

Landscape of Early Neuropsychological Changes in AD/ADRD Webinar Series

National Institute on Aging

Division of Behavioral and Social Research

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Virtual Meetings



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Acronym Definitions

AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRD	Alzheimer's disease-related dementia
AgeCoDe	Ageing, Cognition, and Dementia in Primary Care Patient
AI	artificial intelligence
APOE	apolipoprotein E
AUC	area under the receiver operating characteristic curve
BHR	Brain Health Registry
BSR	Division of Behavioral and Social Research
CNTRACs	Cognitive Neuroscience Task Reliability and Clinical Applications
DEIA	Diversity, Equity, Inclusion, and Accessibility
DELCODE	DZNE Longitudinal Cognitive Impairment and Dementia Study
DetectCID	Detecting Cognitive Impairment Including Dementia
DRIVES	Driving Real-World In-Vehicle Evaluation System
DZNE	German Center for Neurodegenerative Diseases
EAS	Einstein Aging Study
ECog	Everyday Cognitive Scale
ESCAPE	Effects of Stress on Cognitive Aging, Physiology and Emotion
FNAME	Face-Name Associative Memory Exam
MAPP	Multicultural Alzheimer's Prevention Program
MBI-C	Mild Behavioral Impairment checklist
MCI	mild cognitive impairment
MESERO	Memory for Semantically Related Objects
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPS	neuropsychiatric symptoms
ORCA	Online Repeatable Cognitive Assessment
PD	Parkinson's disease
PLWD	people living with dementia
RiSE	Relational and Item Specific Encoding Task
SCC	subjective cognitive change
SCD	subjective cognitive decline
SDOH	social determinants of health
SOBC	Science of Behavior Change
SSD	subsyndromal symptomatic depression
TabCAT-BHA	Tablet-based Cognitive Assessment Tool-Brain Health Assessment

Meeting Summary

Landscape Webinar Series Overview

Early intervention may help prevent AD/ADRD, but there are significant limitations with early prediction of cognitive and functional decline using standard research and clinical tools. The Landscape of Early Neuropsychological Changes in AD/ADRD Project, led by the National Institute on Aging, convened 35 experts from September 2022 to April 2023 for a series of webinars to discuss gaps in measuring early changes in AD/ADRD. These webinars identified constructs and measures that characterize early changes in AD/ADRD beyond cognition alone and discussed how to advance research to develop promising measures into usable endpoints for AD/ADRD prevention trials.

Introduction to the Landscape Webinar Series

Luke Stoeckel, National Institute on Aging (NIA)

In order to test whether an intervention has a causal effect on an outcome through a target mechanism or mechanisms, we need to have valid and reliable measures at multiple levels—for example, brain and behavior—to measure changes in outcomes of interest. We also need to consider whether outcomes are meaningful and whether proximal outcomes lead to changes in distal outcomes, in this case, AD/ADRD prevention. To understand how and when cognitive and non-cognitive changes occur over the lifespan due to a particular illness or disease, several factors must be understood: normal and abnormal development, aging, and changes due to illness or disease. It is also important to measure normal and abnormal changes over the course of a day, days, weeks, and months to better understand whether there are changes due to normal processes like fluctuations in sleep quality, mood/stress, or fatigue. Changes in function are slow, subtle, and variable in early AD/ADRD. Faster detection of small changes in midlife will help improve sensitivity to detect subtle changes and enable assessment of these functions in less time, which minimizes participant and researcher burden and expands data collection opportunities. Finally, we need to develop and validate measures for use in future AD/ADRD prevention trials centered around brain health equity or the fair distribution of brain health determinants, outcomes, and resources within and between segments of the population, regardless of social standing (Rivera-Mindt, 2022). New measures, not just translations or adaptations of existing measures, may be necessary for mechanisms identification.

Dr. Stoeckel presented four questions to guide discussion during each webinar session:

1. What are gaps, barriers, opportunities, and research priorities for measurement development for the detection of early (i.e., before clinical diagnosis) neuropsychological (including non-cognitive) and functional changes related to AD/ADRD that, if addressed, will advance research to inform the design and conduct of prevention trials?
2. What are measurement (e.g., measures, methods) and infrastructure needs? What existing projects, networks, and infrastructure can be leveraged to advance this work?

3. How can this work contribute to research efforts that promote brain health equity and prioritize Diversity, Equity, Inclusion, and Accessibility (DEIA) and open science principles and practices?
4. What are promising approaches that haven't worked or have underperformed and why?

Measurement Needs in the Neuropsychological Field

Bob Bilder, University of California, Los Angeles

Many neuropsychological measurements used today are decades-old legacy measurements that rely on outdated methods. These assessments, which often reduce healthy cognition to 6 or 7 points on a scale, are unlikely to meet the contemporary research needs of neuropsychological (cognitive and non-cognitive) assessment for purposes of AD/ADRD prevention trials, which have advanced significantly since many of these measures and cognitive screening systems were developed. The implementation of updated and new tools is imperative.

The development of new neuropsychological measures is not “one size fits all.” To be integrated into precision medicine approaches, new measures must integrate an array of data types across domains of interest for the assessment of mechanisms and outcomes in AD/ADRD prevention trials. For example, researchers must capture and integrate all types of data, including genotyping data, social determinants of health (SDOH) data, information from legacy databases, and novel data streams (e.g., wearables, passive engagement tools). Beyond data types, measurements must consider differences in language, culture, and identity; must be enabled for all individuals; and must be customizable for those of various abilities. Across these complexities, researchers need evidence-based measures that can test multidimensional traits, leverage response models, optimize testing strategies through adaptation, involve differential item functioning methods, and include person-fit statistics.

Dr. Bilder emphasized several future directions for the field of neuropsychological measures:

- Build on existing measurement platforms and data infrastructures, as well as efforts to identify opportunities for large-scale data acquisition and aggregation;
- Expand focus on common data elements across disorders;
- Leverage data from electronic health records and expand research projects that aim to harmonize data types; and
- Forge new relationships to promote shared standards for digital, mobile, and electronic health initiatives.

