the next few years there will be answers and possible therapies. They point to the myriad of viable, promising drugs in the current pipeline. Will it be a cure? No, not as we know it, but indeed treatments and preventions are possible. Perhaps Tariot said it best. ‘I’d like to think that we can find a way to meaningfully impact AD, or maybe even put it behind us, without losing another generation.”

–ADIN

Latest NIH Alzheimer’s Research Progress Report Available

A new online report from the National Institutes of Health (NIH) highlights recent progress in NIH-supported Alzheimer’s disease research.

Prepared annually by the National Institute on Aging (NIA) at NIH, the latest report—2012-2013 Alzheimer’s Disease Progress Report: Seeking the Earliest Interventions http://tinyurl.com/jwwz9ge discusses the National Plan to Address Alzheimer’s Disease, describes new investments and research priorities, and summarizes research in several areas:

- biology of Alzheimer’s and the aging brain
- biomarkers for Alzheimer’s progression
- genes that may play a role in the disease
- risk factors for cognitive decline and dementia
- advances in detecting Alzheimer’s disease
- translational research to identify and test new drugs
- potential new therapies to treat, delay, or prevent Alzheimer’s
caregiving
- gender and racial differences in the impact of Alzheimer’s

Other features include a video introduction by NIA Director Dr. Richard Hodes, a primer on Alzheimer’s disease and the brain, tables listing NIA-funded clinical trials, and videos that further explain critical areas of study.
Does DDT’s Toxic Legacy Include Alzheimer’s Disease?

Exposure to the pesticide dichlorodiphenyltrichloroethane (DDT) may heighten the risk of developing Alzheimer’s disease, according to a small study published in the January 27 JAMA Neurology online. Researchers led by Jason Richardson at Rutgers-Robert Wood Johnson Medical School, Piscataway, New Jersey, found that older adults with high levels of a DDT metabolite in their blood were four times more likely to have AD than were those with low levels. This resembles the risk conferred by an ApoE4 allele, the main genetic risk factor for sporadic AD. Moreover, the authors report that adding DDT to a neuronal cell line ramped up amyloid precursor protein levels, hinting that the chemical might directly contribute to pathogenesis. If these findings are confirmed by larger studies, they could have implications for the use of DDT worldwide. Though the chemical has been banned in the United States since 1972, many countries still use it, and the World Health Organization recommends it to combat malaria (see Rehwagen, 2006).

Other researchers expressed enthusiasm for the paper and said follow-up studies should be done. “I think it’s very impressive. The strength of the finding was shocking,” said Sid O’Bryant at the University of North Texas Health Science Center, Fort Worth. However, commentators cautioned that these data should be considered preliminary, and that the implications for public health are not yet clear. “For now, this is not something the general public needs to worry about. The findings will need to be replicated and if they are, we still need to determine the level of exposure that is related to increased risk of AD,” Kathleen Hayden at Duke University, Durham, North Carolina, wrote to Alzforum.

A handful of prior studies have hinted that various chemicals, such as air pollutants, lead, and pesticides, increase the risk of cognitive decline or AD (see Feb 2005 news story; Feb 2012 news story; Hayden et al., 2010; Singh et al., 2012). The evidence is stronger for a link between pesticides and Parkinson’s disease (see Nov 2000 news story; Baldi et al., 2003; Tanner et al., 2011; Chhillar et al., 2013). Richardson and colleagues previously found that high serum levels of an organochlorine pesticide, β-hexachlorocyclohexane, quadruple the chances of getting PD (see Richardson et al., 2009; Richardson et al., 2011). That study included 20 Alzheimer’s patients as controls. In these patients, the authors noticed high serum levels of the DDT metabolite p,p’-dichlorodiphenyldichloroethylene (DDE), making them wonder if this chemical might predispose people to AD.

