

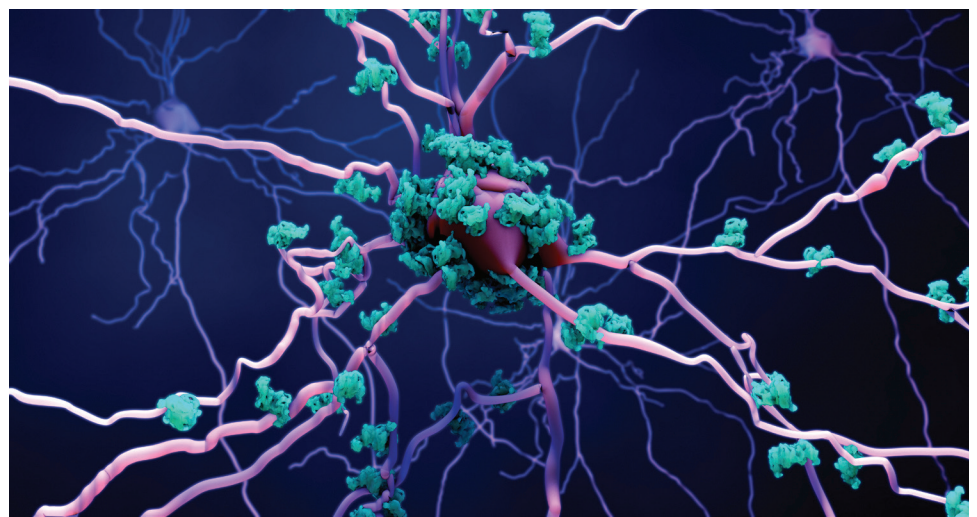
Mind Matters

Alzheimer's Disease Research Center (ADRC) Center for Cognitive Neurology

TABLE OF CONTENTS

- **Section 1:**
Amyloid Hypothesis on a Bumpy Ride
By: Louisa Bokacheva, PhD
- **Section 2:**
Breaking News in Alzheimer's Disease Research
By: Arjun Masurkar, MD, PhD
- **Section 3:**
Seeing What Alzheimer Saw
By: Ricardo Osorio, MD
- **Section 4:**
The Importance of Diversity in Alzheimer's Disease Research and its Early Detection
By: Anthony Q. Briggs, PhD
- **Section 5:**
Meet the New Staff
- **Section 6:**
Upcoming Events
- **Section 7:**
Exercise is Good for the Brain!
By: Zena Rockowitz, MSW, MPA
- **Section 8:**
Counselor Corner
By: Ursula Auclair, LCSW-R
- **Section 9:**
Contact Info

Section 1: Amyloid Hypothesis on a Bumpy Ride *By: Louisa Bokacheva, PhD*



Amyloid beta is a small protein produced in the brain and one of the hallmarks of Alzheimer's disease (AD). Amyloid beta tends to form plaques when misfolded proteins stick together and aggregate. The plaques can be seen under a microscope on thin, specially processed slices of brain tissue. More recently, it has become possible to detect amyloid deposits in living subjects using positron emission tomography (PET) with tracers that bind to amyloid beta.

The presence of amyloid plaques was first linked with dementia in the early 1900s by Alois Alzheimer and independently by Oskar Fischer. In the decades since these early findings, numerous studies have implicated amyloid beta as a key feature of AD pathology. By the early 2000s, the "amyloid hypothesis" became the prevailing approach for understanding AD and amyloid beta became the main target of experimental therapies.

In the past 20 years, multiple investigational anti-amyloid treatments have been developed and studied in hundreds of clinical trials. But even those therapies that successfully reduced amyloid deposits struggled to deliver meaningful improvements in memory and cognition. A drug called aducanumab (Aduhelm), developed by the U.S. company Biogen, is an antibody (a protein used by the immune system to recognize and neutralize pathogens) that targets amyloid plaques. In June 2021, the Food and Drug Administration (FDA), controversially approved aducanumab, despite the negative recommendation of an independent expert panel. In studies of almost 3,500 patients, aducanumab was shown to reduce amyloid deposits, but the clinical trial aiming to verify its clinical benefits is ongoing (ENVISION, NCT05310071).

