NYU Langone Health

Summer/Fall 2021

Mind Matters

Alzheimer's Disease Research Center
Center for Cognitive Neurology

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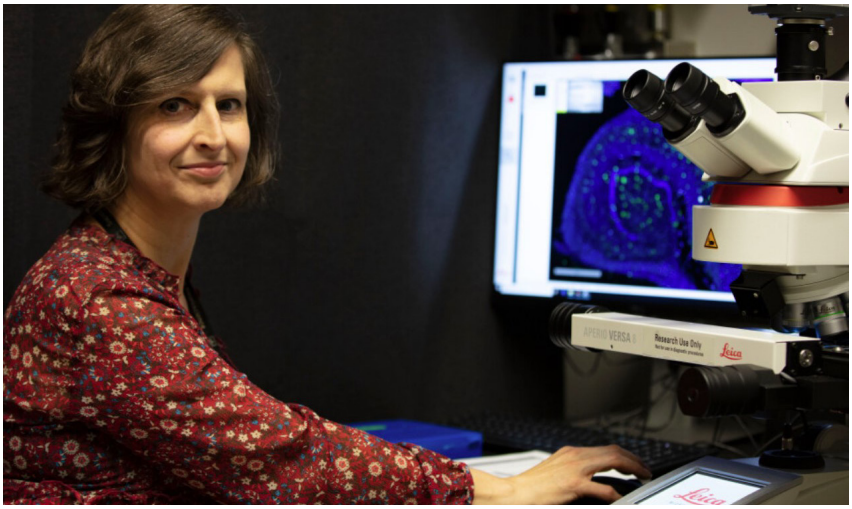
Section 1:
Harnessing the Innate Immune System to Fight Alzheimer's Disease

By: Henrieta Scholtzova, MD, PhD and Louisa Bokacheva, PhD



Immunotherapy, a treatment that recruits the immune system to fight illness, is currently a topic of intense research interest. With the support of the NYU ADRC, Henrieta Scholtzova, MD, PhD, investigates a new therapy that cues the immune system to attack and destroy amyloid beta plaques and tau tangles, which are harmful proteins associated with Alzheimer's disease.

A recent study, led by Dr. Scholtzova and published in the June 15 issue of Brain, has shown that in aged non-human primates, treatment with CpG oligodeoxynucleotides (CpG ODNs) reduced amyloid beta plaques by 59%, compared with untreated animals. This immunotherapy also improved the animals' cognitive functions: treated elderly monkeys solved puzzles and learned to navigate a maze better than aged monkeys that did not receive treatment.

The CpG ODNs are synthetic compounds that contain cytosine-phosphate-guanine (CpG), a short DNA motif usually found in bacteria and viruses. CpG ODNs are recognized by TLR9 receptor on various immune system cells, including the cells of the innate immune system, the body's first line of defense against infection. In response to CpG ODNs, activation of the innate immune system may help the immune cells in the brain recover their function and become more effective at removing amyloid beta plaques and tau tangles. In clinical trials of human vaccines and therapies for infectious diseases and cancer, CpG ODNs have shown excellent safety profiles.

In this study, treatment with CpG ODNs did not cause excessive inflammation or microbleeds—challenging complications that often limit immunotherapy studies.

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Non-human primates were given monthly injections of the drug for two years. In the intervals between injections, the animals' immune system was able to recover without developing excessive inflammation. Meanwhile, control animals received injections of saline solution.

This study comes on the heels of extensive investigations of the CpG ODN therapy, performed by Dr. Scholtzova and her team in mouse models of Alzheimer's disease. Monkeys are excellent models for studying this treatment prior to clinical trials. Not only does their immune system more closely resemble the human immune system, but also similarly to humans, squirrel monkeys develop extensive amyloid deposits around the blood vessels (vascular amyloid).

