

Incorporating the Experimental Medicine Approach in the Development of Primary Prevention Trials for Alzheimer's Disease: A Workshop

***The National Academies of Sciences, Engineering, and Medicine
Division of Behavioral and Social Sciences and Education***

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Acronym Definitions

A4	Anti-Amyloid Treatment in Asymptomatic Alzheimer's
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD/ADRD	Alzheimer's disease and Alzheimer's disease-related dementias
AI	artificial intelligence
AIBL	Australian Imaging, Biomarker, and Lifestyle Flagship Study of Ageing
APOE	apolipoprotein E
BBCSS	Board on Behavioral, Cognitive, and Sensory Sciences
BDNF	Brain-derived neurotrophic factor
BSR	Division of Behavioral and Social Research
CBF	cerebral blood flow
CDC	Centers for Disease Control and Prevention
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DBASSE	Division of Behavioral and Social Sciences and Education
DPP	Diabetes Prevention Program
ELA	early-life activity
ENCORE	Exercise and Nutritional Interventions for Cardiovascular Health
FDA	U.S. Food and Drug Administration
FHS	Framingham Heart Study
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
fMRI	functional magnetic resonance imaging
HC	hippocampus
IGNITE	Investigating Gains in Neurocognition in an Intervention Trial of Exercise
ITT	intention to treat
IV	instrumental variable
LTP	long term potentiation
MRI	magnetic resonance imaging
NACA	National Advisory Council on Aging
NASEM	National Academies of Sciences, Engineering, and Medicine
NIA	National Institute on Aging
PET	positron emission tomography
SMARRT	Systematic Multi-Domain Alzheimer's Risk Reduction Trial
SPRINT	Systolic Blood Pressure Intervention Trial
US POINTER	Alzheimer's Association US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk
VCID	Vascular Contributions to Cognitive Impairment and Dementia

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Executive Summary

Substantial epidemiological research has provided evidence on potential risk factors for Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD), suggesting lifestyle change as a leading intervention for the prevention of AD/ADRD clinical dementia. However, less is known about the mechanisms leading to and helping to maintain behavior change in prevention of AD/ADRD. On October 10–11, 2019, at the request of the National Institute on Aging (NIA), the National Academies of Sciences, Engineering, and Medicine's (NASEM) Division of Behavioral and Social Sciences and Education (DBASSE) organized an Expert Panel to explore advances in incorporating the experimental medicine approach in the development of primary prevention trials for AD, with the goal of informing study design to increase adherence to AD prevention interventions via actionable strategies. Dr. Michael Otto, of Boston University, served as Chair for the Expert Panel.

Dr. Adrienne Stith Butler, Associate Director of the Board on Behavioral, Cognitive, and Sensory Sciences (BBCSS), offered opening remarks about the NASEM, and Drs. Lis Nielsen, Jonathan King, and Lisa Onken of NIA provided background and context for the workshop. Throughout both days, members of the Expert Panel gave presentations related to AD trial cohorts, early outcome assessments for AD cognitive and functional status trajectories, mechanism targets for interventions, motivation for and adherence to interventions, and development of primary prevention trials. The Panel broke into three groups to discuss cohorts, mechanisms issues, and adherence. The Panel concluded the meeting with discussion, synthesis, and key features of future AD prevention trials.

The experimental medicine approach, used in this meeting as a tool to assess behavior change to reduce AD risk, involves identifying an **intervention** of interest (e.g., exercise) and a **mechanism target** with the necessary tools to verify change (e.g., biomarkers measured with biological assays), and assessing how well the intervention generates and maintains **behavior change**. In the context of AD risk reduction, researchers are interested in promoting adherence to health behaviors, such as physical activity, that have been linked to improved cognitive health. The following topics were examined in the context of the experimental medicine approach during the workshop and breakout groups.

Mechanism Targets and Cohorts for Intervention Trials

The panel examined mechanism targets for AD risk reduction interventions, as well as known moderators and ways to measure changes in those targets across various cohorts. Panel members agreed that the Science of Behavior Change (SOBC) experimental medicine approach to AD risk reduction research requires (1) precise instruments and multiple assessments (e.g., biomarkers or psychosocial mediators measured over time), (2) analyses integrated into study designs, and (3) cohorts with all levels of risk. These conditions, however, might require small, early-stage research; intervention phenotyping; and careful assessment of non-responsivity to interventions. Further, multi-stage designs with dynamic intensity levels and multiple recruitment strategies for heterogeneous populations (e.g., social media, churches, synagogues, community centers) could also be considered for AD risk reduction intervention trials.

The use of existing cohort data can decrease participant burden and, when combined with other datasets, can provide a comprehensive data set to understand the mechanism targets of behavior change. The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) and the Generations trial offer useful populations to assess disease progression at an early age (i.e., age 18) and in a healthy older population at high risk for AD, respectively.

Early Outcome Assessments and Paths to Behavior Change

Panel members discussed ways to measure motivation, considered whether biological mechanisms might relate to behavioral mechanisms, and examined how best to provide ongoing feedback to participants during AD risk reduction interventions. The panel agreed that AD risk reduction intervention trials should include early-outcome assessments from multi-modal, multi-level, and adaptive interventions with attention to rescue strategies (built in for when motivation lags). Understanding how to motivate people to embrace a virtuous cycle of health behaviors (e.g., cognitive training can improve sleep quality) and how to measure that motivation could be a useful strategy for behavior change as well. Panel members also highlighted that adherence motivation is a dynamic process, and researchers may need to consider shifting motivational strategies and targets to help maintain adherence in long-term behavioral change studies.

AD risk reduction research satisfying the experimental medicine approach should consider measuring adherence during and after a proposed intervention and performing secondary analysis of existing data (e.g., personality, genetics, mood) to predict short- and long-term intervention adherence prior to beginning an intervention. Most studies do not follow participants over extended time periods during or after a trial; however, if researchers incorporated longitudinal data into their analysis, they could assess how predictors might change over time. Further, adherence to some interventions could be measured in real time via wearable devices (e.g., actigraphs) that can measure movement objectively.

Behavior Change and Adherence to Interventions

Adopting the experimental medicine approach will be useful in considering how interventions can be designed to maximize long-term adherence. This adoption requires a shift of focus away from the distal outcome of promoting cognitive health, which can limit participants' ability to see short-term success. Instead, the experimental medicine approach promotes adherence to a behavioral lifestyle change that could result in improved cognitive health. Adherence "targets" may include affective, social, or motivational processes that can sustain engagement or promote re-engagement in a new health behavior, such as physical activity. Panel members considered study population characteristics relevant to adherence and strategies to promote adherence to AD dementia risk reduction interventions throughout the workshop and breakout groups.

Panel members agreed that it is critical to understand a study population before beginning an intervention and to include participants' opinions in the kinds of interventions offered to maintain adherence. To learn more about a study population, researchers could form focus groups to learn about participants' life histories and create motivation/adherence composite scores to predict and increase motivating factors across populations. Interventions that focus on individual differences (e.g., personality) and those that systematically assess small group versus individual behavior might drive successful behavior change as well.

Moreover, identifying an individual's motivation (e.g., pleasure, curiosity) will help to develop person-centered interventions, and providing a menu of interventions that promote personalized approaches for success at all life stages will help maintain adherence and reduce the impact of progression. Successful AD risk reduction interventions will need to offer opportunities for continued engagement in new lifestyle behaviors after trial completion, and may require incorporating boosters or bridges to community programs.

Behavior change researchers should consider taking advantage of technology that participants already use (e.g., television, gaming) to promote a desired AD risk reduction intervention (e.g., exercise, cognitive training), learning from failed opportunities, and building on existing pragmatic trials, rather than starting anew.

Emerging Theme: Sustainable Partnerships

Throughout the workshop and breakout groups, panel members discussed the need to build interdisciplinary work teams for successful AD risk reduction intervention trials. Panel members considered incentives for engineers and technology experts, professional motivators, entertainers, and professional athletes to enter the conversation. Researchers must find ways to make interventions aesthetically pleasing, engaging, and effective so that participants are encouraged to continue. Promoting long-term change will require establishing sustainable partnerships (e.g., workplace, insurance companies, higher education, churches, foundations, YMCA) and educating those partners on the importance of the proposed interventions.