Webinar Series Guiding Principles

Laura Germine, PhD, McLean Hospital and Harvard Medical School

Challenges to neuropsychological measurement include the need to conduct measurements at several timepoints (e.g., preclinical stages, longitudinally, and in response to treatment), limited resources for research and clinical care, and brain health disparities and equity issues (e.g., patients are not represented in evidence supporting the use of a measure or cannot access care

where this measure is employed). To address these challenges, the Webinar Series Leadership Team outlined four guiding principles for its discussions: (1) Open; (2) Accessible; (3) Inclusive; and (4) Integrated. Dr. Germine posed questions to guide considerations related to openness, accessibility, inclusivity, and integrability of neuropsychological measurements:

- Is this method implemented in a way that is open and will enable transparency and facilitate dissemination of methods, algorithms, and results?
- Does this method permit integration across studies, levels, and modalities?
- What individuals and communities have access to this method?
- What communities have access limitations to this method because of cost, expertise, infrastructure, or generalizability?
- What steps are being taken to ensure that development or application of this method includes those impacted by AD/ADRD and would most benefit from advances in diagnosis and treatment?

Webinar 1 (November 29, 2022): Assessment of Neuropsychological Change Across the Lifespan

Measuring Cognitive Function to Understand AD: Lessons from the Cognitive Neuroscience Task Reliability and Clinical Applications Consortium Study

Deanna Barch, Washington University in St. Louis

Tools and constructs used in clinical neuropsychology are often well-developed and validated. However, these assessments are often disconnected from cognitive neuroscience and animal model studies, lack clear psychometric support or construct validity across the lifespan, and do not clarify non-cognitive mechanisms (e.g., emotion processing, motivation). To overcome these challenges, researchers have sought to leverage tools from the field of cognitive and affective neuroscience, which can measure deficits in discrete cognitive systems, including the domains of reward, motivation, emotion, and social functions. However, the test-retest reliability and psychometrics for these tools across the lifespan are not well understood.

Dr. Barch leveraged data from the Cognitive Neuroscience Task Reliability and Clinical Applications (CNTRACs) consortium to assess the Relational and Item Specific Encoding Task (RiSE). They found that this task, which requires that participants recognize and make specific decisions based on presented images, can distinguish between healthy participants and those living with schizophrenia. Assessing tasks that engage with different features of memory in clinical populations is critical because the results can highlight how a task can interrogate specific neural systems and forms of memory in the context of disease, which may differ from memory performance outside the disease context. It is also important to characterize within-person and within-disease change and heterogeneity. Some tasks have been developed to optimize distinguishing group-level differences, but task design and performance considerations may differ if the goal is assessment of within-person and within-disease assessment.

Research Priorities for Assessments of Neuropsychological Changes Across the Lifespan

Chandra Reynolds, University of California, Riverside

Dr. Reynolds presented research priorities in the field of neuropsychological assessments across the lifespan. These priorities include (1) the use of models to understand a study participant's peak performance for a specific cognitive task or outcome; (2) the need to understand the relationship between childhood, adolescent, and adult cognitive reserves (research suggests that increased early life cognitive abilities are associated with better memory and executive functioning during midlife, indicating that early life reserves may improve later outcomes; (3) the importance of evaluating measures of consistency and dispersion across the lifespan to assess how task performance changes over time; and (4) the need to obtain cognitive neuroscience samples and enroll study participants from diverse populations. In addition, the field needs to prioritize the understanding of genetic contributions to AD risk across the lifespan. Dr. Reynolds and her team identified that DNA methylation effects may play a major role in aging-related pathways related to AD, suggesting the need for additional studies on methylation across the lifespan.

Improving Early Detection of Cognitive Decline in AD

Yakeel Quiroz, Massachusetts General Hospital and Harvard Medical School

Clinical trials of therapeutics that aim to prevent AD progression are complicated by the difficulties of identifying individuals who have not yet begun to exhibit AD symptoms and pathology. To improve preclinical detection of AD, researchers must identify subtle changes in cognitive tests or biomarker measures that reliably predict progression to AD.

To achieve this goal, Dr. Quiroz and her team are studying a family cohort from Colombia with early-onset AD. Family members exhibit characteristic amyloid pathology as early as 28 years old and tau pathology by their late 30s and are diagnosed with mild cognitive impairment (MCI) by 44 years old and AD by 49 years old on average. This family carries mutations in PSEN1, which is predictive of early-onset AD. Dr. Quiroz and her team have developed the Face-Name Associative Memory Exam (FNAME), which can distinguish between cognitively normal PSEN1 carriers and symptomatic PSEN1 carriers. Additional studies using FNAME have revealed that study participants with lower task performance have higher levels of amyloid and tau pathology compared to those with higher FNAME performance. Dr. Quiroz and her team also developed the Memory for Semantically Related Objects (MESERO) task, which can distinguish AD gene-carriers with and without symptoms, and the Multicultural Alzheimer's Prevention Program (MAPP) remote platform, which monitors several cognitive outcomes over time.

Discussion

Preclinical Identification

Identifying individuals in preclinical stages of AD would greatly benefit the ability to enroll such individuals in clinical trials. Many clinical trials and studies of AD enroll only individuals who are 65 years old or older, which prevents researchers from capturing earlier clinical changes.

Diverse Populations and Culturally Relevant Assessments

Studies of neuropsychological assessments must be conducted in diverse populations to assess and adjust for the impact of racial or ethnic identity on the performance of those tools. For example, culturally relevant factors, including language, can influence how individuals perform during assessments. Without assessing tests in diverse populations, researchers may not be aware of factors hindering their ability to take such tests or be included in studies. SDOH should also be considered in each study that evaluates a neuropsychological assessment.

Ecological Validity

Studies of AD must be designed with more ecological validity. Assessing individuals in their everyday environments through passive monitoring mechanisms would be a breakthrough for the AD research community.