To follow up on these results, Richardson and colleagues examined a panel of 16 organochlorines in serum samples from 86 AD patients and 79 age-matched controls seen at Alzheimer’s Disease Research Centers at the University of Texas Southwestern Medical Center, Dallas, and Emory University, Atlanta. The majority of patients and controls had DDE in their blood, but patients had an average of four times as much (see image below), and the researchers calculated that those in the highest tertile had a fourfold increased risk of AD. In addition, AD patients with elevated DDE scored significantly worse on the Mini-Mental State Examination than those with low DDE.

To see if serum DDE reflected the amount in the brain, the authors examined 11 matched brain and serum samples from the Washington University Alzheimer’s Disease Research Center in St. Louis. Quantities of the chemical corresponded closely, they report. They also wondered if the association between DDT and Alzheimer’s might have a biological basis. After exposing a neuronal cell line to 1μM DDE or DDT for two days, they saw a 50 percent jump in amyloid precursor protein, making such a connection plausible. The 1μM concentration compares to serum levels found in people living near DDT dumping sites (see Kreiss et al., 1981; Gaffney et al., 2005).

However, much more work remains to be done to nail down a link between DDT and AD, Richardson told Alzforum. He plans to repeat the study in an independent group of at least 500 cases and 500
controls, as well as analyzing cohorts drawn from the community instead of Alzheimer’s centers. He will also look more closely at how genetics might modify susceptibility to DDT. Richardson pointed out that some healthy people in his study had very high DDE, which implies that some people have protective factors.

If the results are confirmed, what would that mean for public health? Richardson noted that the serum DDE levels measured in his study resemble those in the general U.S. population, as reported by the Centers for Disease Control and Prevention. About 5 percent of the population has levels on a par with the highest group in this study, he said.

Why does the chemical persist more than 40 years after it was banned? DDT still contaminates soil and water, and people continue to be exposed through their diet, Richardson noted. Also, DDE has a half-life on the order of 10 years, allowing it to linger in the body. Younger people tend to have less of the chemical in their blood, but some minority groups, such as Mexican-Americans and African-Americans, carry high levels even at young ages, Richardson said. The reasons are not clear, but may have to do with diet, occupational exposures, or where people live. In countries such as India and Spain, where DDT is still used, exposures are much higher (see Botella et al., 2004; Bhatnagar et al., 2004). There is no evidence of more AD cases in those countries, however:

DDT remains one of the cheapest and most effective ways to fight malaria, which kills about half a million people each year. “The World Health Organization has judged that the ratio of benefits to risks is probably high enough to keep using DDT for very specific purposes,” said Jennifer Weuve at Rush University, Chicago. Future research might look for ways to ameliorate the effects of DDT exposure, commentators said. For example, O’Bryant noted that some previous research suggests that DDE can be removed from the body by ingesting mineral oil (see Rozman et al., 1983).

Researchers agreed that the issue deserves further study. A first step would be for AD research groups to measure DDE levels in their banked serum and brain samples. Prospective studies could clarify whether DDE exposure jacks up the risk of developing dementia. In an accompanying commentary, Steven DeKosky at the University of Virginia, Charlottesville, and Sam Gandy at Mount Sinai Alzheimer’s Disease Research Center, New York City, wrote, “Identification of the important environmental influences that modulate AD risk represents the next great frontier for discovery ... Richardson and colleagues have provided both a wake-up call to explore environmental influences and pointed us to a first area to assess—pesticides.”—Madolyn Bowman Rogers.

Scientists disagree about the long-term consequences of head injury and whether it leads to Alzheimer’s disease later in life (see AlzRisk entry). It may vary from person to person, suggests a report in the January 7 Neurology. Scientists led by Ron Petersen and Clifford Jack from the Mayo Clinic, Rochester, Minnesota, found that in elderly people with mild cognitive impairment (MCI), previous head trauma, sometimes as early as adolescence, translated to more Aβ in the brain later on. “This suggests that in some people, trauma does increase risk of Alzheimer’s,” said first author Michelle Mielke. However, cognitively normal elderly who had a similar trauma history accumulated no more Aβ than controls without trauma. These seemingly disjointed results seem to hint that the long-term hazards of brain injury depend on the person, said Mielke. “Not everyone who has trauma will develop the disease.”

