ALZHEIMER'S DISEASE AS A SPECTRUM DISORDER

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THE PROMISE OF PRECISION MEDICINE, BEHAVIORAL ASSAYS, AND ATTENTION TO LIFESTYLE

INTRODUCTION

As a neuroscientist. I believe the time is ripe for the convergence of two ideas. First is the reframing of Alzheimer's disease (AD). Instead of "one size fits all", the understanding and research directions of AD could benefit from considering it as a spectrum disorder. Second is the application of a particular factor of precision medicine to better understand and more effectively intervene in the progression of Alzheimer's disease.

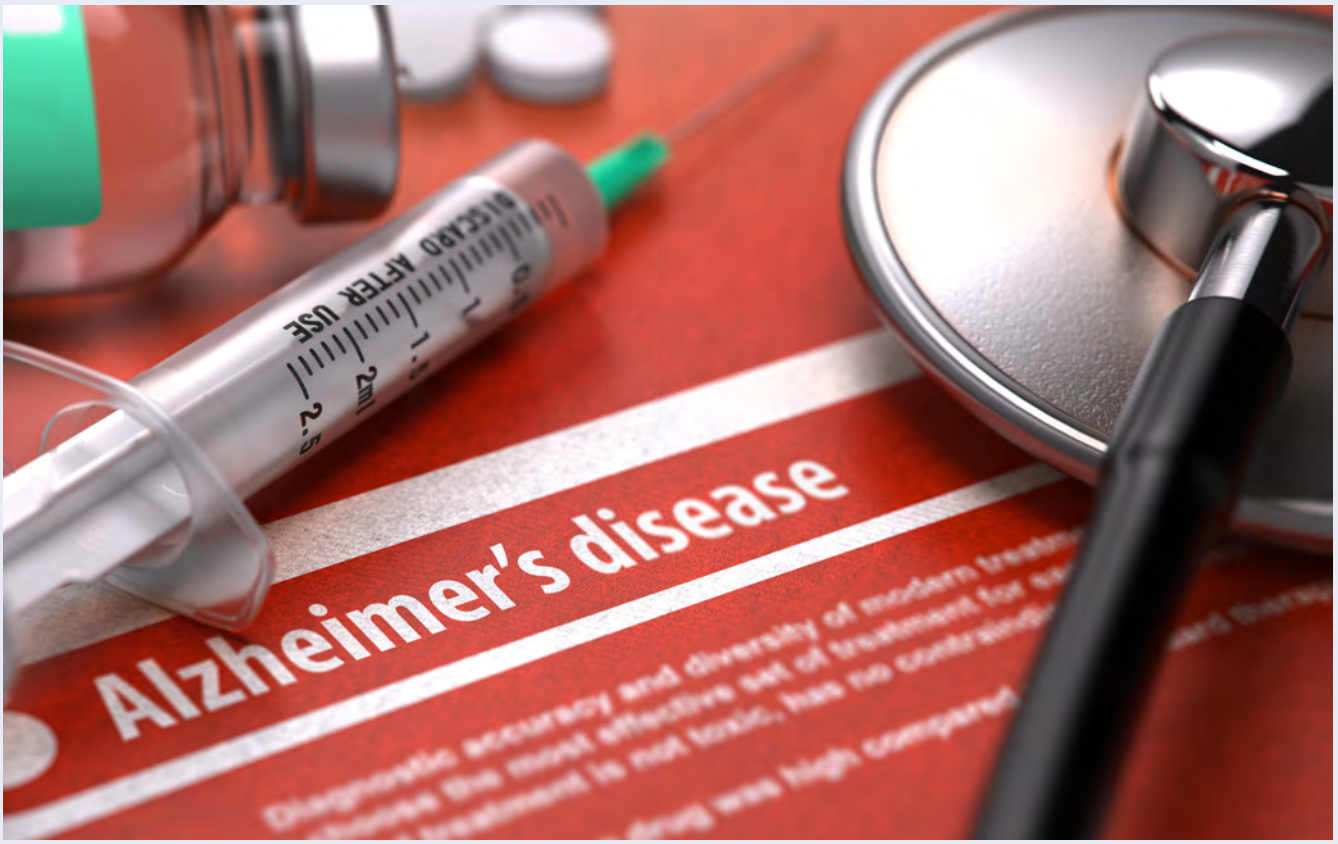
We simply must come to the realization that there are many profiles of AD. The application of precision medicine holds promise for the most effective and efficient way for us to discover and unpack the underlying neurology, genetics, and genomics of varied AD profiles. Although precision medicine solutions are often characterized as still off in the future, if we think of precision medicine in broad terms there is a component of precision medicine that is available to us now, that is, environmental factors. One environmental factor in particular, lifestyle, can fruitfully guide effective individualized treatments and interventions that straightaway could reduce our vulnerability to cognitive decline.