Webinar 2 (December 13, 2022): Subjective Cognitive Change

Subjective Cognitive Decline and Reporting

Rebecca Amariglio, Harvard Medical School and Brigham and Women's Hospital

Subjective cognitive decline (SCD) is defined as self-experienced cognitive decline prior to cognitive impairment. Self-reported complaints and concerns that peak during preclinical and MCI stages typically wane as subjects progress towards AD and become less aware of their cognitive deficits. A study partner is an individual that knows the study participant well and participates in the clinical trial by providing additional subjective reports on concerns that typically begin during preclinical stages and continue to increase as the participant's cognitive decline progresses. Subjective reports from both patients and their study partners can also be used during the clinical study screening process to help enrich a clinical trial study population for individuals most likely to progress to AD or that have a particular biomarker status.

Subjective Cognitive Decline and Stage 2 of AD

Frank Jessen, University of Cologne and German Center for Neurodegenerative Diseases

SCD is the self-experienced persistent decline in cognitive capacity; however, Ageing, Cognition, and Dementia in Primary Care Patient (AgeCoDe) study participants have exhibited objective performance declines in certain cognitive tasks, including word fluency and the Mini-Mental State Examination (MMSE), even before experiencing SCD. Dr. Jessen and his team conduct the German Center for Neurodegenerative Diseases (DZNE)-Longitudinal Cognitive Impairment and Dementia Study (DELCODE), which focuses on the correlation of SCD with AD biomarkers. They enroll individuals with SCD onset in the past 5 years, concerns or worries related to SCD, and confirmation of cognitive decline by an observer. Dr. Jessen and his team then modeled the 5-year cognitive trajectories of participants diagnosed with preclinical or early stages of AD. Importantly, the only group of participants to significantly decline within the next 5 years were amyloid-positive individuals with SCD (compared to amyloid-negative individuals with SCD or controls, regardless of amyloid status). Overall, Dr. Jessen's investigations using DELCODE have

shown that for AD, SCD often indicates the first stage of objective cognitive decline, and SCD together with mild objective cognitive decline indicates stage 2 on the AD continuum.

Role of Dyadic (Participant and Study Partner) Subjective Measures

Rachel Nosheny, University of California, San Francisco, and San Francisco Veteran's Administration Medical Center

Dyadic subjective measures (i.e., measures collected from both a study participant and their study partner) are often used in clinical trials, particularly for screening. Major advantages of dyadic measures include the efficient capture of past cognitive changes, unique insight into outcomes important to patients and their families, and portability and adaptability. One dyadic measure used often in research studies is the Everyday Cognition Scale (ECog), which has been used to evaluate the cohorts with clinical diagnoses in the Brain Health Registry (BHR) and the AD Neuroimaging Initiative (ADNI). Within the ADNI population, Dr. Nosheny and her team found that dyadic ECog scores are associated with cognitive decline and progression to AD. Within the BHR, remotely collected measures, including dyadic subjective measures, could be used to distinguish control individuals from those with MCI, as well as individuals that were amyloid-positive from those that were amyloid-negative. Higher ECog scores reported by patients or their study partners were associated with an increased likelihood of an MCI diagnosis. However, the association between patient- and study partner–reported ECog score is weaker for amyloid-positive patients with MCI because patients often underreport their symptoms; observations such as this may help to identify timepoints when researchers should more heavily rely on the study partner reports. High-priority directions for SCD research include defining the dynamic relationship between patient and study partner reporting across the AD continuum, identifying factors that influence dyadic subjective reports, characterizing SCD in diverse populations, and developing and testing best practices for study partner engagement and incorporation of dyadic measures into clinical trials.

Comparing Individuals with Subjective Cognitive Change and MCI on Daily Experiences of Cognitive Problems

Jacqueline Mogle, Clemson University

Dr. Mogle and her team have focused on assessing how daily experiences of cognitive problems can inform subjective cognitive change (SCC). They created the Daily Memory Lapse Checklist to obtain self-reported information on the frequency of both prospective (e.g., forgot to start a task) and retrospective (e.g., forgot a word during a conversation) memory lapses and have deployed this checklist in several studies, including the Effects of Stress on Cognitive Aging, Physiology and Emotion (ESCAPE) study, which focuses on individuals aged 25–65, and Einstein Aging Study (EAS), which focuses on individuals 70 years old and older. Across both studies, daily diary entries showed that ESCAPE participants (i.e., younger adults) experienced memory lapses on 20–30 percent of study days and EAS participants (i.e., older adults) experienced memory lapses on 30–40 percent of study days. Younger adults typically reported more memory lapses related to chores and appointments (i.e., specific prospective memory lapses), whereas older adults reported more retrospective memory lapses (e.g., related to word choices

or names). As expected, when assessing specific phenotypes, participants with MCI reported the greatest frequency of memory lapses, whereas control individuals reported the least and those with SCD reported an intermediate number of lapses. However, MCI and SCD participants reported similar levels of prospective lapses related to completing tasks, and SCD participants reported higher levels of “other” retrospective lapses (i.e., they knew they were forgetting something but could not determine the task), compared to MCI participants. In addition, EAS participants that were followed longitudinally displayed an increase in memory lapse complaints over time, compared to their reports at baseline.

Discussion

Outcome Considerations

Speakers emphasized that certain self-reported outcomes are reliable, particularly those that require the patient to compare their cognitive performance to others. However, even though task performance can be less reliable as cognitive decline progresses, outcomes related to consistency in assessment performance are helpful in monitoring a patient’s trajectory.

Worry and Personality

Self-reported measures of worry may predict cognitive decline and increased likelihood of amyloid-positivity. Speakers hypothesized that higher levels of worry indicate a faster rate of decline. However, levels of worry may also be related to other personality traits and conditions, such as neuroticism and depression, and thus mechanisms underlying worry would need to be disentangled to develop a valid self-reported measure of worry.

ECog

More research is needed to determine how individual ECog items differ between self- and study partner-reported SCD, and how assessment performance may be impacted by demographic factors and SDOH.

SCD Assessments as Outcomes Measures

Participants noted that SCD assessments can be difficult to compare across studies because many studies use very different assessments, which are necessarily tailored to their patient populations’ conditions and study objectives. Measures of SCD can also be difficult to use as clinical trial outcomes because, in the case of AD, patients will become less aware of their condition as the trial progresses and thus the reliability of self-reports declines. Participants emphasized that if measures of SCD are included in clinical trials, these measures must be clinically meaningful to patients.