continued on next page

In July 2022, a report published in *Science* (*Blots on a Field?* by Charles Piller) revealed that a series of influential publications on amyloid and Alzheimer's disease appeared to have contained doctored results. Although the studies in question dealt with a single form of amyloid (called AB*56), the incident has prompted scientists to reexamine their focus on amyloid beta as the driver of AD. The revelations also put a spotlight on the National Institute of Health, which continues to support amyloid-related studies and spent \$1.6 billion on them in this fiscal year alone, almost half of its overall AD budget. In the opinion of Dennis Selkoe (Harvard University), one of the creators of the amyloid hypothesis, if current phase 3 clinical trials of three anti-amyloid treatments fail, "the amyloid beta hypothesis is very much under duress." Although the amyloid hypothesis is unlikely to go away anytime soon, it is yet again the subject of active discussion.

In the latest twist of this story, at the end of September 2022, one of these anti-amyloid drugs, lecanemab, developed by Biogen and Japanese pharma group Eisai, was reported to slow cognitive and functional decline by 27% relative to a placebo. These results were observed in a global, phase 3 trial of 1,795 subjects with early AD (Clarity AD, NCT03887455). The companies announced that the FDA considers the results of this trial as confirmation of the drug's clinical benefit. The phase 3 trial data on another anti-amyloid drug, gantenerumab (Roche), are expected to be published soon.

The ADRC is contributing to studies of anti-amyloid therapy by taking part in clinical trials supported by the National Institute of Aging. The VIVA-MIND study (NCT03919162) is a phase 2 trial that evaluates the efficacy and safety of varoglutamstat (PQ912; Vivoryon Therapeutics, Germany) in patients with early Alzheimer's disease. PQ912 is expected to slow down the progression of memory and thinking problems by inhibiting the formation of a toxic amyloid protein, known as N3pE.

Another study, APOLLOE4 (NCT04770220), is a phase 3 trial that evaluates the efficacy and safety of valiltramiprosate (ALZ-801), developed by U.S.-based company Alzheon, in subjects with two copies of APOE4 gene, the strongest risk factor gene for AD. ALZ-801 is designed to prevent the formation of soluble clumps of amyloid proteins called amyloid oligomers.

The latest developments in studies of amyloid beta, both troubling and encouraging, promise to bring greater clarity to the role of different forms of amyloid and energize the discussion of the of AD mechanisms. The momentum generated by this discussion has the potential to open new directions of inquiry and lead to the development of novel therapeutic approaches for AD.

Section 2: Breaking News in Alzheimer's Disease Research By: Arjun Masurkar, MD, PhD

The NYU Alzheimer's Disease Research Center (ADRC) is at the forefront of new discoveries that advance our understanding and treatment of Alzheimer's disease (AD) and related dementias.



Highlighted below are two recent studies that feature contributions to our center.

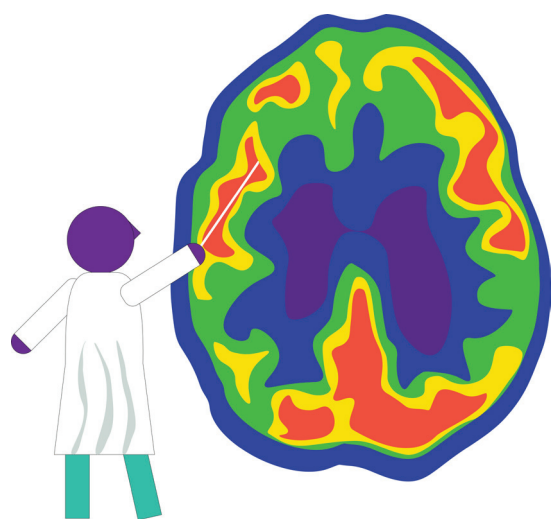
The first study, published in *Nature Genetics*, concerns genetic risk factors for AD and related dementias. Genetic risk factors are variations in the genetic code that do not guarantee that someone will develop AD or another dementia, but rather increase one's individual risk by a small amount. Such risk factors can not only help predict someone's likelihood of developing dementia, but more importantly can also shed light on biological mechanisms that can be studied to develop new treatments. This study pooled data from NYU's and many other ADRCs, as well as other national and international consortia, to compare the genetics of over 100,000 people with AD and nearly 700,000 people without AD – the largest study to date of dementia genetics. The result of this collaborative study was the finding of 75 genetic risk factors, 42 which were brand new. While some known pathways related to amyloid, tau, and inflammation were implicated by these genes, 31 new biochemical processes were uncovered that had not been previously associated with dementias. This provides an incredibly rich resource for scientists – including those at the ADRC – to further investigate in the laboratory how the information on these pathways can be leveraged as new drug targets.