In the following sections I first review the idea of Alzheimer's disease as a spectrum disorder, followed by a brief discussion of the link between AD as a spectrum disorder and the promise of precision medicine. In the final section I describe several aspects of precision medicine's lifestyle components that provide immediate ways by which we can intervene to reduce vulnerability to cognitive decline, especially when considered together with new validated behavioral assays of cognitive function.

ALZHEIMER'S DISEASE AS A SPECTRUM DISORDER

While earlier criteria for diagnosing AD were based on clinical criteria alone, newer criteria for AD have been established that now include the clinical characteristics of AD as well as the pathological features of the disease. The new criteria include the use of imaging and other biomarkers to aid in diagnosis and in understanding the underlying neurologic and genetic bases for behavioral changes associated with AD. Additionally, clinical features of AD are now being supplemented with innovative behavioral assessment tools, the findings from which reinforce the idea of the spectrum of AD (mirroring in many ways the evolution of thinking that led to the establishment of autism as a spectrum disorder).

A number of studies have begun to reveal varied patterns of behavioral changes and abnormalities



in AD patients. Many of these studies point to the fact that not all patients exhibit the full range of behavioral abnormalities associated with AD, and many behavioral changes do not seem directly correlated with impairments in cognition. For example, in a study of behavioral changes in AD where the frequency and severity of ten commonly reported behaviors was assessed, it was reported that the most common behavior was apathy, exhibited by 72% of the patients, followed by agitation (60%), anxiety (48%), dysphoria (38%), and disinhibition (36%). Agitation, dysphoria, and apathy, were significantly correlated with cognitive impairment, but many other behavioral measures were not. These findings, and others, point to the idea that despite having a diagnosis of AD, individual patients can have quite different clinical/behavioral profiles, and while some behavioral changes can be linked to cognitive changes, others are not. Patterns of behavioral changes can be variable from patient to patient, even within a diagnostic category, e.g., mild, moderate or severe AD. It is in this sense that AD should be reframed as a spectrum disorder, setting the stage for the application of the relatively new field of precision medicine, one of the most promising and innovative approaches in modern medicine.

ALZHEIMER'S DISEASE AND THE PROMISE OF PRECISION MEDICINE

Precision medicine, sometimes called personalized medicine, refers to the tailoring of medical treatment to the individual characteristics of each patient. Several core components of precision medicine have been identified, including comprehensive risk assessment, tools for preclinical detection of pathophysiological processes, and interventions tailored to an individual's drivers of disease. These components, and others, speak to the potential power that precision medicine could have both in identifying specific profiles of AD, and in turn developing more effective interventions and treatments that can be targeted at specific aspects of the disease.

Considerable research is focused on understanding genetic risk associated with AD. However, it is likely that environmental factors also will be key to risk assessment and to understanding and developing the most effective interventions. For example, it is well known that traumatic head injury increases the risk for AD. There are now established protocols for treating traumatic head injury, as well as individual counseling protocols to reduce future risk

in cases of traumatic head injury, including patient management, and frequency of surveillance for preclinical AD. While treatment options can alter the course of vulnerability to AD for some individuals, it is less effective for others. Precision medicine can begin to help us understand why this is so, by uncovering how head trauma might interact with existing but undetected or latent pathophysiological processes and certain genetic dispositions that aim some individuals toward AD vulnerability. Two other core components of precision medicine, tools for preclinical detection of pathophysiological processes, and interventions tailored to an individual's drivers of disease have been viewed by many as interventions purely at the molecular level, including discoveries of a range of identified biomarkers that might correlate with behavioral changes that help define and diagnose the disease.