Further detailed studies, including brain MRIs and analyses of biofluid biomarkers, are underway to understand the mechanism of immune response to treatment with CpG ODNs. These studies will also advance research on how Alzheimer's disease starts and progresses, by supporting the discovery of biomarkers to help diagnose the disease and track its development in patients.

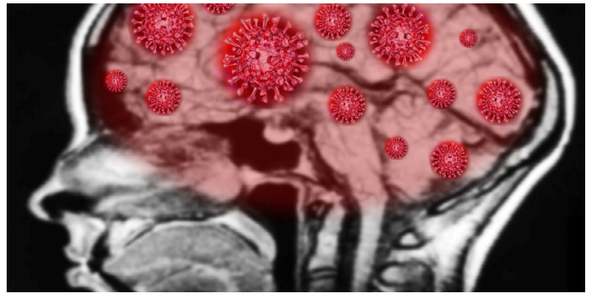
A clinical trial is currently being developed by Dr. Scholtzova and Dr. Wisniewski to test the safety and efficacy of the CpG ODN therapy in human subjects. Overall, Dr. Scholtzova's research will help to further understanding of the immune system's role in neurodegeneration and may lead to the development of new therapies against Alzheimer's disease.

(Publication in the journal *Brain*: In addition to Scholtzova, other NYU Langone researchers included Thomas Wisniewski, Akash Patel, Sara Krivoshik, Xuewei Pei, Elizabeth Cho, Margish Ramani, and Yongzhao Shao, PhD. Other co-investigators are Pramod Nehete, Bharti Nehete, and Lawrence Williams, at the University of Texas)

Section 2:
COVID-19 and Cognition
By: Omonigho Michael Bubu MD, MPH, PhD

In the United States, the Coronavirus disease-2019 (COVID-19) pandemic has resulted in 33.6 million confirmed cases and over 603,000 deaths as of June 25, 2021. These numbers are more than the combined numbers of American lives claimed in World War I, the Vietnam War, and the Korean War altogether. Well-known pulmonary complications of COVID-19 are the main culprits for most of the deaths reported. However, the effects of COVID-19 on the nervous system is now increasingly recognized. Currently, there is convincing evidence that severe acute respiratory syndrome-associated coronavirus 2 (SARS-Cov-2), the etiologic agent of COVID-19, can affect the nervous system, with damage and neurologic alterations. In a study conducted within a large hospital network in Chicago, Illinois, neurologic manifestations were present at Covid-19 onset in 42% of patients, at hospitalization in 63% of patients, and at any time during the disease course in 82.3% of patients. Notably, more than 30% of patients presented with impaired cognition at COVID-19 onset.

Neurologic manifestations of COVID-19 patients range from



nonspecific and moderate symptoms such as headache, muscle pains, and loss of smell or taste to severe symptoms including diseases of blood vessels in the brain and brain infections. Most of the acute severe neurologic symptoms occur only in a minority of patients with usual risk factors and are associated with poor outcomes, including death. However, most COVID-19 patients exhibit only minor or mild neurologic symptoms. More importantly, new research now suggest that there may be long-term neurologic consequences in COVID-19 survivors. Notably, increasing evidence suggest that there may be subtle but real brain damage occurring in many survivors, causing neurobehavioral, psychological and cognitive problems, that maybe indistinct but pervasive.

Previous studies of patient survival after an intensive care unit (ICU) stay suggest that many critically ill patients with COVID-19 will face long-lasting physical, cognitive and/or mental health deficits. One study-enrolled adults with respiratory failure in the medical or surgical ICU, and evaluated them for in-hospital delirium, and assessed global cognition and executive function 3 and 12 months after discharge. A longer duration of delirium in the hospital was associated with worse global cognition and executive function scores at 3 and 12 months. These kinds of cognitive deficits in memory, attention, and executive function, in normal daily life may show up as difficulties remembering names, remembering familiar faces and places, having normal conversations, sustaining thoughts, handling finances and medications, understanding written materials, and even being able to function optimally at work. We anticipate similar effects in patients with COVID-19 ICU survivors with possible long-term psychological effects including neuropsychiatric illnesses like anxiety, depression, and post-traumatic stress disorder (PTSD).