The second study, published in *Frontiers in Aging Neuroscience*, concerns the role of blood vessels in AD. While AD is considered a degeneration of brain cells, in recent years there has been increasing evidence that blood vessels in the brain both contribute to and are a target of the disease. Most of these studies have focused on arteries, but considerably less focus has been placed on veins. In a collaborative effort among NYU ADRC researchers and colleagues in the Department of Radiology, this study applied advanced magnetic resonance imaging (MRI) techniques to visualize the very small and thin veins deep in the brains of ADRC

participants at various stages of AD. The experiments revealed that the visibility of these veins changed in a way to indicate decreased oxygen metabolism in the brain. Furthermore, this visibility declined with increasing stages of AD and was associated with cognitive and functional features of disease. These results implicate the deep veins in AD, both as a possible contributor to disease but also as a novel early imaging marker.

Section 3: Seeing What Alzheimer Saw By: Ricardo Osorio, MD

Positron emission tomography (PET) imaging, known as a PET scan, is an increasingly common brain imaging technique. Doctors may use a PET scan in combination with a CT scan (PET-CT) or an MRI scan (PET-MR). PET-CT or PET-MR scans can show three-dimensional images of the inside workings of the human body. The main strength of these imaging modalities is that they can show not only what an organ looks like, but also how it is functioning. PET images are generated using chemical compounds (tracers), in which one atom has been replaced by a short-lived radioisotope. PET tracers can be synthesized from almost any biologically significant molecule, from glucose to pharmaceutical drugs, without altering their function, and administered by an intravenous injection. PET tracers are injected in small doses, and because of this they do not cause any biological effects and add little radiation exposure to the subjects. Importantly, PET scans measure rates of various important physiological processes including glucose metabolism – an indicator of energy use by an organ or tissue – as well as the uptake of neurotransmitters, such as dopamine, serotonin, acetylcholine, blood flow, protein build-up, drug effects, etc.



PET scans can be used in Alzheimer's disease (AD) research, to investigate changes in brain glucose metabolism, various neurotransmitter systems, neuroinflammation, and, most importantly, the accumulation of proteins that are characteristic of the disease, mainly amyloid plaques and neurofibrillary tangles. Traditionally, these pathological hallmarks of AD, made famous by Alois Alzheimer at the turn of the 20th century, could only be seen on the brain autopsy of deceased patients with dementia. With several PET tracers currently available for AD imaging, we can now visualize amyloid and tau deposits in living patients and healthy volunteers. This has helped researchers develop a view of AD as a continuum starting from an asymptomatic stage, during which AD pathology develops, often for many years, without noticeable symptoms, later progressing to early disease with mild memory and cognitive impairment, and ending in what we know as AD dementia. Using PET imaging to detect the AD-related brain changes in living subjects is already advancing our understanding of the disease, helping to create sensitive tools for early diagnosis and monitoring of treatment effects. PET imaging with several new tracers for amyloid and tau imaging, some already FDA approved and others still under development, are currently offered to ADRC participants.

Section 4: The Importance of Diversity in Alzheimer's Disease Research and its Early Detection By: Anthony Q. Briggs, PhD

Alzheimer's disease (AD) is the most common form of dementia and the sixth leading cause of death in the United States. An estimated 6.5 million people live with AD, and about 1 in 9 (10.7%) adults ages 65 years and older have the disease. Research reveals racial and ethnic disparities in the prevalence of AD. Black/African Americans are two to four times more likely to risk experiencing AD and related disorders compared to Non-Hispanic Whites. Evidence suggests that there are multiple risk factors that may contribute to this (cultural, genetic, biological, and environmental), as well as inequities in health care access and knowledge.