"ALL THE LIFESTYLE COMPONENTS DISCUSSED HERE CAN BE ENGAGED WITH RELATIVELY LOW COST. THEY ARE NON-INVASIVE AND NON-PHARMACEUTICAL, AND IN THAT REGARD THEY POSE LITTLE RISK (EXERCISE AND DIET PROGRAMS SHOULD BE UNDERTAKEN UNDER PROFESSIONAL SUPERVISION). MOREOVER, THERE IS GOOD EVIDENCE THAT, SEPARATE FROM THEIR POSSIBLE POSITIVE IMPACT ON BRAIN FUNCTION, THESE ACTIVITIES SIMPLY CAN ENHANCE QUALITY OF LIFE."

BEHAVIORAL ASSAYS

Recently, however, there has been recognition of the potential diagnostic and predictive utility of new behavioral assessment tools, because they link so directly to the most obvious defining characteristic of AD, cognitive decline. For example, I and my colleagues at Emory University developed a behavioral assay for assessing cognitive function in humans. This test was adapted from our earlier work in nonhuman primates studying the effects of damage to the hippocampus, a brain structure now understood to be important for memory function in many species, including humans. Our innovative behavioral assessment originally used an infrared eyetracking device to scan and record eye movements while subjects viewed familiar and novel pictures. More recently we have adapted standardized computer webcams to measure eye tracking, and the test can be taken on an internet-connected laptop computer from anywhere in the world and the results sent to the individual or the individual's healthcare team. Our approach has been aimed at preclinical detection of oncoming cognitive decline based on our understanding of the underlying neurology of memory function. Behavioral assays like these are fast becoming part of precision medicine approaches because of their ability of these assays to selectively target dysfunction in particular brain regions and even specific brain structures (e.g., the hippocampus, one of the brain structures first affected during the onset of AD). This kind of behavioral information will become invaluable in uncovering the relationships between behavioral symptoms in preclinical and established AD, and biomarkers, genetics, and pathophysiologic processes underlying the disease.

ALZHEIMER'S DISEASE, LIFESTYLE, AND BEHAVIORAL ASSAYS

Lifestyle can play a significant role in brain health. Moreover, making certain lifestyle choices or changes might be protective against cognitive decline, and I will briefly review some findings that support this idea.

Diet

There is good evidence that certain diets support both body and brain health. The DASH diet (Dietary Approaches to Stop Hypertension) has the goal of preventing and lowering high blood pressure, a risk factor for cognitive decline and dementia, such as AD. A key aspect is reducing salt intake in addition to determining how many calories you should eat for your age. The Mediterranean diet has a focus on heart and brain health and diabetes prevention. It is based on the idea that people living in countries bordering the Mediterranean Sea live longer and suffer less than Americans from a range of medical ailments.

More recently, the combination of these two diets referred to as the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Disease) has shown some promising evidence of positively influencing maintenance of cognitive function. The goal of this diet is to prevent Alzheimer's disease. In a recent study carried out at Rush University medical center the mind diet lowered the risk of Alzheimer's by as much as 53% in participants who adhered to the diet rigorously and by 35% and those who followed the diet moderately. While these diets all can have benefits, the findings are not definitive, and more long-term, randomized comparison studies are needed for each. My NeuroTrack colleagues are currently engaged with Martha Claire Morris, a nutritional epidemiologist at Rush University Medical Center and the developer of the MIND diet and together they are carrying out long-term observational studies assessing the relation between MIND and cognitive function.