The findings support the idea that traumatic brain injury (TBI) joins a complex array of insults that can lead to Alzheimer’s, but does not cause it directly, said Murray Raskind, VA Puget Sound, Seattle, who was not involved in the study. “It adds to the evidence that traumatic brain injury lowers the threshold for the AD process,” he told Alzforum.

While some studies suggest that traumatic brain injuries heighten the risk of dementia (see Wang et al., 2012), others find no such association (see Dams-O’Conner et al., 2013). To probe possible mechanisms, scientists have looked at postmortem brains either soon or long after a person had an injury. Almost a third of these people die with significant tau and Aβ pathology (see Johnson et al., 2012). In-vivo biomarkers paint a complementary picture whereby after acute trauma, cerebrospinal fluid Aβ falls and tau rises (see Franz et al., 2003). Amyloid imaging results suggest that Aβ deposits stick around for up to a year or more (see Nov 2013 news story). However, researchers have scant data on longer-term consequences. Mielke and colleagues scanned peoples’ brains years, even decades, after trauma, to see if head injury led to more amyloid, impaired metabolism, or lower hippocampal volume later in life.

The researchers analyzed a subset of participants from the Mayo Clinic Study of Aging (MCSA), which recruited people aged 70 to 89 from Olmsted County, Minnesota, beginning in 2004. These volunteers, 589 in total, had undergone positron emission tomography imaging with Pittsburgh compound B (PiB) and fluorodeoxyglucose, as well as magnetic resonance imaging. They also self-reported any past instance of head trauma that involved at least a brief loss of memory or consciousness. Based on cognitive testing, the researchers divided the sample into 448 cognitively normal people and 141 with MCI.

Though comparable numbers of people from each group reported previous head trauma—17 percent in cognitively normal subjects and 18 percent for people with MCI—they differed with respect to how trauma predicted amyloid buildup. In cognitively normal people, amyloid accumulated to the same degree whether or not they had previously experienced an injury. However, in those with MCI, people with past brain injuries had 18 percent more amyloid in the brain, and a fivefold higher likelihood of a positive amyloid scan. Neither FDG-PET nor MRI measures correlated with head trauma.

The results imply that traumatic brain injuries lead to elevated amyloid in old age, but only in some. “We need more research to find out who is most vulnerable,” said Mielke. The researchers looked at whether ApoE4 heightened that susceptibility, but saw no relationship in the normal group, and could draw no conclusion from the MCI group because so few carried the risk allele. How much time had passed since the injury also seemed to have no influence. While those with MCI were older than the cognitively normal people, both groups averaged about 57 years between trauma and imaging. This means the former had no more time to develop pathology than the latter, Mielke said. Curiously, people in the MCI group scored equally well, or poorly, in cognitive tests whether they
had suffered head trauma or not. The authors noted that this would be unexpected if head trauma leads to AD. They pointed out that the most vulnerable may have been excluded from this study because they already had been diagnosed with Alzheimer’s. The study design, which relies on splitting the cohort into normal and MCI groups, by way of clinical criteria, precludes addressing that possibility. Likewise, it is possible that brain Aβ was normal in the control group because anyone with elevated levels of the peptide had already developed MCI, the authors wrote.

Longitudinal data will be key for probing the long-term effects of head trauma, Mielke said. While she and colleagues will continue to follow this particular cohort in the MCSA, which is expanding to include people as young as 50, the ideal study would monitor people continuously from the time of injury into older age and record their biomarker trajectory. Researchers could then see if amyloid appears early on and is cleared, whether head trauma accelerates amyloid deposition as people age, and whether trauma increases risk of AD. Raskind agreed that prospective longitudinal studies in humans with recent head injuries and in transgenic animals will be needed to solidify a link between TBI and Alzheimer’s. Given that the two seem to be connected via pathology, if scientists better understand the brain’s response to TBI, they may gain important insights about AD as well, he told Alzforum. Tau pathology has also been linked to trauma and could be better assessed once imaging ligands for tau becomes available (see Nov 2012 conference story).