The National Institutes of Health (NIH) Revitalization Act, passed almost thirty years ago, mandated appropriate strategies for minority inclusion in all NIH-funded research. Yet, racial and ethnic groups remain underrepresented, notably Black/African Americans in AD studies. It is known that this population faces multiple challenges in participation in clinical studies because of historical mistrust, institutional barriers, discriminatory practices, ideologies and attitudes about AD research, and study inclusion criteria that is more favorable for White participants. It is vital in dementia research to focus on understanding the mechanisms and drivers that cause AD across races and to incorporate culturally competent recruitment of participants. Diverse research recruitment helps advance scientific discovery, promote health equity and social justice, reduce biases, and include a variety of personal lived experiences.

This is particularly relevant to me and the nature of my work. I am a scientist and a new junior faculty member at the ADRC, and one of the first Afro-Caribbean-American (Grenadian heritage) faculty in the Department of Neurology. I am also a Scholar of the ADRC's Research Education Component, which provides multi-disciplinary, cross-institutional training and mentoring for early career investigators of AD. The aim is to train the next generation, while promoting diverse backgrounds, experiences and voices.

My research centers on subjective cognitive decline (SCD), which is a self-reported worsening of memory impairment, thinking, and mental abilities despite normal testing on objective cognitive tests. Observational studies in Non-Hispanic Whites show that SCD can, but not definitively, occur 10-20 years prior to an AD diagnosis. While there is much interest in better assessing SCD as a possible precursor to AD, there is a significant research gap in the understanding SCD across racial and ethnic groups. As such, my primary focus is to investigate the characteristics and drivers of SCD in older Black/African Americans. Specifically, I study the association of SCD with biological markers of AD and vascular health, as well as sleep, psychosocial risk factors, socio-economic status, educational attainment, and other social determinants of health.

I hope that my research will help to further the biological understanding of SCD among Black/African Americans and other underrepresented groups, and to improve its practical assessment as a possible risk factor for AD. Overall, by rethinking ways to capture symptoms of disease risk and progression at an earlier stage, we may be able to bring a better quality of life to a diverse population aging adults.

Section 5: Meet the New Staff



Tatianne Martinez has joined the ADRC as a Nurse Practitioner. She has been in the field of nursing for the past 10 years, initially receiving her Bachelor of Science in Nursing from NYU's College of Nursing. She started her nursing career at North Shore University Hospital providing bedside care as an RN in Med-Surg and Telemetry while pursuing her Masters of Science in Nursing from Hofstra University. After graduating, she began practicing as an ANCC board certified Family Nurse Practitioner and previous to the ADRC, served as a provider in Primary Care and Cardiology for the adult and elder population. In her role as a clinician with the ADRC she will be meeting with research participants for evaluations. In her free time, Tatianne enjoys baking, traveling and being a foodie.



Matt Karimi joined the ADRC Data and Biomarker Cores as a Research Data Associate and Study Coordinator. He grew up in New Jersey and graduated from NYU in 2019. Matt interned for two years with Dr. Henrieta Scholtzova in the Wisniewski Lab at the NYU Langone CCN to grow his experience in lab research and to study the processes underlying the development of dementia. He hopes to better understand how dementia impacts people in order to learn what can be done to support them. Matt currently lives in the East Village and he loves exploring the city with his family and friends, meeting new people and animals, thrift shopping, and struggling to jam out on the piano.



Natalie Toomajian is a volunteer at the ADRC, providing support to the Psychosocial Core by administering psychosocial tests. She received her Bachelor's degree in Biopsychology, Cognition, and Neuroscience from the University of Michigan in 2019, and has since worked as a lab manager for Dr. Andrei Cimpian's Cognitive Development Lab at NYU, studying children's development of group stereotypes. Though she's worked predominantly in young child developmental research, Natalie plans to pursue her doctorate in clinical neuropsychology, studying the psychosocial factors that influence age-related cognitive impairment in older adults. In her free time, Natalie loves re-watching her favorite TV shows, exploring the city with her friends, and playing card games.

Section 6: Upcoming Events

The ADRC is hosting a Learn at Home series where you can watch a presentation from the comfort of your home. Here is the schedule:

Brain Aging and Oral Health:

Bei Wu, PhD • Friday, November 18, 2022, 12-1 pm

Alzheimer's Disease and Amyloid Plaques: Separating Fact From Fiction

Arjun Masurkar, MD, PhD • Thursday, December 15, 2022, 12-1 pm

"Brain Fog" After COVID

Michael Bubu, MD, PhD • Friday, January 13, 2023, 12-1 pm

Lifestyle Changes for a Healthy Brain: The Power of Diet, Exercise, Stress Reduction, Nutrition, and Sleep in Reducing Your Chances for Developing Alzheimer's Disease

Ricardo Osorio, MD • Friday, February 10, 2023 12-1 pm

RSVP Here:

https://is.gd/CCN_EVENTS_RS

Additionally, physicians will be presenting to Creative Social Solutions in November, December, and January, as well as the Alzheimer's Association in February.