Meeting Summary

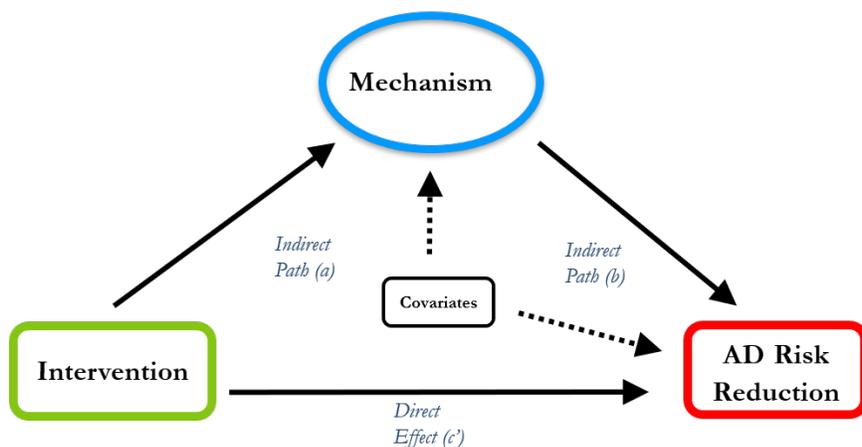
Welcome and Overview of Meeting

Adrienne Stith Butler, Associate Board Director, Board on Behavioral, Cognitive, and Sensory Sciences (BBCSS)

Michael Otto, Chair, Workshop Organizing Committee

The National Academies of Sciences, Engineering, and Medicine (NASEM) is a nonprofit organization that was established by the U.S. National Academy of Sciences Charter (1863) to investigate, examine, and report on any subject of science or art at the request of any government department. The NASEM provides independent policy advice across seven major program units, organized by scientific discipline, including the Division of Behavioral and Social Sciences and Education (DBASSE) chaired by Dr. Susan Fiske. The NASEM is currently investigating the role of behavioral science in Alzheimer’s disease (AD) with publication to occur later this year. On behalf of the NASEM, Dr. Stith Butler thanked the National Institute on Aging (NIA) for sponsoring and the NASEM staff for their help in organizing this workshop.

Dr. Otto introduced the experimental medicine approach as it will be used in workshop discussions. The approach aims to identify the key mechanisms underlying successful (or unsuccessful) behavior change, offering intermediate targets to assess the cause of behavior change.¹ For the purposes of preventing AD, the experimental medicine approach focuses our attention on identifying and targeting mechanisms of behavior change that will promote adherence to a health behavior and



ultimately reduce the risk of AD. Using the experimental medicine approach, a proposed mediation model would identify a potential mechanism that promotes adherence, examine whether an intervention engages or influences that mechanism, measure variables that capture change in that mechanism, and determine whether changes in those variables impact changes in adherence to the health-

Figure 1. Proposed Mediation Model

promoting behavior (Figure 1). In the context of AD risk reduction, the focus of the experimental medicine approach is promoting adherence to health behaviors, such as physical activity, that have been linked to improved cognitive health.

¹ Riddle M. (2015) News from the NIH: using an experimental medicine approach to facilitate translational research. *Transl Behav Med*, 5(4):486–488.

Because AD appears to affect the brain long before apparent cognitive impairment is observed, it may be beneficial to begin prevention interventions earlier in life. However, early (and therefore longer) intervention may make clinical trial enrollment more difficult and adherence less likely. The proposed mediation model, therefore, provides a framework to address issues related to the development of interventions for AD prevention. This workshop focused on how researchers can use the proposed mediation model to better understand how to address issues in AD trial cohorts, recommended intervention (e.g., exercise, cognitive training, multi-modal), mechanisms, adherence, and proxy outcomes.

Sponsor's Welcome

Lis Nielsen, Jonathan W. King, and Lisa Onken, NIA

Behavioral and social research on aging at NIA encompasses studies of (1) health, function, and wellbeing, as well as age-related diseases; (2) the processes of aging as they unfold over the full life course (e.g., early-life impacts, mid- and late-life plasticity, reversibility of risk); (3) biobehavioral and biosocial integration to elucidate mechanisms and processes that drive aging outcomes; and (4) use-inspired basic research and mechanisms-focused intervention science informed by the Science of Behavior Change (SOBC) experimental medicine approach and the [NIH Stage Model](#).

NIA's Division of Behavior and Social Research (BSR) manages active research portfolios on topics related to Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD), including *cognitive and dementia epidemiology* (to capture changes over the full life course); *behavioral and social pathways* (to support examination of risk and protective factors, their causal role, and their potential malleability); *early psychological indicators* (e.g., early changes in cognition, affect, and decision making); and *prevention* (e.g., developing interventions targeting malleable behavioral and social mechanisms on the causal pathway to AD/ADRD). Prevention of age-related cognitive decline involves long-term lifestyle changes. The BSR portfolio provides a framework for addressing this and other issues that are important for the AD research field.

These goals are aligned with recommendations from the 2013 National Advisory Council on Aging (NACA) review of BSR, which highlighted the need to study early-life prevention, with a focus on

- elucidating the pathways by which social, psychological, economic, and behavioral factors affect health;
- identifying the causal mechanisms that account for observed associations; and
- targeting these mechanisms to modify individual behaviors and social contexts to promote health and prevent disease.

Efforts in other research fields have successfully illustrated the importance of behavior change for improved health outcomes. For example, the National Diabetes Prevention Program (DPP) investigated an intensive lifestyle program, a dietary program, and drug treatment (Metformin) on type 2 diabetes prevention and weight loss. The DPP found that participants who made lifestyle changes lost more weight than both the placebo and medication groups, and some participants maintained their exercise regimens years later.

Biological evidence also suggests that the simple process of taking medication can successfully treat disease, yet many individuals do not adhere to medication guidelines (e.g., a Canadian study illustrates that patients did not adhere to statin regimen after myocardial infarction). The lack of full adherence to medication and lifestyle interventions suggests the need for further research into the mechanisms regulating behavior change and promoting long-term adherence. Panel members were asked to consider what motivates people to adhere to lifestyle changes and what factors predict sustained engagement critical for success in the context of AD.

Although the biological mechanisms through which physical activity influences cognitive function and other factors along the AD pathway are important, this workshop is focused on the use of the experimental medicine approach to identify and measure the mechanisms underlying initiation and maintenance of behavioral patterns (such as physical activity) that may prevent the onset of AD before the disease begins. Research on the mechanisms that promote engagement in and adherence to behavioral regimens that offer cognitive benefits is sorely needed. The extent to which AD progression begins before clinical symptoms appear remains unknown, and conducting a multiple-decade primary prevention study may not be a realistic undertaking. Therefore, NIA hopes this workshop will inform the design of studies to increase adherence to AD prevention interventions via more actionable shorter-term strategies.

Cohort Concerns: The Who, What, When for Interventions and Risk Outcomes

Presentation: Cohort Concerns: The Who, What, & When for Alzheimer's Prevention Trials
Deborah Barnes, University of California, San Francisco

It is important to understand how cognitive decline occurs in both normal and AD populations. Researchers should attempt to intervene before and during disease progression to shift the trajectory of cognitive decline. In addition, because of the long preclinical period in AD, researchers should consider who to target and when to intervene (e.g., optimal age, sex, race, ethnicity), as well as what drives the motivation to adhere to interventions.

Because age is the number one risk factor for AD, and because incidence doubles every 5.5 years after the age of 65, researchers may be able to achieve better primary prevention if they target younger populations with less neuropathology. The study of younger populations is challenging, because they have fewer cognitive impairment incidences and can be more difficult to follow and motivate than older populations. However, disease progression is more difficult to stop in older populations with greater neuropathology.

Moreover, the field should consider both the mechanism of an action and the time to benefit from an action, though the earlier an intervention is started, the greater the chance of success. An exercise intervention can be implemented at any age (even with AD patients), but participants must maintain the regimen to see continued benefits. In contrast, cognitive training has longer-lasting effects, and cognitive reserve may build over a person's lifetime. These results suggest that, although cognitive training may improve cognitive function at any point in the life course, early intervention may be best. Interventions targeting cardiovascular disease (CVD) may require early intervention (e.g., midlife) and long follow-up (5 years or more) for maximum benefit.

Preventative AD trials should consider targeting participants from high-risk populations—for example, those with genetic risk factors (e.g., Apolipoprotein [APOE] ε4). Recent studies (e.g., Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability [FINGER] trial and UK Biobank) suggest that AD interventions can offset genetic risk. In addition, populations with a family history of AD, subjective memory decline, or low cognitive performance may be attractive study enrollees because they are highly motivated to change their behavior.

Prevention efforts are likely to be most effective when researchers target personalized, modifiable risk factors (e.g., exercise for individuals with sedentary lifestyles; CVD interventions for individuals with prediabetes or borderline hypertension; multi-domain interventions, such as the Systematic Multi-Domain Alzheimer's Risk Reduction Trial [SMARRT] for individuals with multiple risk factors; and inclusion of participants in decision making). The SMARRT trial, for example, is enrolling participants to assess demographic and cognitive status in patients with two or more modifiable risk factors (i.e., a high-risk population); the intervention includes health coaches and nurses who create personalized, risk-reduction goals and action plans for each participant.

Discussion

The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study included a cognitive training booster 1- and 3-years post-intervention, which enhanced the long-term cognitive benefit observed even years later. Researchers should consider the need for boosters in future clinical studies.