Samuel Gandy, Mount Sinai Medical Center, New York, cautioned in an email that with the currently available amyloid ligands, researchers may be unable to capture the full picture of amyloid in the brain. Imaging agents miss diffuse amyloid deposits, which make up the majority of those that occur after brain injury, he wrote.—Gwyneth Dickey Zakaib

The National Institutes of Health has selected eight projects to receive support to answer some of the most fundamental problems on traumatic brain injury, including understanding long-term effects of repeated head injuries and improving diagnosis of concussions.

Funding is provided by the Sports and Health Research Program, a partnership among the NIH, the National Football League, and the Foundation for the National Institutes of Health (FNHI). In 2012, the NFL donated $30 million to FNHI for research studies on injuries affecting athletes, with brain trauma being the primary area of focus.

Traumatic brain injury (TBI) is a major public health problem that affects all age groups and is the leading cause of death in young adults. Recently, concern has been raised about the potential long-term effects of repeated concussion, particularly in those most at risk: young athletes and those engaged in professions associated with frequent head injury, including men and women in the military. Current tests cannot reliably identify concussions, and there is no way to predict who will recover quickly, who will suffer long-term symptoms, and which few individuals will develop progressive brain degeneration, called chronic traumatic encephalopathy (CTE).

“We need to be able to predict which patterns of injury are rapidly reversible and which are not. This program will help researchers get closer to answering some of the important questions about concussion for our youth who play sports and their parents,” said Story Landis, Ph.D., director of the National Institute of Neurological Disorders and Stroke (NINDS), part of NIH.

Two ($6 million each) are large, cooperative agreements focused on defining the scope of long-term changes that occur in the brain years after a head injury or after multiple concussions. The cooperative awards form a partnership between NINDS, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and multiple academic medical centers.

NIH also will fund six pilot projects totaling just over $2 million that will last up to two years and are designed to provide support for the early stages of sports-related concussion projects. If the early results are encouraging, they may become the basis of more comprehensive projects. The NIH institutes responsible for managing these grants are NINDS, NICHD, and the National Institute on Deafness and Other Communication Disorders (NIDCD).

The eight projects were selected by the NIH following a rigorous scientific review process. The cooperative awards bring together two teams of independent scientists to study and compare the brains of donors who were at high or low risk for developing long-term effects of TBI. Ten neuropathologists from eight universities will coordinate to describe the chronic effects of head injury in tissue from hundreds of individuals in order to develop standards for diagnosis. The project includes four teams that will correlate brain scans with changes in brain tissue, using a variety of techniques. This may open the possibility of using these advanced brain imaging techniques to diagnose chronic effects of TBI in living individuals. The investigators in the two projects will also help NIH develop a registry dedicated to enrolling individuals with a history of TBI who are interested in donating brain and spinal cord tissue for study after their death. The new NIH Neurobiobank will coordinate the tissue collection, data gathering, and also distribute biospecimens, along with relevant information to enable other scientists to access this valuable tissue.

The two cooperative agreements are:

- CTE and Post-traumatic Neurodegeneration: Neuropathology and Ex Vivo Imaging
  Principal Investigator: Ann C. McKee, M.D., Boston University School of Medicine and U.S. Department of Veterans Affairs

At present, the diagnosis of CTE is made by examining the brain after death; however, the range of specific features that identify this disorder has not been established. One goal of Dr. McKee’s project
is to define a clear set of criteria for the various stages of CTE and to distinguish it from Alzheimer’s, amyotrophic lateral sclerosis, and other neurodegenerative disorders in post-mortem brain tissue. Once these characteristics have been defined in brain tissue, the imaging teams at Washington University in St. Louis and Massachusetts General Hospital in Boston will correlate them with brain scans to identify features that might eventually be used to diagnose CTE in individuals during their lifetimes.