Webinar 3 (January 17, 2023): Digital Phenotyping and Measures

Digital Technologies: Present and Future

Rhoda Au, Boston University

Digital technologies are being rapidly integrated into research studies. Most biomedical studies have incorporated digital phenotyping technologies, but the need to translate and validate

these data into digital biomarkers remains a common priority within the AD research community. To create effective digital biomarkers, the AD field must identify methods to collect meaningful information passively, with minimal burden on study participants. Dr. Au recommends that the digital biomarker field follow the precedent set by blood-based biomarkers. Many studies began collecting and storing blood samples long-term before biomarkers were commonly used; that storage of blood samples over time enabled the robust analysis of biomarkers when they began to emerge. Similarly, studies should collect digital data in its raw native format and store it for later use when digital biomarkers are established and validated. For example, Dr. Au and her team have worked with the Framingham Heart Study to collect digital voice recordings from participants since 2005, but only recently began to publish on voice-related markers. Dr. Au and her team have also developed a digital protocol with the Davos Alzheimer's Collaborative that uses smartphones and tablets to perform cognitive assessments. This protocol is being deployed successfully across the globe, likely in part because of the widespread use of the smartphone. Dr. Au emphasized that accelerating digital technologies requires the invention of new strategies, such as a digital writing tool to assess handwriting changes over time, eye-tracking sensors in smartphones, or passive engagement technologies that leverage embedded sensors to collect multi-modal data on a more continuous basis but do not require active participation from the subject. Current study design, harmonization, and analysis standards (i.e., norms) may not fit and should not be made to fit the needs of digital studies. Thus, new approaches to study design, harmonization, and analysis are needed.

Measuring Learning and Decay with High-Frequency Assessments

Jason Hassenstab, Washington University in St. Louis

Using smartphone-based cognitive assessments, researchers can feasibly collect repeated measures over time without high participant burden. These assessments are critical in AD and ADRD research because repeated, or “burst,” measures can help interrogate memory and learning changes over extended periods. Dr. Yen Ying Lim (Monash University) developed a smartphone-based statistical learning paradigm called the Online Repeatable Cognitive Assessment (ORCA), which teaches participants to match Chinese characters with English translations. Dr. Hassenstab worked with Dr. Lim to develop a shorter version of the original ORCA protocol—Mobile ORCA—that includes six, 2-minute sessions over 2 days, compared to 25 minutes per day for 6 days. Testing revealed that the shorter test performed similarly to the original version. Participants given the same characters over two testing days performed better the second day (more than 80 percent correct, compared to 70 percent), whereas those given a new set of characters performed similarly both days. These results indicate that the Mobile ORCA can be used to assess learning over time.

Dr. Hassenstab and his team also focus on assessing long-term forgetting (i.e., recall after 7 days), which is an outcome that is able to distinguish between AD mutation carriers and non-carriers. Dr. Hassenstab and his team have evaluated remote word recall and card matching tasks in a volunteer control population and found that these tasks accurately capture initial

learning and long-term forgetting outcomes. The next step for this project is to evaluate the remote tasks in an AD patient population.

From Wearables to Invisibles

Dina Katabi, Massachusetts Institute of Technology and Emerald Innovations, Inc.

A central principle underlying the importance of digital technologies is the reduction of burden on study participants. Dr. Katabi and her team aim to assess whether digital technologies can be developed that require zero active engagement from participants and instead capture all necessary data passively. Dr. Katabi and her team have developed the Emerald sensor, which assesses sleep, mobility, interpersonal interactions, vital signs, and other activities passively, using radio signals that are analyzed by artificial intelligence (AI) methods and compared to gold-standard technologies. For example, the Emerald sensor can track an individual's movements, even if the individual is in another room, with 98 percent accuracy, compared to Vicon motion capture devices. Mobility tracking can help determine whether an individual is experiencing agitation, a known symptom in AD, by measuring pacing behavior; in one case, data collected using this device was provided to a patient's doctor, allowing the patient to be placed on a new medication that alleviated agitation.

The Emerald sensor can also evaluate parameters, including brain waves and breathing patterns during sleep, relevant to neurological disorders. Because Parkinson's disease (PD) is associated with sleep disorders, Dr. Katabi and her team evaluated whether the Emerald sensor could identify individuals with PD based on nocturnal breathing patterns. In a study of more than 7,000 participants, Dr. Katabi's team was able to distinguish PD patients from control participants with 90 percent accuracy. In addition, they used the sensor and its internal AI methodology to analyze data collected from a longitudinal sleep study and found that the sensor could accurately predict which individuals would eventually develop PD over 6 years, compared to those that would not.

Discussion

Raw Digital Data

Best practices for collecting digital data include storing these data in raw formats. Raw data can be used in numerous analyses, whereas processed data is more limited in its downstream uses. Thus, to ensure that data collected can be used for currently unknown future projects, the storage of raw digital data is a major priority.

Smartphone Eye-Tracking

Eye-tracking assessments can be conducted using smartphones, but may be more cumbersome to perform (e.g., lighting requirements and daily calibrations).

Sensor Specificity and Scalability

Dr. Katabi confirmed that sensors, such as the Emerald sensor, can use machine learning classifiers to accurately distinguish specific individuals in a group setting, such as a nursing home. The Emerald sensor has been tested primarily for in-home use, but many of these

sensors likely will have the ability to be scaled up for use in larger populations and settings after further development.

Clinical Meaningfulness

In clinical practice, digital data from multiple devices and assessments likely will need to be combined in order to obtain a clinically meaningful signal that can be used by physicians to determine treatment choices or diagnoses. Data from isolated devices and assessments likely will be insufficient, but the combination of data across multiple cognitive assessments and devices will provide the information needed to facilitate clinically meaningful decision-making.

Barriers to Digital Development

One of the primary barriers to digital tool and biomarker development is the peer-review process, which is based on comparing new and innovative data and strategies to those that are currently possible and available. Digital tool development requires some paradigm-shifting, particularly in the peer-review process, because many of these tools are not comparable to those developed or tested previously, and thus new review processes are needed.