Early Outcome Assessments for AD Trajectory

Presentation: The Path to Zero Is One: Accelerating Innovation and Discovery for AD through a Precision Brain Health Approach

Rhoda Au, Boston University

The incidence rate of AD in the United States is increasing because the population is aging rapidly, and researchers continue to use the same approaches to study and treat AD. However, the heterogeneity of the disease (i.e., neuropathology, pathological hallmarks, cognitive function) complicates the development of tools to prevent the disease. Digital technology could lead to great advances in precision AD treatment. Optimization of brain health through technology could result in earlier detection of the disease, thereby reducing the incidence rate and associated health care costs.

The Framingham Heart Study (FHS) was established in 1948 to assess factors that contribute to CVD. Dr. Au's research team was concerned that the cognitive tools used in the FHS, as well as tools used abroad (designed mostly for highly educated English speakers), did not capture appropriate cognitive information. Therefore, Dr. Au introduced the use of digital technologies to capture responses (voice and drawing) and generate digital phenotypes to assess early cognitive changes in diverse populations in a natural manner. Using well-characterized recordings from FHS across the entire adult lifespan, her team captured heterogeneity in the AD population. Though the recordings provide a large, rich data source to construct an individual's profile, it can be challenging to analyze the complex signals over time. Thus, developing methods for sharing these data broadly with the data science community (e.g., artificial intelligence [AI], machine learning) is also critical to

maximizing the potential scientific discovery from these types of resources. Her team is also launching a study to assess digital cognitive tests along with amyloid and tau positron emission tomography (PET) scans to determine digital profiles that highly correlate with gold standard AD imaging biomarkers. The objective is to develop surrogate digital biomarkers that are easily scalable and could be used to rapidly screen patients likely to be at risk for AD. Through expansive use of digital technology, Dr. Au's team has built a multi-technology system with Linus Health to monitor brain health in a cost- and time-effective way.

However, to continue to assess cognitive performance in the rapidly changing technological environment, researchers must think outside of the disease to understand the inside of the disease. For example, researchers could consider leveraging NIH-funded longitudinal studies of other disease states to more fully characterize preclinical AD heterogeneity and examine how other diseases contribute to increased risk for AD. This effort requires collaboration with experts (e.g., open science), often outside of academia, and bridging the gap between the academic world and the technology community.

Discussion

The number one concern for digital technology work is data security. Dr. Au's team works with Sage Bionetworks and Kryptowire to ensure privacy and promote sharing. The Alzheimer's Disease Discovery Foundation, in collaboration with Gates Ventures and other organizations, is also exploring possibilities in the area of data security. Dr. Au does not believe that European Union laws that prevent data sharing will hinder future research efforts. Rather, working within the European Union's parameters will help ensure that privacy protection and data security measures are maximized, in order to increase the impact of digital technology in AD research. Because NIA requires data sharing, more researchers will likely learn to safely and effectively share data.

Although digital technology advances provide new opportunities to assess the heterogeneity in the AD population, funding agencies have been slow to understand the technology and to fund this type of work. Further, studies centered on the use of digital technologies are difficult to successfully move through the standard peer-review process because most AD researchers are not familiar with these approaches, and well-defined methods to assess them do not exist.

Presentation: Our Experience with Recruitment of At-Risk Participants for Alzheimer's Prevention Trials

Stephen Salloway, Brown University Medical School and Butler Hospital

Prevention research is transformative and has an impact on people at risk. Further, people with the highest risk for AD are inspirational. People with autosomal dominant genes who are at increased risk (50 percent) of early-onset AD often feel a responsibility to science and a motivation to participate in studies. In this population of people at increased AD risk, plaques begin forming as early as 20 years before cognitive impairment, providing an opportunity to assess tools to prevent disease progression.

Choosing the most appropriate study population is complicated. Primary prevention trials study individuals who do not yet show evidence of AD pathology (e.g., plaques and tangles). However, secondary prevention trials study individuals who show evidence of pathology but do not have

clinical symptoms. Because amyloid plaques increase with age in people who are cognitively normal and plaques are low in number before age 60, researchers do not have an accurate way to use amyloid plaques as a biomarker for AD risk before cognitive impairment.

Amyloid and tau PET tracers have aided in the identification of disease stage. For example, the Australian Imaging, Biomarker, and Lifestyle (AIBL) Flagship Study of Ageing assessed whether biomarkers, cognitive characteristics, and health and lifestyle factors were associated with AD development. Overall, this study found that the rate of change in both plaques and cognitive decline varied by amyloid status. Specially, cognitive decline was often detectable in participants who were amyloid positive and APOE ϵ 4 carriers. More sensitive cognitive assessments to measure subtle changes could help researchers to determine how interventions impact progression in this population. However, cognitive change occurs in a complex environment (e.g., comorbidities, risk amplification or protective genes, enhanced cognitive reserve), and the factors that contribute to cognitive impairment risk may be modifiable.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) clinical trial assessed cognitively normal individuals aged 65 to 85 with positive amyloid scans (high risk for AD-related memory loss) and found that 50 percent of those participants also had evidence of tau spread, suggesting their cognitive status might change over the course of the study. Therefore, knowing a patient's tau status could be extremely important. PET biomarkers to identify tau are expensive, and research into blood-based biomarkers is advancing quickly and should provide a more economical option.

Prevention trials require large samples and long duration, as well as an understanding of the optimum target age and genetic and lifestyle predispositions. Because it is difficult to determine clinical outcomes, researchers may need proxies to measure subtle changes in cognitive performance. This may require machine learning and more robust data analytics, risk behavior analysis, and data sharing with study participants. To more fully understand risk factors and prevention success, researchers will need a more diverse study population and may choose to involve a study partner, even when not required.

Dr. Salloway manages a multidisciplinary outreach team consisting of not only researchers and staff, but also community volunteers, a prevention registry, and social media outlets to increase study recruitment. The team at Brown also uses the alumni network to gather biomarker data. Dr. Salloway's team performs a psychological readiness evaluation to ensure that both the participant and study partner are prepared for the study (and receive status updates). Status updates appear to be a motivation for study participation.

Dr. Salloway emphasized that increasing awareness of AD prevention trials through media coverage and community outreach is critical for stimulating interest in AD/ADRD prevention research. AD prevention registries are being used at the local and national levels to screen and direct people to prevention trials.

Discussion

Much of the work in primary prevention will likely occur in high-risk populations. It does not appear feasible at this point to accurately assess subtle cognitive changes in middle-aged, low-risk populations.

Researchers should be realistic in what they share with study participants (and in publications). They should not be overly hopeful and should ensure that blame is not placed on the individuals (i.e., do not suggest that people develop AD because they behaved a certain way). Current projections suggest that even if all risk factors were eliminated, only one-third of AD cases would be prevented. Dr. Salloway agreed that his team is focused on modifying AD risk, rather than promising prevention.

Mechanism Targets for Interventions

Exercise

Presentation: Moderators and Mediators of Exercise Effects on Brain and Cognition

Kirk Erickson, University of Pittsburgh, Planning Committee Member

Although the mediation model (Figure 1) presents an approach in which intervention and risk are opposing, researchers should consider how moderators of this process might influence mechanisms regulating risk, intervention success, and sustainability (e.g., age, race, ethnicity, intervention duration). Animal studies have provided an understanding of the molecular and neural mechanisms regulating cognitive effects of physical activity. However, because sample sizes are small and translational animal models are few in number, less is known about what mediates human exercise adherence and motivation. Consideration of what drives behavior (e.g., adherence to lifestyle interventions) from the standpoint of multiple interconnected mediators (e.g., cellular and molecular, structural and functional, behavioral and socioemotional) will provide a more useful approach to disease prevention. For example, an individual can go for a run, but what occurs immediately following that run (e.g., eating unhealthy food) could hinder the benefit of that run (act as a moderator). In contrast, if an individual reads a book immediately following a run, it may augment the physical activity benefit (also acting as a moderator).

Additional outcomes associated with physical activity, such as angiogenesis, cerebral blood flow, or sleep, likely influence cognitive outcomes. Therefore, researchers should consider the assessment of various physiological systems, likely with their own moderators and mechanisms (e.g., brain-derived neurotrophic factor [BDNF], inflammatory cytokines, amyloid, hormone therapy, baseline fitness), to better understand cognition. Further, genetic background (e.g., APOE ϵ 4) and amount of physical activity are likely to influence cognitive performance. More specifically, Head and colleagues showed that high physical activity nearly eliminated the increased risk of AD in APOE ϵ 4-positive individuals.² However, small sample sizes limit the statistical power to draw conclusions from this and other similar cross-sectional studies. Therefore, a more targeted, person-centered approach is necessary to move the field forward. Through a Phase III randomized clinical trial of cognitively normal older adults, Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE), Dr. Erickson's team is assessing how moderate physical activity in older adults influences cognitive change using a variety of measures.