- Neuropathology of CTE and Delayed Effects of TBI: Toward In Vivo Diagnostics
  Principal Investigator: Wayne Gordon, Ph.D., Mount Sinai Hospital, New York City

The goal of Dr. Gordon's project is to identify and describe the chronic effects of mild, moderate and severe TBIs and compare these with the features of CTE. Dr. Gordon and his colleagues at the University of Washington in Seattle will comprehensively evaluate brain tissue obtained from an ongoing study of thousands of people, the Adult Changes in Thought (ACT) study, funded by the National Institute of Aging. They also will examine brain tissue from donors who suffered severe TBI and were cared for in the TBI Model Systems program funded by the Department of Education's National Institute on Disability and Rehabilitation Research. In Dr. Gordon’s project, neuroimaging teams at Massachusetts General Hospital, Oregon Health Sciences University in Portland, and the University of Washington will use a variety of sophisticated brain scanning techniques in patients with a range of head injuries, as well as on post-mortem tissue, to identify potential markers that may eventually be used to diagnose the degenerative effects of TBI in people.

“The investigators will collaborate to develop diagnostic criteria for identifying the chronic features of the entire scope of brain trauma ranging from mild TBI to full-blown CTE, and then work to extend these criteria to living humans using some of the most advanced neuroimaging tools available,” said Walter Koroshetz, M.D., deputy director of NINDS.

Although the two cooperative agreements focus on different aspects of TBI, their combined results promise to answer critical questions about the chronic effects of single versus repetitive injuries on the brain, how repetitive TBI might lead to CTE, how commonly these changes occur in an adult population, and how CTE relates to neurodegenerative disorders like Alzheimer’s disease,” Dr. Landis said.

The pilot studies will focus on improving the diagnosis of concussion and identifying potential biomarkers that can be used to track a person’s recovery. The six pilot grants are:

- Cortical GABA in Pediatric Sports Concussion
  Principal Investigator: Jeffrey G. Ojemann, M.D., Seattle Children's Hospital

The brain contains numerous chemicals such as gamma-aminobutyric acid (GABA), which is important for many brain functions, including cognition and movement, and may be altered by traumatic brain injury. Magnetic resonance (MR) spectroscopy is a scanning technique that can measure a variety of brain chemicals, including GABA. The goal of Dr. Ojemann’s project is to use MR spectroscopy to monitor GABA levels in adolescents who have sports-related concussions and compare those levels to uninjured controls. The researchers also will conduct preliminary comparisons of GABA levels with existing cognitive measures such as memory tests and structural brain imaging. Diagnostic tools that can reliably detect when the brain is injured and when it has recovered following a concussion are essential for determining when it is safe to resume normal activities.

- Evaluation of Spot Light: A Concussion Injury Management App for Youth Sports
  Principal Investigators: Lara McKenzie, Ph.D., Center for Injury Research and Policy, The Research Institute at Nationwide Children’s Hospital, Columbus, Ohio and Dawn Comstock, Ph.D., Colorado School of Public Health, University of Colorado, Denver

Guidelines exist to help doctors diagnose and manage sports-related concussions, but guidelines are
not fully supported by evidence-based research, are applied inconsistently, and those responsible for the care of injured athletes do not always fully communicate with each other. The goal of Drs. McKenzie and Comstock’s project is to test the effectiveness of Spot Light, an easy-to-use mobile application (or app), developed by Inlightened, LLC. This app was designed to help doctors, coaches, athletic trainers and parents of young football players track the progress of a young athlete from the time of a concussion injury until they are cleared to return to play. The researchers want to know if the app will result in more concussions being reported, a greater number of referrals to doctors and better adherence to return-to-play guidelines. The goal is to improve diagnosis of concussions that are occurring among young athletes, and ensure that they are receiving appropriate care and are fully recovered before getting back on the field.