Webinar 4 (March 28, 2023): Neuropsychiatric Symptoms, Behaviors, and Socioemotional Function

Mild Behavioral Impairment and Neuropsychiatric Symptoms

Yonas Geda, Barrow Neurological Institute

The Mild Behavioral Impairment checklist (MBI-C) can measure how neuropsychiatric symptoms (NPS)—including apathy, depression, anxiety, and hallucination—lead to AD/ADRD. The MBI-C is a rating scale for NPS in pre-dementia populations consisting of five domains: (1) interest, motivation, and drive; (2) mood or anxiety; (3) gratification delay and impulse control; (4) comportment and empathy; and (5) strongly held beliefs and sensory experiences. Scores on this scale suggest that NPS increases risk for MCI while physical activity, particularly less intense activity, decreased the risk. Dr. Geda presented four potential mechanisms linking NPS with MCI and dementia: (1) an etiologic pathway that involves NPS triggering MCI onset; (2) a shared risk factor such as amyloid deposition; (3) a reverse causality, indicating neuropathological changes leading to MCI and then NPS; and (4) an interaction between NPS and amyloid deposition that accelerates development of MCI.

Precision Phenotyping of Mild Behavioral Impairment and the Early Detection of Dementia

Ipsit Vahia, McLean Hospital and Harvard Medical School

Depression occurring in later life has a greater association with AD onset than depression present in earlier life. Dr. Vahia's research focuses on precision phenotyping of MBI in later life, particularly for subsyndromal symptomatic depression (SSD). SSD does not meet accepted criteria for major depression, is three to five times more common in older adults than younger adults, and can strongly impair behavior and quality of life. Chronic and recurring SSD leads to

an elevated risk of dementia, and this risk begins to emerge 11 years before diagnosis, with more than nine times higher incidence during the year of diagnosis. In one study, more than 59 percent of 1,998 participants developed NPS before MCI, including 30 percent of those participants who developed AD. Irritability was found to be the most prevalent NPS domain, followed by depression, insomnia, and anxiety. Dr. Vahia noted that MBI is distinct from depression. Using the Emerald sensor, his group evaluated parameters relevant to SSD, including the stereotyped locomotor activity patterns for pacing, apathy, and behavioral disturbance. These measurements can offer a guide for clinicians to appropriately adjust pharmacotherapy and behavioral activation approaches.

Changes in Emotions and Behavior in AD/ADRD

Virginia Sturm, University of California, San Francisco

Emotions are short-lived phenomena that underlie affective symptoms, which may be altered in individuals with AD/ADRD. Psychologically, emotions alter attention, shift certain behaviors, and engage memory networks; physiologically, emotions rapidly organize the responses of disparate biological systems including facial expression, voice, and autonomic activity. The generation and experience of an emotion activates multiple brain regions in the salience network, which can be monitored by neural brain imaging technologies such as MRI. MRI analyses have demonstrated lower brain volume and functional connectivity in individuals with behavioral frontotemporal dementia, and an increased connectivity in individuals with AD. Dr. Sturm's team quantifies emotion and behavior in AD/ADRD by (1) monitoring the autonomic nervous system (e.g., heart rate, respiration rate); (2) coding facial behavior (e.g., facial muscle action units, facial expression); and (3) documenting subjective experience, including responses to questionnaires (e.g., what emotion did you feel most strongly while watching the film?). This data collection involves several methodological challenges for which solutions are needed. Monitoring the autonomic nervous system requires updated measures and faster data processing innovations. Facial behavior coding similarly requires more precise automatic systems to replace slow manual processes. Remote assessment tools must be developed and refined to overcome the limited ability of laboratory-based assessments to study large and diverse samples in the real world.

Discussion

Collaborative Opportunities

Clinical diagnosis of NPS associated with AD/ADRD is challenging because emotions are difficult to quantify. Participants suggested enhancing collaborations between clinicians and researchers by leveraging their collective expertise in the neuropsychology field.

Embracing New Technologies

The neuropsychology field has been slow to adopt recent advances in technology for clinical diagnosis and care because clinical neuropsychologists rely on traditional assessments (e.g., questionnaires, checklists). Participants noted the importance of balancing these assessments with new digital data collection tools. Additional work is required to evaluate and validate these new digital data collection tools against traditional assessments.

Biomarkers Workshop

Recent discoveries have led to the identification of key imaging and blood-based biomarkers (e.g., amyloid, p-tau, NFL) for diagnosing, predicting, and monitoring AD/ADRD. Participants recommended planning a workshop that focuses on biomarkers for AD/ADRD, as well as their potential connections with NPS for MBI.

Webinar 5 (March 28, 2023): Clinical and Real-World Measures

Advancing Approaches for the Early Detection and Diagnosis of Cognitive Impairment in Everyday Clinical Settings

Kate Possin, University of California, San Francisco

More than 50 percent of people living with dementia (PLWD) are not diagnosed, and those with MCI are even less likely to receive a diagnosis. Dr. Possin is part of Detecting Cognitive Impairment Including Dementia (DetectCID), a consortium that aims to improve these detection rates. To meet this goal, the consortium has developed and evaluated the Tablet-based Cognitive Assessment Tool-Brain Health Assessment (TabCAT-BHA), which is performed by providers after a concern is raised by the patient, relative, or care partner. Compared to the written Montreal Cognitive Assessment (MoCA), the digital TabCAT-BHA can more accurately distinguish amyloid-positive and amyloid-negative individuals. Thus far, DetectCID has found that effective detection paradigms must (1) engage providers as partners; (2) be easy to access via electronic health records; (3) address the needs of an increasingly diverse older adult population; (4) be flexible to include care partners; and (5) link diagnosis to improved care.

Compared to non-Hispanic White individuals, Hispanic, Black, and Asian individuals are significantly less likely to be diagnosed with dementia or MCI. To improve care for underrepresented populations, Dr. Possin emphasized the need for more data and algorithms to develop new approaches and for the continued development and validation of culturally and linguistically appropriate assessments. Machine learning and algorithmic approaches can help identify unflagged patients at risk and inform future precise diagnostic procedures.