Exercise

Research focusing on investigating the association between physical activity and healthy aging has provided clear evidence of reduced morbidity and mortality rates. More recently, the question of focus has been whether physical activity and exercise can contribute to healthy brain aging. Regular exercise increases the flow of blood and oxygen to the brain and could facilitate a cascade of positive effects, including building better connections between brain cells, promoting release of beneficial proteins and other biochemical effects, increased secretion of neuroprotective factors and brain-derived neurotrophic factors, all of which can support brain function. A review of studies on aging, exercise and cognitive function recently published in the Journal of Aging Research reported the findings from several longitudinal studies, wherein older adults that participated in physical activity showed less cognitive decline over follow up periods ranging from 2 – 10 years. The impact on cognition of physical activity also finds support in reported intervention studies where older adults who have participated in a physical activity program that produced increased cardiorespiratory fitness can show enhanced cognitive performance. Physical exercise could be a promising inexpensive and non-pharmaceutical intervention to prevent age-related cognitive decline, and a healthy lifestyle option. Nevertheless, the evidence is still limited as to whether, what kind, and how much exercise might be protective for cognitive decline. Systematic longterm studies are still needed to better understand exercise's protective impact on dementias, such as AD.

Stress

High levels of perceived chronic stress are associated with an increased risk of and amnestic mild cognitive impairment (aMCI, a possible preclinical stage of Alzheimer's disease) according to a recent aging study carried out at Albert Einstein School of Medicine and published in 2015. A perceived stress scale (PSS) was administered annually to 507 participants aged 70 and older for an average of 3.6 years. During this time 71 of the subjects (14%) we're diagnosed with aMCI. For every five-point increase in PSS score, the risk of developing aMCI increased by 30%. These findings suggest that perceived stress can be a predictor of aMCI. Because perceived stress is a modifiable risk factor it could be targeted in preventative interventions including various cognitive behavioral therapies as well as pharmacological interventions. In many ways, the same holds true for other forms of stress, including chronic pain and other causes of emotional stress. Nevertheless, despite a large body of evidence linking both daily and chronic stress to dysregulated endocrine function and to decline in cognitive function, we do not know how stressful experiences directly affect cognitive function.

Sleep

Mounting evidence points to a potential connection between sleep and cognitive function. A recent review from the University of California, San Francisco published in 2014, provided evidence from observational studies that support the roll of sleep disturbances in the development of cognitive impairment. According to the study's scientists, these findings suggest that the sleep-wake cycle plays a crucial part in brain aging pointing to a potential avenue for improvement of cognitive outcomes in people at risk of cognitive decline

and dementia. Several biological mechanisms might underlie the association between sleep and cognition but these pathways are not completely understood. Future studies that aim to clarify the association between sleep and cognition might help to identify people at risk of cognitive disorders and to facilitate the development of novel therapies to treat and potentially prevent sleep disturbances in cognitive impairment.

"LIFESTYLE CAN PLAY A SIGNIFICANT ROLE IN BRAIN HEALTH. MOREOVER, MAKING CERTAIN LIFESTYLE CHOICES OR CHANGES MIGHT BE PROTECTIVE AGAINST COGNITIVE DECLINE, AND I WILL BRIEFLY REVIEW SOME FINDINGS THAT SUPPORT THIS IDEA. "

Cognitive Training

It has been supposed popularly that cognitive training programs are readily effective as tools to maintain and even improve cognitive ability. However, the outcome effects across controlled systematic studies have been variable. Recent studies, including meta-analytic reviews published by the American Psychological Association, have pointed only to the possibility of short-term, specific training effects that do not generalize beyond improvement on the actual tests themselves. One exception to these findings has been for visuospatial memory, where limited evidence suggests that such effects might be maintained. Interestingly, visuospatial memory is one of the aspects that is currently at the forefront of the behavioral assays described in the previous section (Alzheimer's Disease and the Promise of Precision Medicine). A newly published review in a United Kingdom gaming journal in the area of gamification – using game-like features, including competition, graphics, and other game design elements – indicates that tasks that are more game-like help to engage participants and encourage behavioral change. There is evidence that a lack of participant motivation has a negative impact on the quality of data being collected, with tasks being too boring and repetitive for participant attention to be sustained. Gamified training appears to be highly engaging and does boost participant motivation, but mixed effects on task performance were reported. Nevertheless, gamified approaches appear promising, and a recent article in the Proceedings of the National Academy of Sciences suggested that future research should focus on what training regimens and what training conditions result in the best transfer effects. These findings would set the stage for systematic investigations of the underlying neural and cognitive mechanisms, and help identify which individuals could most benefit from cognitive training.