• **Eye Movement Dynamics: A Rapid Objective Involuntary Measure of Concussion/Mild Traumatic Brain Injury**  
  Principal Investigators: Nicholas Port, Ph.D. and Steven Hitzeman, O.D., Indiana University School of Optometry, Bloomington

People can choose where to look, but they do not have much control over some of the intricate eye muscle movements that are usually made without thinking. Studies have shown that eye movement problems are common in mild traumatic brain injury patients. Drs. Port and Hitzeman, in collaboration with team trainers and physicians at Indiana University and local high schools, plan to take advantage of the involuntary, reflex nature of eye movements. They will develop a portable eye tracking instrument that can be used to help diagnose concussions on the sidelines and to monitor injury progression in high school and college athletes. Drs. Port and Hitzeman will compare the eye tracking data to results from a commonly used cognitive test to determine if changes in eye movement can serve as a biomarker for sports-related mild traumatic brain injury. If successful, this study will help provide an objective and more reliable measure to detect traumatic brain injury than is currently available.

• **Imaging and Biomarkers in Adolescents Cleared for Return to Play After Concussion**  
  Principal Investigator: Harvey Levin, Ph.D., Baylor College of Medicine, Houston

Sports concussions may cause persistent long-term effects in young athletes -- in some cases, even after they have been allowed to return to play. Using a variety of neuroimaging techniques, Dr. Levin and his group will look at the effects of sports-related concussions on brain structure and function one month following injury in adolescents who have been cleared to play. In addition, this project will evaluate microRNAs (miRNAs) as potential biomarkers for concussions and recovery. These are small portions of RNA (a molecule that is similar to DNA, which contains our genetic code) that play a role in turning genes on or off. The researchers plan to measure levels of specific miRNAs and determine if they correspond with cognitive test results and neuroimaging data.

• **Somatosensory Processing — Assessing Youth Sport-Related Concussion and Recovery**  
  Principal Investigator: Stacy Jennifer Marcus Suskauer, M.D., Kennedy Krieger Institute, Baltimore

The somatosensory system provides information about our environment — for example, what an object feels like to the touch — and may be affected by brain injury. Dr. Suskauer and her colleagues will investigate whether somatosensory system information processing (SSIP) could be used as a biomarker for concussion and recovery in youth aged 13-17. For these experiments, the researchers will use a new portable device that delivers vibrations to fingertips. Perception of the vibrations reflects activity of sensory neurons in the brain, thereby providing a measure of SSIP. The researchers will also investigate whether changes in SSIP are related to differences in certain brain chemicals after head injury.

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Metabolites are small molecules formed in the body as a result of the normal breakdown of proteins, drugs and other large molecules. The collection of all metabolites in the body is the metabolome. Studies have suggested that head injury may change levels of various brain byproducts, but this has not been researched in a systematic way. Dr. Whalen and his group plan to use an experimental model of traumatic brain injury to conduct a detailed analysis of changes in the brain metabolome following concussion. The researchers will compare those differences with serum byproducts to determine if the changes can be revealed in blood samples. The results of this project may uncover metabolites that contribute to serious effects of traumatic brain injury and may help identify potential targets for detecting and treating concussions.


“Investigators will collaborate to develop diagnostic criteria for identifying the chronic features of the entire scope of brain trauma ranging from mild TBI to full-blown CTE, and then work to extend these criteria to living humans using some of the most advanced neuroimaging tools available.”

-- Walter Koroshetz, M.D., deputy director of NINDS
High Estrogen Levels and Diabetes May Raise Risk of Dementia in Women

Dr. Pierre-Yves Scarabin, of the French National Institute of Health and Medical Research in Villejuif, France and his team of investigators have found that high estrogen levels in combination with the presence of diabetes may pose a risk for developing dementia. Results of the research were published online in the January 29 issue of Neurology.

Scarabin’s research team measured blood estrogen levels of 543 women 65+ without cognitive problems, along with 132 women with dementia. The cohorts were a subgroup of the Three-City Study of vascular risk factors of dementia in French patients 65 and older. Everyone was evaluated for dementia risk factors, some of which were high blood pressure, abnormal blood clotting and diabetes.

The team found that the women with high estrogen levels were more than two times as apt to develop dementia compared with the low estrogen group. Furthermore, they found that those women with both high estrogen levels and diabetes were 14 times more likely to go on to develop dementia compared with those who did not have diabetes and had low estrogen levels. The team discovered that women with dementia and diabetes had estrogen levels 70% higher than the women who only had diabetes.