Real-World Measures of Cognition

Lauren Nicholas, University of Colorado

Cognitive impairment impacts many aspects of everyday life, including finances (e.g., forgetting to pay a bill, or spending impetuously). By analyzing consumer credit reports, Dr. Nicholas and her team found that PLWD have a unique financial presentation. Approximately 6 years prior to the first clinical manifestation of dementia, individuals who eventually developed dementia were more likely to miss a bill payment or develop a subprime credit score. This financial phenotype is not seen in individuals with other conditions, such as arthritis and glaucoma. Linking such measures of daily life to diagnoses and clinical outcomes requires access to multiple data sources, including claims, actigraphy, autopsy, cognitive assessment, and biomarker data.

Strengths of real-world measures include that these measures typically have lower cost and lower burden than regular data collection, can help identify solutions outside of traditional health care, and can clarify how dementia impacts daily activities. Challenges to these measures include that (1) certain measures pose privacy concerns; (2) pertinent information is often found in disparate datasets; (3) prospective measures can become obsolete; and (4) the automation of everyday life (e.g., automatic payments) can mask everyday impacts. Overall, however, implementing real-world measures into study designs may help predict or detect cognitive impairments earlier than clinical measures.

Driving Real-World In-Vehicle Evaluation System

Ganesh M. Babulal, Washington University School of Medicine in St. Louis

Digital real-world measures enable the longitudinal and continuous evaluation of individuals in their everyday environments. These measures hold promise for personalizing baseline reference standards that can help assess the onset of disease and impact of interventions. For example, Dr. Babulal and his team assessed the driving performance of cognitively normal individuals and found that amyloid-positive drivers were more likely to fail a road test faster and make 2.5 more errors than an amyloid-negative individual. To further interrogate contextually meaningful driving behavior, Dr. Babulal and his team developed the Driving Real-World In-Vehicle Evaluation System (DRIVES) tool, which can be incorporated into a vehicle to continuously collect data on driving behavior, such as speeding, braking, destinations visited, and number of trips made from home. Analyses using this tool found that individuals with preclinical AD drive less frequently, particularly at night, and were less prone to adverse driving behavior (e.g., speeding), compared to controls; these results indicate that in early AD stages, individuals are aware of their neuropsychological limitations and engage in self-regulation (i.e., driving less and more carefully). In addition, a model composed of data related to driving alone, age, and APOE $\epsilon 4$ status could accurately predict (AUC=0.96) whether an individual was likely to develop AD based on CSF biomarkers. Analyses also showed that as the level of amyloid-positivity increases, the risk of adverse driving behaviors (speeding, hard breaking, accelerating) also increases, indicating that individuals become less able to self-regulate as AD progresses. Further, individuals with poor attentional control at baseline were found to exhibit faster decline of driving performance than those with higher attentional control. Dr. Babulal has also found that driving behaviors can be significantly impacted by sleep behavior, with sleep apnea increasing the odds of engaging in dangerous driving behaviors, such as speeding, braking hard, or accelerating suddenly.

Discussion

Diagnosis and Detection in Primary Care

Participants discussed the likely reasons underlying the underdiagnosis of dementia. Primary care physicians are often tasked with addressing a vast range of different conditions and diseases. Providers wish they had more training for some of these. Incorporating assessments and measures derived from non-traditional health care data, such as driving and credit information, may help improve detection and diagnosis within primary care settings.

Linkages of Datasets and Privacy

Linking data that have not previously been deeply associated with health care, including driving data and credit reports, to traditional health care data can provide a more complete and comprehensive view of an individual's everyday life and health. This potential motivates contemporary research interest in open science and releasing data to the broader scientific community. However, the openness of data and the combination of multiple sensitive data types poses significant privacy concerns that require a thoughtful approach. Participants suggested engaging with bioethics experts, patients, and industry to hear their perspectives and allow those thoughts to inform practice.

Self-Regulation

Participants noted that Dr. Babulal's presentation revealed that individuals with AD are less likely to drive at night. This finding suggests that as individuals become more cognitively impaired, they may begin to self-regulate, leading to less driving during not only evenings but also during inclement weather. As individuals progress toward AD, however, the ability to self-regulate diminishes and individuals begin to make more errors, including adverse driving events that result in a higher crash risk.

Moving Real-World Data to the Clinic

The goal of using real-world data in the context of dementia is to provide physicians with a readout that informs next steps for patient care. Ideally, a device such as DRIVES can provide physicians with a determination related to the likelihood of cognitive impairment, which can enable the physician to perform additional tests to confirm diagnoses and next steps. Without the implementation of real-world data, such a diagnosis may go undetected. In addition to detection, real-world data can also be used to monitor individuals' progression and well-being over time, enabling physicians to review these data to determine whether care strategies need to be updated or altered based on changes in behavior.

Health Inequities and Structural Challenges

The biomedical health care field is fraught with health inequities and structural barriers to care. The field needs to rethink the role that digital data can play in fostering an open, accessible, and inclusive approach to dementia to improve health care for the entire dementia patient population. For example, not all patients drive or handle finances, which would lead DRIVES and credit reports to be ineffective in informing care for these individuals. Thus, researchers must identify inclusive and alternative sources of real-world data that can be informative for the entire patient population.

Webinar 6 (May 3, 2023): General Discussion

Introduction

Luke Stoeckel, NIA, and Maiya Geddes, McGill University

In order to address the many challenges canvassed during the webinar series, the field needs to conduct more mechanism-focused research. Only approximately 11 percent of prevention trials propose a specific mechanism. Dr. Geddes presented on two frameworks that address target

mechanisms: the Science of Behavior Change (SOBC) conceptual framework aims to help identify measurable and malleable target mechanisms across different environments and outcomes, and the Operating Conditions framework helps identify moderators of target mechanisms to determine the conditions under which a specific intervention will be effective.

Review of Webinars and Outcomes

Webinar 1: Assessment of Neuropsychological Change Across the Lifespan

Maiya Geddes, McGill University

During this webinar, speakers presented on their work related to cognitive assessments (including the MESERO and FNAME) and research programs focused on detection (e.g., MAPP Remote, CNTRACs). Speakers and discussants identified a need to expand the current notion of cognitive measurement to capture outcomes specific to social cognition, emotional processing, reward/motivation, effort mobilization, and decision-making. In addition, most studies on cognitive assessments to date have been completed in non-representative populations, and thus studies with representative populations are imperative. This webinar resulted in four action items for the AD/ADRD and neuropsychological assessment fields (shown below).