Section 7: Exercise is Good for the Brain! By: Zena Rockowitz, MSW, MPA

Exercise is good for the brain! Regular exercise works on the brain by strengthening the heart and lung function, reducing stress, improving mood and attention, protecting brain cells, increasing blood flow, and preventing neuroinflammation. Overall, exercise protects the brain and improves memory and thinking abilities.



Research suggests that physical activity can help prevent Alzheimer's disease (AD) and other dementias, while a sedentary lifestyle contributes to an increased risk of these conditions. What is less well understood is what role exercise can play in changing

the disease trajectory for patients who are already experiencing cognitive impairment, and what kind of exercise is best for them. NYU researchers are working to answer this question.

NYU is one of several medical centers across the country that participated in a national clinical trial called EXERT (NCT02814526), led at NYU by Dr. Martin Sadowski. This clinical trial looked at exercise in adults experiencing mild cognitive impairment, a precursor to AD. In particular, the study looked at the impact of different types of exercise on slowing the progression of memory symptoms.

Participants, a total of 296 men and women between the ages of 65 and 89, visited the YMCA four times per week, over 18 months, and participated in a personalized exercise program. Half of participants performed aerobic exercise and the other half performed stretching/balance/range of motion activity. Participants were supervised by a trainer during the first 12 months and exercised independently for the next six months. At the end of 12 months of supervised exercise, participants in each training group underwent a series of cognitive and memory tests as well as brain MRI and measures of AD biomarkers in blood and cerebrospinal fluid. Comparing the two exercise groups may help to understand which type of exercise has greater benefits for cognition and memory.

This research could help determine if neurologists should one day write prescriptions for aerobic exercise. The results may also have future implications for insurance coverage of exercise. For older adults, the World Health Organization recommends 150-300 minutes of moderate-intensity aerobic exercise every week, or at least 75 minutes of vigorous aerobic exercise, or a combination of moderate and vigorous aerobic exercise mixed with strength training. To exercise safely and achieve the greatest benefits to your health, speak with your doctor before starting a new exercise program.

Section 8: Counselor Corner By: Ursula Auclair, LCSW-R

Dear Ursula,

I am writing to you for guidance on how to help my mother who was diagnosed with Alzheimer's Disease (AD) six months ago. We have known for a while that "something was not right", but attributed it to age (she is 79), hip surgery, and the pandemic.

My brother and I do not agree as to how to deal with our mother's confusion, forgetfulness, and delusions. My brother believes that if we just tell her "as it is", including correcting her and telling her when she repeats herself, she will understand and accept what we tell her.

Unfortunately, this has resulted in a lot of arguing and crying and our mother has expressed suspicions and doubts about our intentions regarding her wellbeing. Keep in mind that my mother has good days where she appears to be more like herself, but other days are more challenging. Here are some examples:

She confuses her grandchildren and does not remember how many she has (three). She insists on leaving, going back “home” and on one occasion has confused me with my deceased father. She asks how many people she should cook for (she has not cooked in a year), mentioning “all the others”, while it is just her in the apartment. Most of her finances are now managed by us, but there have been issues with her getting money and not remembering what happened with it, causing her to accuse us of stealing.

This is now also affecting my relationship with my brother, since I find his reactions to my mother often harsh and unnecessary, while he accuses me of patronizing and infantilizing her, thereby making her worse. Any suggestions?

– Bewildered and Sad

Dear Bewildered and Sad,

Thank you for writing and reaching out with such a poignant description of a heartbreaking situation. You and your brother are not alone, although it may feel that way. Each person diagnosed with dementia is unique in their symptoms, but the struggle to adjust and come to terms with the illness has common features. Up front, I want to congratulate you on having worked out how to handle practical issues such as finances.