Research has shown that COVID-19 may cause brain damage through encephalopathies that can show up as delirium/psychosis and no distinct MRI or CSF abnormalities. Other pathways include causing inflammatory neurological syndromes including encephalitis and myelitis, increasing the risk of ischemic strokes by creating a pro-thrombotic state. COVID-19 patients have also presented with peripheral neurological disorders including Guillain-Barre syndrome, brachial plexopathy, and other miscellaneous central disorders. Neuropathological studies have not yet demonstrated marked injury nor presence of SARS-CoV2 in the brain areas responsible for respiratory control or the carotid bodies. However, studies have shown patients (age range 63–90) exhibiting modest hypoxia-related neuropathological changes.

In summary, although most patients recover from COVID-19, both short and long-term cognitive and neuropsychiatric effects are a strong possibility. Severe COVID-19 patients experience high levels of pro-inflammatory cytokines and acute respiratory dysfunction and often require assisted ventilation in the ICU. These factors substantially increase the risk of cognitive decline. More importantly, COVID-19 induced direct negative effects of the immune reaction, and possible aggravation of pre-existing cognitive deficits, may ultimately increase the risk of de novo induction of a neurodegenerative disease like Alzheimer's disease. It is therefore expedient for health care providers to provide continued assessment for neurocognitive deficits in COVID-19 survivors.

Section 3:
Word Search

Alzheimer's word search

E K X K T R S U A W C C S T L B P
G P D Y R S R E M E M B E R I N G
A T V M E X R F K R H E Y Y A I C
T H L E A U N S E Y J S T I N W S
S T A M T A B Y E P O I N R O X L
Y A T O M T A M P R L S E B R I F
L U E R E X B D A K J O I S E F E
R T S Y N F U X O W C N T Y S J Q
A X T L T K B J C J E G A M E Y I
E H A O S U F G B F I A P P A D Y
Q W G S E A J Z R Z B I B T R O U
Z G E S S G F G V F D D Z O C P E
G F J P A R V I B J O I I M H K R
J D E M E N T I A G I R B S D B B
Z I I J S A J Z J X A O S B W V F
W B K U I Y S R E M I E H Z L A R
Y D I Z D D H C J F Q R G B O D P

Alzheimer's Dementia Diagnosis Disease Early Stage
Late Stage Memory loss Patient Remembering
Research Symptoms Treatments

Section 4:
ADRC New Procedures
By: Arjun Masurkar, MD, PhD and Rachel Weintraub-Brevda, PhD

We at the NYU ADRC want to remain at the forefront of the Alzheimer's disease (AD) field as new ideas and techniques move us towards better diagnostics and therapies. In an effort to revamp our research, we have added several innovative and cutting-edge procedures to our ADRC study. These new methods are in the domains of imaging scans and digital biomarkers.

1. Imaging scans: The gold standard way to confirm AD is to show amyloid plaque and tau-based tangles upon autopsy, which

had been a limitation for AD research focusing on early stages. In recent years, chemical tracers for amyloid and tau have been developed that, when used with Positron Emission Tomography (PET) scans, enable non-invasive confirmation of amyloid and tau in living persons. This enables a safe and innovative way to image markers of AD in the brain and determine their influence on cognition, behavior, and function. We are implementing amyloid PET and tau PET scans that, when combined with MRI, permit state-of-the-art research on AD risk and help identify and differentiate AD from other neurodegenerative diseases.