- Invest in culturally, linguistically, and sociodemographically diverse longitudinal samples that begin earlier in the lifespan, capture comorbidities, and integrate neurobiological and behavioral markers (e.g., AD biomarkers, SDOH, mobile sensors, emotional, behavioral, and clinical outcomes, genetics).
- Identify strategies to harmonize cognitive measures across studies (e.g., by applying qualitative/global measures and innovative psychometric approaches).
- Expand native measurement beyond “cold cognitive” functioning to capture social cognition, emotional processing, reward/motivation, effort mobilization, and decision-making.
- Validate innovative approaches to track intra-individual change across a range of timescales.

Webinar 2: Subjective Cognitive Change

Laura Germine, McLean Hospital and Harvard Medical School

This webinar focused on SCC and SCD and how to correlate those constructs with AD risk. Subjective reports from patients and care partners can vary along the AD continuum; as the patient’s disease progresses, their self-reports can become less reliable, and thus reports from family members and care partners are increasingly valuable. Speakers and discussants in this webinar identified the need for more research to determine how to incorporate SCC/SCD in AD prevention trials (possibly in combination with biomarkers), how to engage study partners to improve the use of dyadic measures, and how to better understand variations in SCC/SCD in different populations.

Dr. Germine outlined several action items resulting from this webinar (shown below).

- Compare measures of SCC/SCD (e.g., everyday, dyadic, brief) for association with biomarkers, objective performance, and AD progression.
- Identify factors that influence SCC/SCD measurement across communities.
- Develop best practices for participant engagement.

Webinar 3: Digital Phenotyping and Measures

Bob Bilder, University of California, Los Angeles

During this webinar, speakers and discussants focused on the current and future potential for digital technologies in the assessment of early cognitive changes in AD/ADRD. Speakers summarized findings associated with the Emerald AI device, which can accurately monitor breathing, sleep, interpersonal interactions, mobility, and behavioral symptoms, and the ORCA, which assesses learning. Speakers and discussants emphasized the need to shift toward tools that enable passive engagement of subjects. More research is needed to assess the value proposition for patients to use digital technologies and generate validity data to promote widespread use. Dr. Bilder presented key action items that resulted from this webinar (shown below).

- Conduct community-partnered participatory research, including user interface and user experience projects.
- Adopt privacy and safety standards, as well as clear data use agreements.
- Develop standards for validation, including outcome definitions and probabilistic thresholds.

Webinar 4: Neuropsychiatric Symptoms, Behaviors, and Socioemotional Function

Maiya Geddes, McGill University

This webinar focused on the assessment of NPS, behaviors, and socioemotional function in relation to AD/ADRD. Key questions raised during this webinar included (1) how to distinguish NPS that are *psychological* reactions from disrupted affect regulation driven by pathology; (2) what role anosognosia plays in this area; (3) how to deconstruct symptoms into dimensional constructs in order to map onto neurobiological systems and identify therapeutic targets; and (4) how to optimally track intraindividual change over time in emotion and behavior. Dr. Geddes presented three action items that resulted from this webinar (shown below).

- Apply a multidisciplinary approach combining psychometric expertise, computational methods, and repeated measurement of affect/behavior in longitudinal preclinical cohorts.
- Develop new methods and digital measures for automation, remote assessment, innovation in data processing, and comparability over time.
- Plan a workshop focused on objective physiologic and behavioral biomarkers of NPS.

Webinar 5: Clinical and Real-World Measures

Maiya Geddes, McGill University; Lisa Barnes, Rush University; and Kate Possin, University of California, San Francisco

This webinar focused on ecologically valid, real-world measures to assess behavior and detect cognitive change, as well as other indicators of AD/ADRD pathology. Speakers and discussants emphasized the importance of linking real-world data (e.g., claims data, consumer credit data), cognitive assessments, and blood-based biomarker data to inform clinically meaningful changes in health care. They also noted challenges in linking these data related to privacy and permissions, as well as challenges related to obtaining critical data from disparate datasets. Key questions that arose from this webinar include:

- What are the most promising clinical and real-world measures, and how do they help detect clinically meaningful outcomes?
- How will the field develop universal platforms for integrating data streams and improve electronic medical record intra- and interoperability?
- How can the field balance benefits to the individual, family, and society with personal privacy and autonomy?

Dr. Bilder presented three key action items that resulted from this webinar (shown below).

- Compare different novel measures related to AD onset and biomarkers.
- Create new architecture for health data aggregation.
- Develop regulations, guidelines, and shared policies.

General Discussion

Participants engaged in moderated discussions, which are summarized in the themed sections below.

Harmonization

The AD/ADRD field needs to identify strategies to harmonize datasets in order to conduct well-powered mechanisms research. One major challenge to harmonization is that many studies do not collect item-level data—a requirement for harmonization—because the process is expensive. In addition to collecting item-level data, studies should also collect demographic and SDOH data to improve abilities to harmonize across those parameters.

Diversity and Engagement

Assessing cognitive measures in representative patient populations over time is critical to improving the well-being of everyone affected by a condition. Participants emphasized the importance of collecting longitudinal data from underrepresented populations to evaluate how commonly used assessments function and can be broadly used. They recommended that researchers begin partnering with existing cohorts and studies to implement measures of interest and accelerate the collection of relevant data. Researchers must also stop relying solely on the health care system to recruit patients to a study, but also include enrollment via community-based approaches. All approaches require engaging with necessary stakeholders,

including patients, caregivers, and providers, to ensure that measures in a given study are clinically meaningful.

Engaging with More Unique Perspectives

To optimize an assessment or study's usefulness to research and clinical settings, researchers must engage with people from many unique perspectives, including patients, family members, caregivers, providers, and communities.