² Head, E., Powell, D., Gold, B.T., and Schmitt, F.A. (2012). [Alzheimer's disease in Down syndrome](#). *Eur J Neurodegener Dis*, 1(3):353–364.

Cardiovascular Disease Risk Reduction

Presentation: Cardiovascular Pathways to Dementia Prevention: New insights from Intensive Systolic Blood Pressure Lowering

Jeff Williamson, Wake Forest Baptist Health

Many entry pathways exist for vascular pathology of AD/ADRD. Vascular Contributions to Cognitive Impairment and Dementia (VCID) produce a variety of tissue injuries, and white matter degeneration is most commonly seen in people with high vascular disease burden. However, many gaps in knowledge remain, and few translational animal models are suitable for mechanistic studies.

Early evidence suggests that lowering blood pressure has a positive effect on the brain; however, an optimal target blood pressure for the aging adult is unclear. NIA accessed data from the Systolic Blood Pressure Intervention Trial (SPRINT) study, one of the largest blood pressure studies to date, to examine the effect of intensive high blood pressure treatment (compared to standard treatment) on cognitive impairment in a diverse adult population (e.g., age, sex, race, ethnicity, frailty), excluding individuals with stroke. Study participants receiving either standard or intensive treatment exhibited decreased blood pressure and mortality with similar adverse effects and adherence levels. Combined, adjudicated scores for mild cognitive impairment (MCI) and probable dementia decreased by 15 percent in the intensive treatment group compared to the standard treatment. Participants on standard treatment also exhibited higher rates of amnesic MCI than those in the intensive treatment group, indicating greater progression to dementia, 2 years after treatment.

In the SPRINT study, 92 percent of patients were followed through the final cardiovascular follow-up. At 3 years post-intervention, two-thirds of the study population was retained through primary care physician monitoring. Participants' Montreal Cognitive Assessment scores increased after age 75, suggesting the need for more focus on this population when assessing the role of cardiovascular intervention on cognitive performance. Although cardiovascular disease appears to have a critical window of buildup, researchers must find vascular markers at earlier ages to determine possible links to brain dysfunction and dementia. The MarkVCID group has identified both imaging- and blood-based biomarkers and is supporting independent validation studies for these biomarkers in a real population (with more heterogeneity).

Discussion

Researchers can study populations with highly prevalent risk factors (e.g., high blood pressure) to make a large impact on prevention of AD/ADRD.

Although researchers can no longer mimic the SPRINT trial in the United States, Brazil and China are in the process of doing so, and the need for observational studies remains. Pairing a cognitive study with a cardiovascular health study can be very successful, but it is important to proceed with caution. SPRINT only assessed mid-life hypertension risk. If recalculated across all age groups, risk may have influenced the results.

From a clinical standpoint, clinicians and patients, including those who have suffered from stroke, must consider whether the risk of morbidity and mortality is greater with or without cardiovascular

medication. Dr. Williamson agreed that medication poses risk for dehydration; however, he still recommends that patients use medication when necessary to prevent the risk of mortality from cardiovascular disease.

Cognitive Training

Presentation: Mechanistic Targets and Moderators for Cognitive Training and Exercise: Similarities, Differences, Potential for Synergy

Michelle Voss, University of Iowa

Researchers can use biological age as a proxy for chronological age, and they can apply cognitive and/or physical activity interventions at different time points along the aging trajectory. Muscle contraction at different intensities initiates physical activity and activates homeostatic signaling mechanisms that communicate with other organ systems, including the brain, via blood circulation. Animal models suggest that factors secreted from muscles increase central BDNF in the hippocampus (HC), which subsequently facilitates synaptic plasticity and resilience to injury. When these BDNF terminals are blocked during exercise, downstream effects on memory in the HC are also blocked.

Human data suggest that magnetic resonance imaging (MRI) or functional MRI (fMRI) can track changes in brain function initiated by physical activity. Although central BDNF cannot be measured in vivo in the human brain, translational research may benefit from tracking blood-based biomarkers that predict protective benefits of physical activity instead. Further, since AD pathologies spread along paths of functional brain networks (e.g., amyloid and tau), functional network analyses with minimally invasive MRI methods may provide potential avenues to evaluate the success of AD prevention interventions over time.

Because muscle biopsies immediately before and following exercise in older adults involve high burden on participants, researchers could instead measure byproducts of physical activity metabolism, such as blood lactate, which has been proposed to cross the blood–brain barrier and directly influence BDNF in the HC. If clinicians identified a patient's blood lactate level that promotes cognitive benefits, they could determine the optimal exercise intensity and duration for that individual (and when to modify intervention duration or intensity as the individual adapts). However, the degree to which increased exercise intensity (and lactate) impacts cortisol (stress) and affective responses that could affect adherence, especially in the aged population, is an important consideration for future research.

In addition to physical activity, perceptual tuning, the inherent encoding of an individual's environment for appropriate processing by inhibition of unnecessary distractions, can allow individuals to perform at higher cognitive levels. In aging, however, this inhibition begins to break down, and individuals cannot prevent distractions. Cognitive training can help tune perceptual discrimination that has started to degrade. For example, Mishra and colleagues showed in aged rats and humans that targeted cognitive training results in enhanced perceptual discrimination even after the training is complete.³ Lee and colleagues showed that individuals who performed home-

³ Mishra, J., de Villers-Sidani, E., Merzenich, M., and Gazzaley, A. (2014). Adaptive training diminishes distractibility in aging across species. *Neuron*, 84(5):1091–1103.

based, online, phased adaptive training exhibited improved speed and overall performance compared to those who did not perform adaptive training. Perceptual tuning training, therefore, may provide a foundation for performing everyday activities because the training continues in the brain long after the activity ends.

Presentation: Preventing Cognitive Decline and Alzheimer's Disease Dementia: Evidence for Cognitive Training

George Rebok, Johns Hopkins University

Cognitive training, including guided practice tasks using repetitive exercises, could be a useful tool for the aging population at risk for cognitive impairment. This is particularly important because it is estimated that 20 percent of the world's population will be over age 65 by 2030. Of note, rates of AD are higher in African Americans and Hispanics. However, few cognitive training studies include ethnic minorities, with the exception of the ACTIVE trial.

A recent NASEM report⁴ that assessed various classes of cognitive impairment intervention (e.g., blood pressure management, physical activity, cognitive training) suggested, based largely on the ACTIVE trial, that cognitive training can slow the progression of cognitive impairment and that public health communications should highlight the use of cognitive training as a tool for delay of cognitive impairment. However, little evidence suggests that cognitive training can prevent dementia. To date, meta-analyses of the usefulness of cognitive training for dementia care remain inconclusive, mainly because of (1) a lack of double-blinded, randomized, active-controlled trials; (2) underpowered samples; (3) lack of standardization, follow-up, or consideration for individual differences; (4) practice or retesting effects; and (5) poor communication about methods and terminology.

The ACTIVE trial, funded by NIA and the National Institute of Nursing Research, included more than 2,800 adults aged 65 and older from six sites across the country. It serves as a useful example of how training in basic cognitive abilities (e.g., memory, reasoning, and processing speed) could impact real-world tasks in the aging population. The trial includes a 20-year follow-up that links personal information (e.g., credit and driving histories) and social determinants of health (e.g., economic stability, education, neighborhood and built environment) to intervention success. Data from the 10-year follow-up showed that individuals who received cognitive training performed better in memory, speed, and reasoning assessments, including tasks on everyday living, compared to controls. Like other studies of this kind, the attrition rate was 5 percent per year, and reasons for drop-out were similar across groups.

The ACTIVE trial was likely successful in slowing the rate of cognitive impairment because it provided unique in-person trainings with certified instructors, social engagement, active learning exercises with real-life examples and strategies to solve everyday problems, and booster training sessions. In addition, though not systematically collected, many ACTIVE trial participants noted

⁴ National Academies of Sciences, Engineering, and Medicine. 2017. *Preventing Cognitive Decline and Dementia: A Way Forward*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24782>.

improved cognitive performance (e.g., the confidence to drive a vehicle or enroll in a computer class).

The ACTIVE trial sought not only to assess how cognitive training impacted cognitive impairment but also to determine whether it influenced the rate of incident dementia. Using a definition of incident dementia based on a combination of interview- and performance-based methods, the researchers found that signs of dementia were similar across control and training groups 5 years after the trial. However, data from the 10-year follow-up time point showed that more speed training sessions was associated with delayed dementia onset. The speed training sessions had an adaptive feature, which may explain why this form of cognitive training showed the greatest effect.

Although the ACTIVE trial did not assess biomarkers, researchers in the ACTIVE team are beginning to consider other covariates that might be driving responses. For example, researchers found that cognitive training participants have greater brain connectivity than those with no training. Future long-term, broader studies are critical, including those that involve multimodal training techniques.