2. Digital biomarkers: The early stages of AD and related dementias may go undetected because current methods are not sensitive enough to detect and track subtle problems. To capture these early changes, we are harnessing advances in mobile and wearable technologies to track "digital biomarkers." First, we are quantifying the gait of our participants using a walkway embedded with sensors. Gait changes can include a decrease in walking speed, an inconsistency of stride, and other changes which can be seen in very early stages of AD and related dementias. Secondly, we are analyzing sleep patterns by providing participants with actigraphy watches that digitally track movements during sleep. While dementia is typically associated with cognitive impairments, it can also lead to problems with sleep, including alterations in daytime activity levels, sleep quality, and awake/sleep patterns. Lastly, we are developing methods to quantify cognitive tests traditionally done on paper. For example, using a digital pen on a tablet, a dynamic tracking of a clock drawing can be analyzed with respect to speed, accuracy, and strategy that may reveal indicators of future decline or stability.

All of these new procedures will be explained in further detail during the consent process and will help in the fight against AD and related dementias. The NYU ADRC is unique and innovative in its focus on early stages of dementia and we will continue to include the most ground-breaking diagnostics for early detection of subtle changes.

Section 5:
Hearing Loss and Aging
By: Joshua Chodosh, MD and Barbara E. Weinstein, PhD

Hearing loss is a frequent problem affecting many of us, as we age. Although there are many causes of hearing loss the aging process is the most frequently associated condition. A more specific cause is unknown. Age related hearing loss (ARHL) affects some people as they enter their 7th decade of life (60 years and older) and by the time we are in our 80s, we have as much as an 80% chance of being affected. It is important to understand the manifestations and implications of this most common form of hearing loss, AHRL.

What does this mean functionally? AHRL involves the loss of specific cells that sit inside a part of the inner ear called the cochlea. When it is AHRL, it is never sudden but a very gradual loss over years such that we or others might not even notice that there is a problem until it becomes more severe. ARHL typically affects reception of high frequency sounds (think of these as high in pitch) which is why it is often referred to as a "high-frequency" loss. The sounds which are high in pitch are not easily detected and become more volume dependent to be able to hear accurately or at all. In the English language, these are the consonant sounds in our words, sometimes referred to as the "hard" sounds like, t, s, f, g, k, etc. While these sounds tend to be soft in volume and difficult to detect, they are visible on the lips which can assist assigning meaning to the words which may be inaudible. In addition, persons with ARHL, are able to hear low frequency/pitch sounds such as background noise. Hence, a symptom of ARHL is having trouble filtering out background noise such as when in a noisy public place like a restaurant. Because loud noises typically become more unpleasant or uncomfortable, we will hear someone's conversation considerably more easily in a quiet place.

How do we measure hearing function? Hearing ability is most commonly measured in a sound booth where the audiologist presents different frequency sounds at different levels of loudness and asks the patient to identify when they hear the sound. Missing a sound of a certain frequency and volume (loudness) is used to create an audiologic profile indicating whether one has hearing loss and of what type. This information is also used in the proper fitting of hearing aids for those with identified loss.

Since the objectively measured audiologic profile is not always predictive of functional hearing capacity, assessing hearing difficulty through a self-report of symptoms related to hearing offers many advantages. There are specific validated tools to determine "subjective" hearing difficulty.

Why is hearing so important? Hearing is a social sense. We need to hear to communicate. We rely on understanding another's speech and hearing the words correctly for effective communication. When we have difficulty hearing, listening requires more effort and that effort (sometimes referred to as cognitive load) can be fatiguing. The effort required can be significant enough to require so much energy directed to hearing words that there is no capacity to really listen in a way that allows one to work with the information while in conversation and encode it for remembering easily after the conversation. This is like a being a note-taker during a lecture and then being more reliant on rereading the notes to recall what was said. When hearing is really difficult, the effort required to listen can be very frustrating and tiring, leading one to give up on the conversation and although remaining present, no longer being attentive.