Data Needs

Participants agreed that more normative data on neuropsychological instruments and measures, including versions in different languages, is needed to improve the use of these tools in all populations—including ethnic and racial groups but also specific demographic groups, such as those with low levels of education and literacy. Assessing these tools in different populations is also needed to determine whether the constructs measured by a specific tool are the same across populations. Similarly to other theme discussions, the need for SDOH data, including data on discrimination, immigration history, quality of education, literacy confidence, and zip code, is critical to tailoring assessments to specific populations.

Participants also emphasized the importance of accelerating the use of remote assessments, which can help reach rural and more isolated populations, as well as reduce the burden of participation on patient populations.

Clear Objectives for Digital and Real-World Measures

Participants emphasized the importance of having clear research objectives for the development of digital and real-world measures. Outlining these objectives can help ensure that psychometric tools complete the intended task in a globally relevant manner.

Testing vs. Assessment

Researchers commonly use the words testing and assessment interchangeably, but they are, in fact, different. Testing is one form of assessment, but it does not encompass the vast number of constructs and parameters that assessment involves.

Digital Data Repository

Participants agreed that a major current priority is the need to generate big digital datasets on mobility, voice, and other behavioral parameters and store them in an accessible repository. Creating such a resource will provide researchers with the data to overcome validation challenges for objective measures.

Cognition and Behavior

Researchers have developed and studied many assessments of cognition, which has led to a greater understanding of cognition as an outcome measure. However, research into behavior as an outcome has lagged, likely because of the lack of tools developed specifically to interrogate behavior. Researchers in the field of neuropsychology should conduct studies to develop and assess behavior-focused tools. In addition, standardizing the definition of cognition and behavior, as well as specific behaviors, may help to drive studies in these areas.

Challenges in Behavioral Assessments

Common challenges to evaluating behavioral assessments are the significant noise and heterogeneity in the readouts. Noise and heterogeneity hinder the ability of researchers to identify findings and translate those findings to clinical settings.

Future Research Priorities

Participants emphasized several important future research priorities (shown below):

- How do we assess neuropsychological changes across the lifespan?
- How do we capture SCCs and neuropsychiatric symptoms that are linked with AD/ADRD pathological processes?
- How do we integrate clinical and real world measures to detect early signs of functional changes?
- How do we integrate digital tools, including more precise, real-time, longitudinal, and temporally-dense measurement, into AD/ADRD prevention trials?
- Which factors, including social and structural factors beyond race, ethnicity, and education, have critical roles as mediators of cognitive decline and midlife AD/ADRD risk?

Appendix 1: Participants and Attendees

Invited Speakers

Rhoda Au, PhD, Boston University*

Rebecca Amariglio, PhD, Harvard Medical School and Brigham and Women's Hospital*

Ganesh M. Babulal, PhD, OTD, Washington University School of Medicine in St. Louis

Deanna Barch, PhD, MA, Washington University in St. Louis

Yonas Geda, MD, MSc, Barrow Neurological Institute

Jason Hassenstab, PhD, Washington University in St. Louis

Frank Jessen, MD, University of Cologne and German Center for Neurodegenerative Diseases

Dina Katabi, PhD, Massachusetts Institute of Technology and Emerald Innovations, Inc.

Jacqueline Mogle, PhD, MS, Clemson University

Lauren Nicholas, PhD, MPP, University of Colorado

Rachel Nosheny, PhD, University of California, San Francisco, and San Francisco Veteran's Administration Medical Center

Kate Possin, PhD, University of California, San Francisco*

Yakeel Quiroz, PhD, Massachusetts General Hospital and Harvard Medical School*

Chandra Reynolds, PhD, University of California, Riverside

Virginia Sturm, PhD, University of California, San Francisco

Ipsit Vahia, MD, McLean Hospital and Harvard Medical School*

Moderators

Lisa Barnes, PhD, Rush University

Brad Dickerson, MD, Massachusetts General Hospital and Harvard Medical School

Duke Han, PhD, University of Southern California

Dinesh John, PhD, NIA

Jonathan King, PhD, NIA

Liz Necka, PhD, MA, BSR, NIA

Frank Rudzicz, PhD, MEng, Dalhousie University

Janine Simmons, MD, PhD, BSR, NIA

Marty Sliwinski, PhD, Pennsylvania State University

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Ella Blue

Jessica Boten
Jerry Bower
Kristin Brethel-Haurwitz
Stacy Carrington-Lawrence
Eric Scott Cerino
Nathaniel Ark Chin
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Tiziana Cogliati
Rosaly Correa-De-Araujo
Paul K. Crane
Aleksandra Dakic
Rene Etcheberrigaray
Elena Fazio
Yi-Ping Fu
Hongwei Gao
Melissa Gerald
Richard Gershon
Maryam Ghaleh
Jody Greaney
Maurizio Grimaldi
Paul Grothaus
Erin Harrington
Zoe Hawks
Emily H Ho
Emily Hooker
Todd Horowitz
Janey Hsiao
John Hsiao
Jennifer Isaacs
Petra Jacobs
Mijin Jeong
Amelia Karraker
Pragati Katiyar
Theresa Kim
Rebecca Krupenevich
Jennie Larkin
Kait Lee
Alyssa Lin
Yuan Luo
Kristina McLinden
Isis Mikhail
Manuel Moro
Carmen Moten
Maggie Nellissery

Lis Nielsen
Priscilla Novak
Lisa Onken
Devon Oskvig
Alexander Parsadanian
Georgeanne Patmios
Dana Plude
Nijaguna Prasad
Nadezda Radoja
Susan Resnick
Elise Rice
Rebecca Ricklis
Luci Roberts
Alessandra Rovescalli
Marcel Salive
Sandhya Sanghi
Kenneth Santora
Irina Sazonova
Dana Schloesser
Maureen Schmitter-Edgecombe
Caroline Sferrazza
Nina Silverberg
Shifali Singh
Raquel Sitcheran
Shana Stites
Dory Sullivan
Vijay Sureshkumar
Alexandra Touroutoglou
Melissa Trevino
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Jennifer Turner
Ramesh Vemuri
Molly Wagster
Allie Walker
Fei Wang
Cassie Wheelles
Benfeard Williams
Beth Wilmot
Bonnie Wong
Alison Yao
Afsara Zaheed
Anqing Zheng

*also served as a moderator