Multimodal Interventions

Presentation: Mechanistic Benefits of Concurrent Physical and Cognitive Activity: Interventions Using Technology

Judy Pa, University of Southern California, Planning Committee Member

Concurrent physical and cognitive activity (e.g., exergames, or exercise via game play) can take many different forms, including cybercycling.⁵ Recent work suggests that simultaneous physical and cognitive activity may reduce AD risk and that sequential physical and cognitive activity may also provide benefit.

During concurrent physical and cognitive activity, an increase in BDNF is accompanied by increased long-term potentiation (LTP), a persistent increase in synaptic strength important in learning and memory that is stimulated by the cognitive training and generated by the release of BDNF. Therefore, this concurrent release of BDNF and LTP could lead to augmented memory. Interestingly, immediately following exercise, BDNF, vascular endothelial growth factor, insulin-like growth factor, and norepinephrine levels, as well as HC cerebral blood flow (CBF) are elevated for 10 to 60 minutes. Therefore, there may be a critical window of time for concurrent neural activity to enhance cognitive benefits. In addition, the optimal window for neurogenesis is about 4–6 weeks postpartum, suggesting another important time for learning.

Dr. Pa and colleagues are investigating concurrent cognitive and physical activity in normally inactive and active participants. In this activity, participants spatially navigate through a virtual world using a stationary bicycle in an attempt to feed virtual birds (mimicking the Morris water maze). The goal of the game is to collect food (milestones) and feed as many birds as possible within a set amount of time. The research team has added various social aspects to the exergame (e.g., tail-wagging dog, participant competition) and is working to adjust dosing to account for speed and

⁵ Anderson-Hanley, C., Arciero, P.J., Brickman, A.M., Nimon, J.P., Okuma, N., et al. (2012). Exergaming and older adult cognition: a cluster randomized clinical trial. *Am J Prev Med*, 42(2):109–119.

participant heart rate. Because participants move through a spatial environment with milestones and goals, an adherence mechanism is built in (maybe due to human's natural desire to forage). To maintain participant motivation, researchers must consider feedback and rewards (e.g., incentives, new variations/versions) and how to sustain cognitive advantages.

A main challenge to concurrent use of physical and cognitive activity is maintaining target engagement to enhance cognitive function. Many measurable mediators (e.g., CBF, BDNF, HC volume) exist. However, much less is known about the mechanisms that regulate how these and other mediators (e.g., normal aging, APOE ϵ 4 carriers, and exercise) affect one another. Furthermore, although evidence suggests that older adults embrace technology-based interventions, researchers must consider adherence in more vulnerable populations, such as those with medical morbidities or barriers to participation (e.g., physically disabled people).

Discussion

Dr. Pa's researcher team could consider pairing a drug intervention with the concurrent physical activity and cognitive training program to enhance the effect. They could also consider how other measurements of vascular change or arterial stiffness and compliance might change with exercise. Dr. Pa confirmed that her team has considered the importance of developing vascular imaging biomarkers for this purpose. However, because having multiple measurements over time would be useful, her team must first develop new versions of the exergame to provide opportunities for multiple testing periods. Dr. Smith suggested the use of doppler or near infrared spectroscopy based hemodynamic monitoring as efficient means of quantifying cerebrovascular changes in the arterial supply.

Presentation: Social Contexts as a Motivator (and Deterrent) for Cognitive and Physical Activity in Older Adults

Michelle C. Carlson, John Hopkins University, Planning Committee Member

Remaining socially engaged in purposeful activities appears to be beneficial for maintaining cognition and neuroplasticity through life and meets a late-life developmental desire to give back. Because individual motivation, life choices, and access to opportunities vary, assessing social engagement can be challenging. Many investigations have effectively shown the positive influence of moderate-to-high-intensity physical activity on cognition in aging adults. Dr. Carlson suggested that a complementary and overlapping focus be placed on the benefits of low-intensity activity on neurocognitive health. Low-intensity physical activity may be more achievable for deconditioned, sedentary, and socioeconomically disadvantaged individuals, thereby increasing adherence and engagement in those at greatest cognitive risk. Participants may be able to perform low-intensity activity in their own environment (i.e., in the real world). Research combining movement (physical activity) with cognitive engagement through purpose (social engagement) will likely be successful and has the potential to prepare individuals for real-world independent functioning. For example, in a sociodemographically high-risk cohort, 1,000 extra steps per day in complex outdoor environments was associated with larger HC volume, suggesting a relationship between physical

movement through environmental engagement and cognitive function.⁶ Moreover, early-life activity (ELA; e.g., playing sports, playing a musical instrument, learning a second language) appears to be related to late-life cognition and brain health.⁷ Specifically, individuals who self-reported greater amounts of ELA exhibited higher levels of education and better executive function and memory, as well as morphological changes in the brain (e.g., increase in HC volume in men and increase in amygdala volume in men and women).

Intervention work by Dr. Carlson and many others over the past decade is moving to multi-modal designs that incorporate cognitive, physical, and/or social engagement, such as through the FINGER trial. The FINGER trial assessed the impact of a series of physical and cognitive training and cardiovascular management activities performed at home and at a study site and is now the basis for other U.S.-based multi-site trials.

Between 2006 and 2012, Dr. Carlson and colleagues conducted a large-scale randomized controlled trial of Experience Corps, an intergenerational volunteer-based mentoring program in elementary school children to promote reading, math, library support, and positive communication behavior. Experience Corps was designed to integrate physical and cognitive activity through high levels of weekly social engagement with teachers, children, and fellow volunteers. Retired volunteers were recruited to help school children in the urban communities where they lived, resulting in a cohort of primarily African American adults, who are often under-represented in cognitive intervention studies. This group of adults was particularly interesting to target because walking half a mile or more safely in their community can be difficult, absent this kind of opportunity. This 2-year, high-intensity service program was the first of its kind to create a multi-modal study that participants enjoyed by virtue of purposeful social engagement.

Data suggest that Experience Corp led to modest benefits across indices of lifestyle activity,^{8,9} cognition,¹⁰ and psychosocial wellbeing,¹¹ and increased HC and total brain volume in men and women.¹² Given the encouraging results conducted in a group at elevated sociodemographic risk for cognitive and functional declines, follow-up of the full trial cohort using Centers for Medicare &

⁶ Varma, V.R., Chuang, Y., Harris, G.C., Tan, E.J., and Carlson, M.C. (2015). Low-intensity daily walking activity is associated with hippocampal volume in older adults. *Hippocampus*, 25(5):605–615.

⁷ Moored, K.D., Chan, T., Varma, V.R., Chuang, Y.F., Parisi, J.M., et al. (2018). Engagement in enriching early life activities is associated with larger hippocampal and amygdala volumes in community-dwelling older adults. *J Gerontol B Psychol Sci Soc Sci*, 10.1093/geronb/gby150 (advance online publication).

⁸ Gruenewald, T.L., Tanner, E.K., Fried, L.P., Carlson, M.C., Xue, Q.L., et al. (2016). The Baltimore Experience Corps Trial: Enhancing generativity via intergenerational activity engagement in later life. *J Gerontol B Psychol Sci Soc Sci*, 71(4):661–670.

⁹ Parisi, J.M., Kuo, J., Rebok, G.W., Xue, Q.L., Fried, L.P., et al. (2015). Increases in lifestyle activities as a result of experience Corps® participation. *J Urban Health*, 92(1):55–66.

¹⁰ Carlson, M.C., Saczynski, J.S., Rebok, G.W., Seeman, T., Glass, T.A., et al. (2008). Exploring the effects of an “everyday” activity program on executive function and memory in older adults: Experience Corps. *The Gerontologist*, 48(6):793–801.

¹¹ Fried, L.P., Carlson, M.C., Freedman, M., Frick, K.D., Glass, T.A., et al. (2004). A social model for health promotion for an aging population: initial evidence on the Experience Corps model. *J Urban Health*, 81(1):64–78.

¹² Carlson, M.C., Kuo, J.H., Chuang, Y.F., Varma, V.R., Harris, G., et al. (2015). Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes. *Alzheimers Dement*, 11(11):1340–1348.

Medicaid Services (CMS) data is under way to inform the program's long-term impact on risk for dementia and disability.

Although Experience Corp was successful, this high level of weekly activity has limitations. For example, participants with some physical or cognitive difficulties may not be ready to undertake this kind of social engagement. However, Dr. Carlson suggested that researchers could build appropriate scaffolding so that all individuals can move from low to high engagement. For example, Dr. Carlson's team has repurposed a stroke rehabilitation program "Bandit," an underwater three-dimensional game, to help individuals at all levels of physical function (e.g., severe chronic obstructive pulmonary disease [COPD]) play a cognitively and physically integrated activity game that immerses them in a virtual environment. Researchers must also consider the contributions of environments where participants live. Often those with the highest sociodemographic risk of cognitive decline due to individual factors, such as education, income, and race/ethnicity, live in environments associated with greater overall health risks (e.g., low income and education, high crime, limited access to grocery stores and park space). Community interventions can target both.