You did not mention how and where your mother was diagnosed. At the NYU Pearl Barlow Center for Memory Evaluation and Treatment she would be given tests (MRI, scans, etc.), neurologists would evaluate her cognitive abilities and assess her family history, available supports, friends, hobbies, and interests. If the doctor felt your mother was depressed, anxious, or her family and friends expressed similar concerns, they would be referred to me for individual, couple, family, and/or group psychotherapy. Our social worker is available for referrals and concrete support to agencies that specialize in dementia.

The first step is accepting that this is an organic progressive disease. Your mother is not lazy or obstinate, which means that no matter how much your brother corrects her, she will not get better. This step sounds easy, but it is not. It entails saying goodbye to the mother you know, which is even harder, as you mentioned, that with this disease, someone can appear to be their old self at times. It means accepting that your mother is at her best in this moment. Unfinished business, grievances, old hurts, and jealousies will not be rectified by your mother anymore, but this does not mean you can't have a loving relationship with her.

I am sure that you and your brother have your mother's best interests at heart (otherwise, you would not have contacted me). Your brother needs to accept this first step, that no matter how often he corrects her, her memory will not improve. Instead, she will just feel defensive, like she has done something wrong. I say this because if she knew she was repeating herself she would not do it. Accepting this is hard. For some people it might feel

like giving up on the person, since our culture tends to confuse acceptance with giving up.

The next step is based on the first and the premise, that you both want to care for your mother. This entails accepting who you are as a person, and is a chance to learn more about yourself, your “strengths” and “weaknesses”, your frustration tolerance, and ability to be patient. This has nothing to do with being a “good” or a “bad” person.

The fact that you wrote for guidance and not your brother, makes me wonder if there has always been a division of labor, where one of you focuses on getting things done while the other is contemplating the ‘bigger picture’? I am mentioning this to introduce the idea that both of you can be a team in caring for your mother.

Your brother may be focused on having your mother join his reality, “snap out” of her delusions. He argues that there is no one else in the apartment, that she has not cooked in a year, while your focus is on avoiding outbursts and appeasing her. Your brother may equate agreeing with her as lying, but he may accept the idea of redirecting her attention, or distracting her, which sometimes works. He may also need more time away from direct contact with your mother, especially when he is tired or stressed, and instead could focus on, planning for future needs (example: making doctors' appointments).

For you, there may be a playfulness in being with your mother at this time, and the idea of “Yes, and?” could help. “Yes and?” is taken from improv theatre where two people go along with whatever the other brings up. Instead of saying “what!? That is crazy”, the response has to be “Yes, and?” Your brother may not be a candidate for this (I mentioned accepting who we are, right?), but you might.

Imagine these two scenarios:

Scenario 1, The “Yes and” Method:

Mother: Where is my mother? I want my mother!!

Son: Your mother? What would you need her for?

Mother: Breakfast! She makes my breakfast.

Son: Oh, I see!

Mother: Yes! Every day she makes my breakfast. So where is she, why isn't she here?

Son: Well, I don't know but it sounds like you are hungry.

Mother: Of course I am hungry!

Son: So why don't we go and look for something to eat.

Scenario 2:

Mother: Where is my mother? I want my mother!

Son: Your mother? What are you talking about? Your mother died over 20 years ago!

Mother: What?!! My mother is dead!? Oh my god! How did this happen? How come nobody told me?? I need her!! I just saw her yesterday!

Son: That is impossible! I told you she is dead!

Mother: Oh my god, oh my god, I need her, what am I going to do?
[sobbing, shouting...]

The first scenario shows how there can be a compromise between telling “as it is” and plain “lying” and it relies heavily on everyone’s ability to think on their feet, to not be too stressed, too tired, too frustrated, or too scared. “Failure” is built in and forgiveness of yourself and your mother is paramount. The second scenario creates more chaos and stress.

Lastly, if possible, share your feelings early on with supportive family and friends, and take breaks for self-care when and if it is possible and safe. Your network can be tapped into for help.

To summarize:

Accept your mother as she is, accept who you are with all the warts, and learn about yourself. Get as much help as you can find. All the best to you, your brother, and your mother!

Ursula

Section 9:
Contact Info

NYU Langone Alzheimer’s Disease Research Center

145 East 32nd Street, 2nd Floor

New York, NY 10016

Ph: (212) 263-3257

Fax: (212) 263-2991

Web Address: <https://www.med.nyu.edu/adc>