CONCLUSIONS

Reframing Alzheimer 's disease as a spectrum disorder sets the stage for applying the promising approaches and the several components associated with precision medicine. The use of behavioral assays and the focus on lifestyle and potential lifestyle changes are two powerful components of precision medicine that can be implemented immediately. We now have validated behavioral assays by which we can periodically and routinely measure an individual's cognitive status. The development of these behavioral assays provides targets for systematic investigations aimed at uncovering how these lifestyle components affect cognitive function. The lifestyle components discussed here, for the most part, can be engaged with relatively low cost and limited time commitment. They are non-invasive and non-pharmaceutical, and in that regard they pose little risk (exercise and diet programs should be undertaken under professional supervision). Moreover, there is good evidence that, separate from their possible positive impact on brain function, these activities simply can enhance quality of life.

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FUNDING KEY RESEARCH FOR ALZHEIMER'S DISEASE

Melinda Kelley from the National Institute on Aging in the US, speaks to Editor Laura Evans about raising awareness of Alzheimer's disease and how funding for research is allocated to the National Institutes of Health…

Alzheimer's disease is a global health challenge. The most common form of dementia, Alzheimer's disease, affects an estimated 46.8 million people worldwide in 2015 with that number expected to double every 20 years. In the USA alone, in 20131, 5.2 million people – aged 65 years and over – were affected by this condition. It is reported that by 2030, that figure will grow to 8.4 million and 13.8 million by 2050.

The United States' National Institute on Aging (NIA) is one of 27 institutes and centres of the National Institutes of Health (NIH). NIA is at the forefront of research activities dedicated to understanding the nature of aging, supporting the health and well-being of older adults, and extending healthy, active years of life for more people.

Adjacent Government Editor Laura Evans talks to NIA's Melinda Kelley to find out more about the work they do to support research into and raise awareness of Alzheimer's disease.

"What is really critical is the fact that the drugs currently approved to treat Alzheimer's don't really address the underlying disease's process. Most people feel like the really big goal ahead of us is developing either preventative therapies or interventions for people who are living with the disease already."

"There is a lot of information out there. We, as well as some very large Alzheimer's groups in the US and around the world, provide a lot of health information. But people may not be getting the information they need, about how important it is to go to your doctor. At the same time, we are reaching out to health care providers, providing them with assessment tools and clinical trial information. However, I do think people recognise that the disease is a critical issue for many of us personally and for society in general."

In 2012, the National Plan to address Alzheimer's disease in the US was unveiled. The Plan's main aim is to address the major challenges presented by Alzheimer's, and it outlines and tracks the various goals and activities involved – from advancing scientific collaboration to improving patient care.

"The National Plan goes beyond what we do at the NIH and the NIA," says Kelley. "It includes research, but also care and services and there are other parts of the Federal government – as well as non-governmental organisations – here in the US that help address the needs of people with Alzheimer's disease and their families."

"It's not just about the need for future successes in preventing and curing Alzheimer's, because we have lots of people who right now need supportive care and community services. The NIH funds caregiving research, but there are many parts of the Federal government that address care and support issues, and that's all part of that National Plan," Kelley explains.

"But NIH, and in particular NIA, leads the way in making sure the research gets implemented. The main research goal is prevention or intervention for Alzheimer's by year 2025 – which is coming up quickly from a research perspective. Clinical trials can take a number of years – running the trials themselves and recruiting enough people to take part take time."

The recent released, US legislatively mandated report – Stopping Alzheimer's Disease and Related Dementias: Advancing our Nations' Research Agenda – is separate from the National Plan. However, it is a US government document – a "bypass budget" – that lays out the NIH's estimates for the funding needed to implement its research plans, as Kelley explains.