Adherence

General Adherence Issues

Presentation: Cognitive Behavioral Strategies to Increase Intervention Adherence

Neha Gothe, University of Illinois at Urbana-Champaign

Research suggests that exercise interventions can impact cognitive function, with theory-based interventions being the most beneficial. In addition, self-efficacy is an important predictor of initiation of and adherence to exercise interventions among older adults, and self-efficacy is highly modifiable (drawing upon experience or social persuasion). However, some individual and contextual factors may be more difficult to change (e.g., environment, neighborhood, demographics, personality traits).

Components of self-efficacy interventions for exercise adherence vary and include goal setting, feedback, removing barriers, and social support. All interventions should consider human behavior, the learning process, and the context of that behavior, with the goal of improving participant physical and emotional states.

Dr. Janet Larson's Active for Life: COPD trial seeks to assess how increasing time spent in light physical activity and decreasing time spent in sedentary behavior impacts COPD patients. This 10-week intervention (with up to 1-year follow-up) built around increasing self-efficacy for COPD patients (e.g., muscle soreness) suggested that behavioral change could have sustained effects (longer than 1 year).

Both psychosocial and neurocognitive approaches to increase exercise intervention adherence warrant consideration. For example, many individuals must deal with several tasks throughout their daily life (e.g., family, work), and those with the ability to arrange, integrate, and control cognitive actions (i.e., higher-level executive functions) may show increased adherence.

Researchers can use the experimental medicine approach to assess self-efficacy and determine how interventions that increase self-efficacy might influence behavior. However, much work remains to develop appropriate interventions and ultimately change behavior. Further, researchers should consider not only whether participants are attending the required trial sessions but also whether they are exercising for the prescribed intensity and time. The incorporation of confidence surveys at baseline and throughout a trial may help determine changes in self-efficacy over time. Researchers and clinicians must determine the best way to engage participants throughout the trial (as their confidence changes over time), as well as after the intervention ends.

Targets for Exercise Adherence and Ways to Increase Engagement in Exercise

Presentation: Targets for Exercise Adherence and Ways to Increase Exercise Engagement

Panteleimon (Paddy) Ekkekakis, Iowa State University

Strong evidence suggests that no single intervention other than exercise can influence so many combined outcomes (e.g., risk reduction for vascular disease, BDNF upregulation, HC plasticity, brain mass preservation, angiogenesis, neuroinflammatory inhibition, beta amyloid clearance in animal models). However, controversy remains regarding the benefits of exercise on cognitive function. Because most clinical trials for AD have failed, and many pharmaceutical companies have lost interest in pursuing AD research, prevention trials focused on physical activity hold promise. Dr. Ekkekakis urged panel members to consider ways in which the field can resolve the controversy around whether and to what extent exercise is beneficial for cognitive improvement and AD prevention. To resolve these controversies, researchers must address questions surrounding patient motivation to engage in physical activity interventions.

For primary prevention of AD, researchers should consider biomarkers as the primary outcome, rather than cognition. Once an individual is cognitively impaired, it may be too late to make substantial cognitive improvements. Pittsburgh compound B PET scan data suggest that by the time that cognitive symptoms appear the disease has plateaued and brain mass has already been lost. In those cases, exercise may aid in maintaining function and physical capacity, as well as help caregivers, but it will not reverse the effects of AD. Biomarkers could reframe the AD trial framework.

Proposals for exercise intervention trials often include prescribed exercise plans with a distinct lack of sophistication for those prescriptions (e.g., exercise will simply make life better). People are asked to adhere to exercise interventions because it is “good for their health,” with the expectation that people are rational and interested in their health and wellbeing. However, even individuals who are interested in their health and wellbeing likely will not adhere to their exercise prescription. Exercise is a unique case in public health, in which discordance between the knowledge of usefulness of the behavior (e.g., awareness of the health benefits) and doing the behavior (e.g., actual engagement in exercise) exists. For many people, the idea of exercise itself provokes negative memories (e.g., physical education, youth sports, adult weight loss), and changing that immediate reaction can be challenging.

In addition, clinicians recommend the amount of time a person should exercise (30 minutes currently). However, the critical issue is whether people will adhere to those guidelines. Dr.

Ekkekakis has adopted the Affect Heuristic model, where the mediator of adherence is pleasure and enjoyment (which may function through endocannabinoid system activation). This work has been difficult to fund and assess. However, some clear takeaways from this line of work have emerged, including the three-domain range of exercise intensity (i.e., moderate, heavy, severe). Severe exercise tends to make individuals feel worse, whereas heavy exercise causes a mix of positive and negative affect. Therefore, the recommendation for 30 minutes of exercise (reaching approximately 70 percent maximum intensity), puts patients at risk for feeling worse during exercise.

Discussion

Study designs must be flexible; for example, the current exercise trial by Dr. Pa and colleagues allows participants to select the path to follow (e.g., park, neighborhood) and health education subject matter. Choice seems to stimulate patient engagement. However, controlling for dose-response when participants choose their exercise interventions can be challenging.

Targets for Adherence to Reduce Risk of CVD Interventions and Ways to Increase Engagement in CVD Risk-Reducing Interventions

Presentation: Cerebrovascular Risk Factor Reduction: Movement, Metabolism, and Body Morphology

Patrick Smith, Duke University

The prevalence of cerebrovascular risk factors (CVRFs; e.g., obesity, diabetes), many of which put patients at increased risk for cognitive decline, has increased substantially over the past few decades. Most of these CVRFs (e.g., obesity, hypertension, vascular function, smoking) are modifiable by behavior change, yet individuals continue to behave in ways that put them at risk for disease.

Several strategic circuits within the subcortical and prefrontal brain regions critical for executive function (e.g., cognitive flexibility, vigilance, working memory) are highly susceptible to ischemia; therefore, they have the greatest potential to negatively impact cognition later in life. Executive function is also the cognitive domain most closely tied to functional outcomes among older adults. Therefore maintenance of executive function can mitigate the impact of AD-related neuropathological changes on daily functioning for many individuals at risk for AD-related dementia. Because the progression of amyloid deposition in some individuals cannot be slowed, strategies to preserve executive function offer a unique approach to mitigate the risk of dementia.

Individual differences present at trial entry may explain a substantial degree of variance in cognitive performance throughout a trial, and these individual characteristics are inconsistently measured and/or incorporated in trial outcome statistical modeling. Some clinical characteristics provide critical explanatory information on cognitive changes: chronological age, demographic markers of cognitive reserve (primarily education level), and cardiovascular disease risk burden. Because cognitive changes develop over decades, appear in various ways across premorbid levels of cognitive function, and may accelerate at critical age thresholds, studies that fail to account for these meaningful differences may provide underpowered treatment estimates.

The randomized controlled trial, Exercise and Nutritional Interventions for Cardiovascular Health (ENCORE), assessed how the Dietary Approaches to Stop Hypertension (DASH) diet alone or combined with aerobic exercise impacted blood pressure (primary endpoint) and cognitive function compared to a control condition. Researchers found that synergistic diet and exercise were associated with the greatest improvement in blood pressure. Metabolic measures (e.g., fitness and weight loss) appeared to drive motivation in the study. Further, participants performing diet alone still showed improved blood pressure, which could produce systemic effects important for cognition.

The ENCORE study was extended to the ENLIGHTEN study, which assessed the effects of the DASH diet and exercise on neurocognition in older adults diagnosed with cognitive impairments without meeting criteria for dementia. Researchers found that diet- and exercise-induced improvements in executive function and clinical dementia ratings were associated with additional behavioral and physiological improvements (e.g., aerobic fitness, composite CVD risk, and dietary salt intake). The results of this work suggest that weight loss and fitness improvements may confer cognitive improvements through overlapping metabolic pathways, such as insulin sensitivity, leptin, and insulin-like growth factor pathways. Therefore, if patients lose weight (salient target), they may exhibit changes in leptin (clinical target) and thus improved cognitive function.

It is important to choose mechanistically central targets (e.g., those tied to social or personal values that are naturally reinforced and upstream to multiple AD/ADRD pathways) that can be measured (e.g., step-counts, weight). Sustained adherence to a behavioral intervention is closely associated with self-regulatory capacity and therefore highly influenced by executive deficits. Therefore, people with cognitive impairments may not have adequately preserved executive function to independently evaluate and integrate long-term behavioral changes into their lives. However, if researchers facilitate ongoing self-monitoring of proximal behavioral targets (e.g., step count through Fitbits, diet applications, weight changes), salience, perceived control, and motivation to improve modifiable behavioral risk factors may indirectly increase as well. Recent behavioral treatment success is likely due to integration of executive functioning processes directly into the intervention's self-monitoring (e.g., inhibitory control, enhancing reward sensitization for behavioral targets) without explicitly targeting this treatment component (e.g., food diaries, diet applications, meal planning).