How does hearing loss affect the brain and can this cause dementia? We have brain imaging evidence that hearing loss leads to using different physical places in our brains to process sound. Our brains adjust to using other regions than those that were used before to accommodate sounds. We have learned about this cross-modal plasticity or the ability of an intact sensory modality (e.g., vision) to recruit cortical brain regions from a deprived sensory modality from auditory development studies in children, from mouse studies and more recently from imaging data. It appears, for example, that one memory center, known as the hippocampus, shows more inflammation and deterioration when hearing is negatively impacted. Other studies have shown associations between hearing loss and cognitive decline but this does not mean that hearing loss causes this decline. More research is needed to understand these relationships and this is ongoing.

How can you improve your ability to hear well? Beyond seeing an audiologist who can help optimize hearing via a variety of interventions or protecting hearing from environmental noise, there are other things one can do to address this problem. See your doctor to be sure that you have not accumulated a large amount of ear wax which once removed can restore some amount of hearing. In conversation with others, try to limit background noise and make sure you are able to see the speaker's face for adequate lip reading and use of facial expression – something we all use in communication to fill in the gaps for where we are not sure we have heard clearly. There are hearing assistive technologies that serve as personal sound amplifiers which can be bought over the counter. You can also download an application to your smartphone (if you have one) and use it as an amplifier with ear buds or a headphone. Stay engaged with others! Don't let any difficulty with hearing limit your social interactions. Find strategies including hearing aids to improve your "auditory wellness" if this has become more difficult.

Section 6:
Meet the New Staff!

Dr. Omonigho Michael Bubu is an Assistant Professor and physician scientist at NYU Grossman School of Medicine (NYUSoM), in the Departments of Psychiatry and Population Health, with a programmatic research focus on sleep, aging and Alzheimer's disease (AD) in blacks. Dr. Bubu has graduate, internship, and fellowship-level clinical and research training in neurology, neuro-epidemiology and public health. His research examines how age-related and age-dependent sleep changes, and vascular risk, impact cognitive decline and AD risk, and how they drive AD related disparities. He has received various grants to fund his research, such as the American Academy of Sleep Medicine (AASM) Bridge Award for Early Career Investigators, NYU Alzheimer's Disease Research Center Developmental Grant, and Columbia Center for Interdisciplinary Research on Alzheimer's disease Disparities Pilot Grant. He has collaborated with experts in the field on intramural, foundation and NIH grants, with significant contributions that have improved our understanding of the relationship between sleep, particularly, obstructive sleep apnea and AD. He currently serves as an ad-hoc reviewer for multiple high impact journals including but not limited to Annals of Internal Medicine, Alzheimer's & Dementia, Sleep Medicine Reviews, JAMA Network, SLEEP, Journal of Clinical Sleep Medicine, and Biobehavioral Reviews and Neurology. Dr. Bubu has joined the ADRC team as one of our study clinicians and you may be seeing him at your next ADRC study visit!

Rachel Weintraub-Brevda, PhD has taken on a new role at the ADRC as Program Manager for Professional Education. Rachel will also be working closely with our Neuropathology Core on the Brain Donation Program as well as conducting some neuropsych testing with our participants. Rachel comes to the Center for Cognitive Neurology from the Neuroscience Institute, where she developed many education and outreach initiatives. Before joining NYU Langone, Rachel received her PhD in Cognition, Brain, and Behavior from the Graduate Center, CUNY, where she investigated emotional memory and attention in the brain. When she is not at work, Rachel enjoys spending time with her family and reading about all things!

Zena Rockowitz is our new Recruitment Coordinator for the ADRC, clinical trials, and affiliated studies. She studied psychology at the University of Florida and holds Master's degrees in Public Administration and Social Work from Florida State University. Her background is in policy and outreach with a focus on geriatrics/health care. Despite growing up in Miami, Florida, raised with sunshine and warm beaches, she spent the last seven years in rain jackets in Portland, Oregon. She recently came to New York with two cats in tow (Kitty-Boy and Bunny). Favorite pastimes include reading novels, camping, biking, and exploring the greatest city in the world (NYC).