"In 2011 when the initial legislation was signed by President Obama – the National Alzheimer's Project Act – it made Alzheimer's more visible and we at the NIA started to see boosts in Federal funding for Alzheimer's research."

"Initially, it was a redirection of money from the NIH Director, but by fiscal year 2014 we started to see increased Congressional appropriations – more money from the US Congress – directed to the NIA – to share across the NIH, and then we received a big increase ($350mn) in fiscal year 2016, which is the year we are in now."

"The President puts out a budget each year and Congress decides how much to give us. However, the bypass budget allows the NIH to report, through a separate professional judgement process, how much additional money it would take to reach that goal of treating or curing Alzheimer's disease by 2025," Kelley adds.

"We have now presented the second bypass budget for Alzheimer's disease [the Stopping Alzheimer's Disease and Related Dementias report referenced above]," she says. "We put out a bypass budget for future fiscal years, but if funding comes "early," then we have to accelerate the research as much as we can – this is what happened last year."

As well as research funding, the NIA within the NIH also provides a great deal of information for the public on Alzheimer's disease. It's important to raise awareness and reduce the stigma that still seems to be attached to various types of dementia, including Alzheimer's. One of the major challenges, Kelley agrees, is getting people to discuss memory problems with their doctor.

"I think people are certainly aware of Alzheimer's and know what a huge public burden it is. Everybody knows someone who has had Alzheimer's or one of the related types of dementia – there are a number of Alzheimer's-related dementias, such as frontotemporal dementia, Lewy body dementia, and vascular cognitive impairment/dementia. People know family, friends and others in their community – but there is definitely a stigma," she says.

"THE NIA, NIH, AND THE US GOVERNMENT ARE TIRELESSLY WORKING TOWARDS THEIR GOAL OF TREATING OR CURING ALZHEIMER'S BY 2025. HOWEVER, THERE ARE STILL CHALLENGES AND HURDLES AND ONE OF THE MAIN CHALLENGES IS GETTING PEOPLE TO SEE THEIR DOCTOR, SHOULD THEY HAVE MEMORY ISSUES."

"You probably heard about the actor Gene Wilder who died recently. The US press reported that he didn't want anyone to know he had Alzheimer's, so he was a recluse as the disease progressed, because he didn't want to frighten children who might have seen him in some of his roles.

"There is still a stigma attached to the disease and reducing that stigma and getting people who have memory issues to go to their doctor and talk to them is really important. Even though there is no curative treatment available at present, it's important for people to recognise what is happening," Kelley stresses. "There are also things you can do to support caregivers, to give them a break and help affected individuals and their caregivers plan for the future."

Clinical trials are key to understanding the disease further and help with early diagnosis. However, as Kelley explains, getting the numbers of volunteers required for effective clinical trials is one of the many hurdles to get over in order to reach their 2025 goal.

"The challenge of recruitment for clinical trials is looming ahead of us in order to reach that goal in 2025," she says. "It's very difficult to recruit for all clinical trials across the board and for Alzheimer's in particular; we need thousands of people screened. Most critically, we need people to join prevention trials who don't have cognitive impairment or memory issues.

"We want to see people in their 40s and 50s who might be just at the start of the process, as it is believed that the disease starts decades before you have memory problems – with the build-up of the proteins that cause the biological issues. We want to intervene right at the start, before they even visit their doctor with symptoms. We want to test the effectiveness of giving therapy to people at this very early stage of the process. Expanding the recruitment to this stage could be a challenge."

The NIA, NIH, and the US government are tirelessly working towards their goal of treating or curing Alzheimer's by 2025. However, there are still challenges and hurdles. The NIA provides a great deal of information for the public in order to wipe out the stigma and help people to tackle Alzheimer's head on (see: https://www.nia.nih.gov/alzheimers). It's about everyone involved coordinating and working together to help fill the gaps.

1 https://www.alz.org/downloads/facts_figures_2013.pdf

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“INSTEAD OF “ONE SIZE FITS ALL”, THE UNDERSTANDING AND RESEARCH DIRECTIONS OF AD COULD BENEFIT FROM CONSIDERING IT AS A SPECTRUM DISORDER.”

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