In addition, providing participants with the opportunity to experience early success (e.g., incremental behavioral target) is critical to building self-efficacy for more distal biobehavioral outcomes (e.g., eating more fruits and vegetables rather than measuring weight loss). Increasing the complexity of behavioral interventions will ultimately lower participant adherence; therefore researchers may benefit from selecting simple, naturally reinforced behavioral targets that prioritize participants' individual behavioral goals.

Use of Proxy Treatment Targets to Influence Motivation/Adherence

Presentation: Cohorts, Motivations, Proximal Targets

Michael Otto, Boston University, Planning Committee Chair

It is important to consider whether the success of motivational strategies for AD interventions depends on the phase in which the intervention is offered (i.e., early or late in cognitive decline). For example, risk reduction interventions often work best when the individual has symptoms that can be reduced by the intervention, to help bring about a cycle of reward for the target behaviors.

If symptoms are not present (e.g., young or asymptomatic individuals recruited for prevention trials), researchers could consider using proxy motivators. For example, because exercise interventions have a broad spectrum of action (e.g., treatment of major depression and anxiety, improved sleep and memory) alternative intervention targets can be used as proxy motivators in AD prevention trials. Further, studies have found that late-life depression is associated with increased risk for AD. Therefore, if researchers emphasize the benefits of exercise to treat depression, they can motivate participants to establish exercise routines and achieve short-term payoffs (e.g., treatment for depression) for a long-term goal (e.g., AD prevention). Similar strategies can be used for sleep disruption or early cognitive decline, both risk factors for AD.

Researchers can also use individualized, valued activities as proxy motivators to aid in exercise adherence. For example, evidence suggests that making an engaging book (presented auditorily over a handheld smart device) available only while exercising can provide a natural motivator to exercise. Training in mindful exercise can similarly be used to reduce an individual's negative cognitive habits that detract from pleasure during exercise. Finally, the initial "gamification" of exercise originated from sports, not from computer programming, to enhance enjoyment, sociability, and engagement in exercise. Interventionists can consider sports (e.g., basketball, volleyball, indoor rock climbing) in exercise planning to motivate participants. Given the longevity of exercise behaviors in prevention trials, shifting the target exercise over time may be required to refresh participants' motivation.

Further, in recruitment planning, researchers often attend to participants' symptom concerns, with the notion that participants with the highest concern over the targeted disease (e.g., due to a family history of AD) will be most motivated to join the trial. However, researchers also need to be cognizant of how a participant's fear of symptoms could lead to trial or intervention avoidance. Planning for the full spectrum of concern over symptoms and the degree of engagement-to-avoidance in participants may lead to more optimal recruitment and adherence.

Discussion

Experts on marketing and motivation could inform study design to help increase long-term adherence (i.e., 10 to 20 years). Researchers and clinicians should focus on value propositions for the participants; for example, Chinese technology companies placed a radio on a tracker for older adults so that they could track movement to prevent wandering and detect falls, and participants could listen to their favorite music/shows on the radio. Understanding what causes pleasure from exercise is the key to achieving its cognitive benefit, and that may not require the knowledge of marketing specialists.

Knowledge of the critical type and amount of physical activity to obtain maximal benefit (e.g., high-intensity interval training) and the optimal time to feel pleasure from physical activity is limited. Researchers should recognize consumer confusion about exercise guidelines. The frequent updating of the guidelines suggests that scientists lack the information needed to determine accurate guidelines. Therefore, many consumers may avoid changing their behavior until they believe a definitive recommendation has been made.

Feedback is necessary to attract participants' attention and maintain their motivation levels. Researchers should ask participants to focus on what they can change. Participants should feel accomplishment about positive changes, rather than disengagement about changes not yet achieved. Researchers should also recommend replacement rather than removal (e.g., add more fruits and vegetables rather than remove sweets from a diet).

Dr. Ekkekakis' study has not experimentally manipulated the focus of attention to a particular time before, during, or after exercise. However, his team has attempted to use computer technology to modify implicit association. A panel member suggested that clinicians prescribe modified mindfulness (e.g., playing positive music during exercise) and help participants notice when they feel the most pleasure (e.g., after a workout is complete, during an intense workout).

Researchers could consider a 24-hour lifestyle change in AD prevention, rather than only focus on acute exercise interventions, because physical activity and sleep interact with each other.

Development of Primary Prevention Trials

Presentation: Considerations for Designing AD Primary Prevention Trials

Erin Abner, University of Kentucky

Primary prevention in epidemiology refers to an intervention that occurs before the disease process has begun. Neurodegenerative dementia progression is challenging to track because it occurs over decades. Data from Dr. Abner's community-based dementia autopsy cohorts suggest that many patients have markers of neurodegenerative diseases other than or in addition to those for AD (e.g., not only amyloid and tau, but also alpha-synuclein and TAR DNA-binding protein 43 [TDP-43]). Therefore, if researchers consider other forms of neurodegenerative disease in their assessments, the field may be better positioned to identify specific mechanisms of action and secondary prevention for the underlying disease(s).

Dementia is a multi-etiology condition. FINGER and the Alzheimer's Association U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) are excellent examples of how intervention studies can incorporate various health-related factors (e.g., nutritional guidance, exercise, cognitive training and social activity, and management of metabolic and vascular risk factors) to assess cognition rather than patient AD biomarkers. However, multi-domain intervention studies can be burdensome and decrease overall patient adherence. It is important to consider intervention adherence as not only showing up for study sessions (as measured in the FINGER trial), but also adhering to the prescribed intervention duration and intensity.

Because humans have created easy access to food, water, and shelter, many populations no longer have natural reasons for physical activity. Therefore health-promoting behaviors must either be the result of repeated decisions (e.g., eating a healthy diet and exercising at least 30 minutes per day) or a change to an individual's environment. Although multi-etiology interventions are appropriate, individuals are not easily persuaded to perform activities that do not appear to serve their short-term interests (i.e., "hyperbolic discounting"). Previous success in changing human behavior has occurred largely through policy (e.g., smoking, seat belts, motorcycle helmets), which provides evidence that people will make lifestyle changes given the right conditions. AD researchers should consider including evolutionary biologists in this conversation to shed light on how humans have adapted to their lived environment and how they may be motivated to make lifestyle changes.

Various statistical methods exist to help researchers gain a better understanding of average treatment effects while accounting for adherence. The traditional method of analysis for randomized clinical trials, intention-to-treat (ITT; comparing subjects randomized according to treatment assignment at start of study regardless of actual treatment received), by design does not account for adherence. Instead, ITT provides a treatment effect estimate in the entire population. Per-protocol analysis compares treatments only among persons who complied with their treatment assignment. Therefore, treatment effects from per-protocol analysis are often of more interest to patients. Instrumental variable (IV) analysis adjusts the ITT estimator for adherence to an intervention. An important limitation of IV, however, is that results from this analysis can only be assumed to apply to individuals who would always comply with their treatment assignment (another name for an IV estimate is the "complier average causal effect"). Additionally, IV requires an exogenous variable, called the instrument, that is causally associated with the treatment but does not affect the outcome through any route other than treatment effects. In most clinical trials, randomization assignment can be used as the causal instrument.

Discussion

In addition to IV analysis, researchers could use traditional ITT analysis including dose–response (e.g., number of minutes of exercise completed in entire trial) to address adherence issues.

Positive social messaging is important; messages that link the outcome to a social good that extends beyond individual gain may be more successful in attracting participants and promoting adherence. Participant feedback is important and may help shape adherence strategies.

Individuals who adhere to a trial may be less likely to have cognitive impairment, and those who sign up to participate in trials are often seeking ways to prevent cognitive impairment. The field could explore (1) generalization of current clinical studies to the entire population; (2) instrumental and causal approaches, rather than observational studies; and (3) study designs that address individual baselines and motivations.

The success of intervention trials will likely depend on partnerships and teamwork beyond an academic center. For example, participants in Dr. Salloway's study also act as recruiters and spokespeople. Many highly motivated people (often with family history of AD/ADRD) are years away from cognitive decline, and researchers do not have the resources or time to follow them longitudinally until old age. Instead, researchers should aim to build a preventative lifestyle change model, similar to the fluoride model, for younger populations.