Natasha De La Cruz is the ADRC's new Multicultural Program Coordinator. Natasha is a New Yorker at heart, having been born and raised in Queens, New York. When she was eight years old, her family moved to the Dominican Republic, where she was able to get a true feel for the amazing culture and community. Natasha received her bachelor's degree in Clinical Psychology from La Universidad Autónoma de Santo Domingo (UASD) and previously worked in the San Vicente de Paul Hospital's psychology department before returning to the states. She continued her career working at Clinilabs Drug Development and Research and Columbia University's Taub Institute for Research on Alzheimer's disease and the Aging Brain. Natasha currently lives in New Jersey with her fiancé and two cats, Frankie and Rebecca. She enjoys reading, gardening, and walking with friends.

Charlotte Kwong is an undergrad at NYU, majoring in politics, but on the premed track. She has joined the ADRC as a student research intern working with our Data and Biomarker Cores. A little bit about Charlotte: She is a student-athlete at NYU for Women's Golf and has been playing golf since she was five years old. Charlotte was born and raised in Hong Kong and then came overseas to the United States for high school and college to seek better academic and athletic opportunities. Charlotte plans on pursuing a career in the medical field and is still exploring the subspecialties, but finds neurology very complex and fascinating! Charlotte says "I love the research projects that the ADRC is conducting and being part of the team has been such a joy".

Jon Links joined the team a few months back as a Research Data Associate here at the ADRC working in both the Data and Biomarker Cores. Jon graduated from NYU, where he majored in Biology, and is currently working on obtaining his Masters in Biomedical Informatics at the Vilcek institute of Biomedical Sciences. Outside of work, Jon enjoys listening to music, photography, cooking, and bouldering!

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Gissell Duran is joining the ADRC as a student intern. Her primary focus will be working with the biorepository, administering neuropsych assessments, and working with the gait analysis. She's currently a rising sophomore at NYU studying psychology, child and adolescent mental health, and creative writing. Her goal is to pursue a PhD in clinical psychology and start her own research projects!

Below is snippet from our interview regarding her research experience.

What first inspired you to contribute to AD research?

A few years back I attended an outreach event hosted by the NYU ADRC. There they explained that research often lacks participation from people of color (POC) and that such a lack could lead to negative health outcomes for society as a whole, and for African American communities in particular. For that reason, I felt compelled to contribute. I was also encouraged by the fact that NYU's staff was comprised of diverse individuals, which made me feel at ease and trusting that the ADRC was not merely "talking the talk" without a real investment in POC; they were actually "walking the walk".
Additionally of course, as an artistic person, the idea of studying my very own creatively wired brain (from which my art emanates) just seemed fascinating!

What do you get out of the ADRC experience / is the most gratifying part of the experience?

I feel of worth both because I am (1) providing important data which will benefit the lives of future generations and POC especially, along with the fact that (2) the ADRC staff really respect what I have to offer despite my doubts about my own perceived shortcomings at times. They hear me and deem the things I say of value. It is also just amazing to get to know my own brain, and to have scientific confirmation of the things I already suspected about myself; my biology and why I am the way that I am.

What might you tell someone who is trying to decide whether to participate in ADRC research?

I would say they SHOULD participate. If they were feeling anxious about the prospect, they would do well to understand that the research team never makes you do anything you do not want to, nor is there anything invasive about the experience at all; you are in full control. Furthermore, I would argue they should participate because they will absolutely grow through the experience. The research provides you with data about where you are, and thus gets you thinking about where you WANT to go. Once armed with that knowledge they will likely be more invested in their brain health, motivated to live healthily and enjoy the blossoming of their aging. It reminds me of one of my favorite quotes "one should never cease chiseling one's own statue"; the ADRC pushes me to keep chiseling my statue, and would likely do the very same for them.

Finally, one last fun question: As you are a writer yourself, what is your favorite poem and or book that you might recommend to others in the ADRC?