“Women with both high estrogen levels and diabetes were 14 times more likely to go on to develop dementia compared with those who did not have diabetes and had low estrogen levels.”
More Data on DHA and AD

Michael Rafii, MD, PhD
Director, Memory Disorders Clinic, UC San Diego

There is growing evidence that dietary changes can affect the brain’s structure and even functioning. For example, higher adherence to a Mediterranean-type diet has been shown to be associated with decreased cognitive decline. The typical dietary pattern of the Mediterranean-type diet is characterized by a high intake of vegetables, fruits and nuts, legumes, fish and monounsaturated fatty acids; relatively low intakes of meat and dairy products; and moderate consumption of alcohol. In fact, higher consumption of olive oil, very rich in monounsaturated fatty, is considered the hallmark of the traditional Mediterranean-type diet.

One particular form of omega-3 fatty acid, called DHA, which is the most abundant fatty acid in the brain, has been of particular interest in regards to AD. In 2006, researchers at the USDA Human Nutrition Research Center on Aging at Tufts University found individuals with the highest DHA levels had a 47% reduction in all-cause dementia and a 39% lower risk of developing AD. In that study, which was a nine-year prospective, follow-up cohort study researchers analyzed completed dietary questionnaires and measured DHA blood levels of 899 study subjects who were participating in the Framingham Heart Study.

Neuropsychological testing revealed that all study participants were dementia-free at baseline. Thereafter, subjects had their cognitive function tested every two years using the Mini-Mental State Examination (MMSE). Those who experienced a decline of three or more points on the MMSE from the most recent exam were called back for a neurological and neuropsychological examination. The study population was 36.5% male and had an average age of 76 years. Plasma samples were measured for plasma DHA. In addition, a subgroup of 488 patients completed dietary questionnaires.

During the study period, 99 of 899 subjects developed dementia, including 71 cases of AD. Researchers divided individuals into quartiles according to their blood DHA levels. Those in the upper quartile experienced a significantly lower risk of all-cause dementia and AD compared with participants with levels in the lower three quartiles.

However, there are two ways to measure blood DHA: to directly measure it in the plasma fraction of blood, or to measure it within the red blood cells. It turns out that red blood cell DHA reflects dietary DHA intake up to 120 days, whereas plasma concentrations reflect intake over only the last few days.

Last year, researchers looked at red blood cell DHA levels and found that lower red blood cell DHA levels are associated with smaller brain volumes even in persons free of clinical dementia. The MRI finding of lower brain volume represents a change equivalent to approximately two years of structural brain aging.

For the latest study, Pottala and colleagues looked at the omega-3 fatty acids levels in the red blood cells of 1,111 women who participated in the Women’s Health Initiative Memory Study. The women had MRI scans eight years after the study began to measure their brain volume. They were an average of 78 years old. Those with the highest levels of omega-3 fatty acids in their red blood cells had a 2.7% larger volume in the hippocampus portion of the brain compared with those with the lowest levels of omega-3 fatty acid and those with the highest levels of omega-3 fatty acids in their blood had 0.7% larger overall brain volume compared with those with the lowest levels.

What do these results mean? More data is accumulating that high dietary omega-3 acid levels may reduce the risk of AD in healthy individuals and also reduce the atrophy or shrinkage rate of the brain, including that of the hippocampus. Of course, one must consult with their doctor or pharmacist before purchasing or taking any supplement, as they can interact with medications. But we remain excited about the possibility that diet may influence AD risk.
ADCS Clinical Trials

The following trials have begun but not all sites are up and able to enroll participants. Check the web pages for sites able to screen and check back periodically as the pages are updated as sites come online.

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness
http://adcs.org/Studies/SNIFF.aspx

http://adcs.org/Studies/A4.aspx

http://dian-info.org/

For further information on all ADCS clinical trials please visit:
http://adcs.org/Studies/clinalResearchStudy.aspx

https://twitter.com/ADCSComm

https://www.facebook.com/pages/Alzheimers-Disease-Research/114211355284888?v=wall