I Know Why the Caged Bird Sings by Maya Angelou

Section 7:

Participant Spotlight: Interview with Debra Bramlett aka "Sweet Aminata"

By Marlena Gordon, MSW

Debra is a 65-year-old African American writer/poet living in Downtown Brooklyn. She was first drawn to "magical" Brooklyn from Saint Louis in her mid-20s after reading the inspiring works of the Harlem Renaissance authors. She has been in New York for four decades now, throughout which time she has written countless inspiring works herself. Over the last 10 years however, she has been embarking on other creative ventures under the name "Sweet Aminata" which means "big heart" in Senegalese (loosely translated as "sweet heart" in English). Now in addition to her poetry, she pairs her writing with artistic pieces to further illustrate her words and engage all the five senses. She presents these projects all over New York; from Riker's island as part of her volunteer work, to county fairs. You too can view some of her works on YouTube at tinyurl.com/fp3sjb9j and at tinyurl.com/hr75vbrf. The latter even includes a video of Wanda Sykes reciting one of her poems! Currently, she is also working on a book about her family history, which she hopes to release in December. For fun, Debra loves to bake and cook. She considers it an extension of her artistic persona, as she loves to perfect recipes creatively improvised from scratch. Her specialty is healthy soul food, but she also likes to bake cookies to use as part of her interactive poetry readings (you can use the link above to see some of her incredible looking muffins). Debra also spends her spare time contributing to research as part of The NYU Alzheimer's Disease Research Center's (ADRC) Longitudinal Study, which she has been a part of for almost 3 years.

Section 8:
Upcoming and Past Events

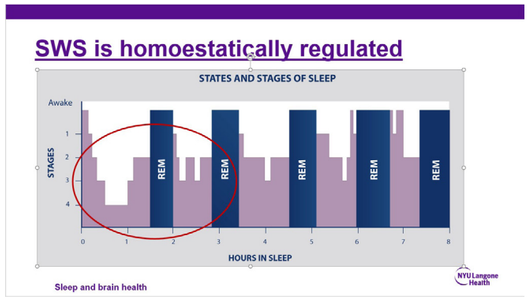
Upcoming Events:

We are excited to continue our Alzheimer's Disease Research Center's "Learn at Home" series. While we had hoped to be back in person, in the best interest of our participants, we will continue our series via our previously successful virtual platform! This has been a great way to discuss topics often brought up during study visits with some of your favorite clinicians via a virtual platform. The best part?? It's all done from the comfort of your living room sofa! At the center, we appreciate your continuous contribution and dedication to our study. This is a small token of our team's gratitude for your support in helping to find a cure for Alzheimer's disease and other related dementias. Keep your eyes out for the new series slated to begin September 2021!

Past Events:

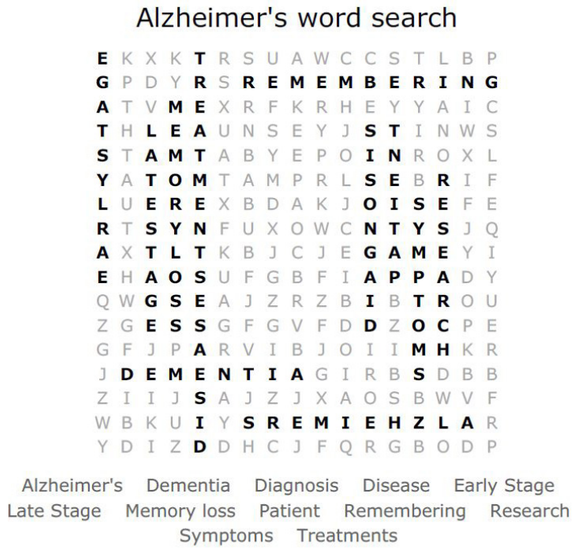
In February 2021, Dr. Ricardo Osorio presented on a topic that seems to be on many people's minds: Sleep and Brain Health.

Here are a few brief slides from the Learn at Home presentation.



SWS = slow wave sleep

Section 9:
Word Search Key



Section 10:
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