Addressing Research Gaps: Breakout Groups

Michael Otto, Boston University; Lis Nielsen, Jonathan W. King, and Lisa Onken, NIA

The research agenda moving forward to promote long-term adherence requires:

- Hypotheses about what features of the intervention are motivating or pleasure-inducing and measures of those intervention features and motivational targets (behavioral, biological)
- Evaluation of whether manipulation of key intervention features influences changes in motivational or affective targets
- Evaluation of whether changes in motivation or affect promote adherence to a physical activity regimen
- Attention to individual factors that might impact differential response

In addition, AD prevention studies beginning in early or middle adulthood will require improved outcome measures. Research should focus on increasing the sensitivity of cognitive tests and potential AD biomarkers. Such measures will enable researchers to more clearly demonstrate the benefits of preventive interventions. In addition, improved measures of factors such as affect and motivation that are hypothesized to promote adherence will also be needed. If the field can find a way to promote the positive affect of exercise, it would likely motivate people to continue with exercise regimens. Studies are needed to test hypotheses about what features of interventions induce motivation and how this can be sustained over many years.

The NIH Science of Behavior Change (SOBC) program was created to address the need for more mechanisms-focused behavior change research focused on targets such as motivation, affect, stress, self-regulation, and other processes that might influence the uptake and adherence to behavioral regimens. SOBC encourages adoption of the experimental medicine approach to behavior change research. This approach requires hypotheses about the processes and mechanisms that drive change, appropriate measures of these processes, and evidence that interventions that influence these processes lead to desired changes in behavior. Many studies do not include tests of mechanistic hypotheses. However, available tools can experimentally test these ideas in clinical trials. Researchers should focus on what motivates people in the population they are studying (e.g., social needs) and how motivation changes over the lifespan (inclusion of young, middle-aged, and older adult populations). There is great need for one to three large-scale studies to address the issues of motivation and adherence 5 years post-intervention (i.e., legacy effects) as well as the consideration of primary outcomes of such trials.

All workshop participants split into three groups to address study designs to elucidate mechanisms that promote adherence (e.g., motivation, affect) to physical activity regimens (or other interventions) to inform future primary prevention approaches for AD and cognitive decline. They were asked to incorporate flexibility into study design and to focus on aging as a life-course phenomenon. Each group was asked to consider group-specific questions as well as the following overarching questions:

- Who is targeted?
- What features of the intervention(s) are motivating or pleasure-inducing (or the contrary)?

- How are targets measured (e.g., through behavior, neuroimaging, biomarker assays, self-report)?
- Does the motivation assay change in response to key features of the intervention?
- Does change in motivation in response to key features of the intervention promote adherence?

Breakout Group Reports

Cohorts

Reporter: *Jeff Williamson, Wake Forest Baptist Health*

This group discussed the right cohort for intervention and the right times to initiate the intervention and to begin assessment of AD or related proxy outcomes. The members concluded that a successful cohort consists of the following features:

- An intergenerational component that can leverage community-based relationships and motivate within and across families and friendships. This would promote long-lasting cultural diversity and social engagement and would provide the opportunity for shorter testing time and more long-term interventions. Researchers could perform pragmatic assessments with electronic health record data as they become available.
- The inclusion of all levels of risk including high risk. However, there must be a mechanism for genotyping or phenotyping at baseline to determine the impact of the intervention in these different populations.
- Multiple recruitment strategies for heterogeneous populations (e.g., social media, churches, synagogues, community centers).
- A menu of interventions that promote personalized approaches to be successful and flexible at all stages of life (helping people adhere to the intervention and reducing the impact of progression) with variable schedules of reinforcement.
- Refined models of dynamic intervention and adherence (as the science and world changes).

Mechanism Issues

Reporter: *Kirk Erickson, University of Pittsburgh, Planning Committee Member*

This group discussed core and theoretically derived mechanistic targets, the range of interventions to be tested, and known moderators for these mechanisms. The group members concluded that the core mechanistic issues for ameliorating AD risk include the following:

- Targets across different analysis levels (imaging to behavioral tests) and the incorporation of that analysis into study design (e.g., similar to SMARRT design in that flexibility in the intervention exists throughout the trial). This might require smaller, early-stage research.
- Precision of instruments and the need for multiple assessments, including appropriate biomarkers over time to better understand how an intervention is working.
- Understanding of how to motivate people to embrace a virtuous cycle of health behaviors (e.g., cognitive training can improve sleep quality) even after life events might have interrupted.
- Study design to promote adoption and adherence across the ages, especially in sedentary

midlife adults.

- Consideration of how biological mechanisms might relate to behavioral mechanisms and how best to provide feedback to participants (e.g., are participants “getting in the lactate or BDNF zone”).
- Secondary analysis of existing study data (e.g., personality, genetics, mood, acute effects of exercise on affect and cognition) to predict intervention adherence or combinations of factors that can predict long-term adherence.
- Consideration of adherence during and after the intervention (i.e., what participants are doing in everyday life, and whether the predictors are similar). Most studies do not follow people over extended time periods; however, if studies added time series data, researchers could assess how predictors might change over time.

Adherence

Reporter: *Michelle Carlson, John Hopkins University, Planning Committee Member*

This group discussed appropriate mechanistic targets to improve adherence; empirical links supporting adherence strategies to appropriate mechanistic targets; targets at the family/community levels and person-level interventions; technology-assisted strategies; and additional strategies relevant to participant age, degree of AD risk, or other moderators of adherence strategies. The members developed the following list of considerations:

- Pattern of dosing: Structure physical activity to promote adherence and how to embrace affective response to gain the maximum reward, pleasure, and long-term sustainability of that behavior.
- Measure adherence in real time: Measure more than simply showing up to the intervention with the use of wearable devices that can measure movement objectively.
- Harness technology (gaming for purpose and pleasure): Take advantage of technology that participants are already using (e.g., television) to promote physical activity and learn from failed opportunities in this area of research.
- Gather the right people (and funding) to build trials: Promote interdisciplinary work teams and reward engineers, professional motivators, entertainers, and professional athletes and exercise professionals who enter the conversation. Researchers need to find ways to make interventions aesthetically pleasing, engaging, and effective so participants are encouraged to continue.
- Understand why people move: There is evidence to suggest that people move for purpose, pleasure, and curiosity. A focus on (1) gamification and increased demand and (2) optimal dosage will help build successful trials. Researchers should also consider what is already available (pragmatic trials) and build on those, rather than starting anew.
- Focus on individual differences: Consider how traits, such as personality, might drive behavior. Systematically assess small group versus individual behavior (six seems to be the magic number for small group behavior).
- Barriers to adherence: Consider the use of a registry where groups donate resources to offset AD risk burden (e.g., gyms, health care, transportation, or other forms of support).

Common Themes from Breakout Groups

Intervention Designs

The idea of multiples was addressed throughout each breakout session, including (1) multi-risk cohorts with multiple risk factors to capture the range between primary and secondary prevention; (2) multi-modal, multi-level interventions or strategy choice over time (changing motivational salience); (3) adaptive intervention approaches with attention to rescue strategies (built in for when motivation lags); and (4) multidisciplinary, multi-field professional collaborations to share expertise and ideas (e.g., the inclusion of marketing and technology professionals to help make aesthetically pleasing, compelling, and effective interventions).

Motivation and Social Engagement

Researchers could form focus groups to learn about participants' life histories and to create motivation/adherence composite scores to predict and increase motivating factors across populations. They could also randomize at the social node (i.e., person connecting a social network) to promote social engagement and to consider self-perception within that social environment. One panel member cautioned against the use of gaming because of habit formation, especially in youth.

Outcomes Measures and Use of Existing Data

The POINTER trial measures adherence in a manner similar to the FINGER trial. Researchers had the capability to improve measurements of adherence for this trial, especially because the primary outcome is often multi-factorial, as in cardiovascular research.

Existing cohort data offer great value, though considering the design of the parent trial is critical. When researchers look beyond a disease and engage other cohorts, they often have a richer population to study. However, the issue of subject burden should be addressed. FHS has expressed willingness to consider clinical trials focused on AD measurements. If researchers want to begin discussions with FHS or other cohort studies, they should justify the value proposition for these research programs.

The DIAN-TU population is a useful population to study because researchers can begin to assess the disease immediately (i.e., age 18). The Generations trial was designed to assess treatment efficacy, safety, and biomarkers in APOE ϵ 4-positive, cognitively normal individuals aged 60–75, providing the opportunity to assess a healthy older population at high risk for AD. Researchers could use available information from the Generations trial (e.g., amyloid PET scans, genotyping, cognition data) to assess whether a lifestyle intervention could positively impact this high-risk population that is no longer being medically treated. Novartis and Banner Alzheimer's Institute might provide access to this information.

Long-Term Lifestyle Changes

Dr. Erickson's study assessing the impact of African Dance on cognition in older African Americans provides evidence that the intervention was motivating and promoted long-term lifestyle changes. Specifically, after a 6-month pilot intervention, participants were eager to continue. Therefore, Dr. Erickson's team developed a separate class through independent funds to support the maintenance of the program. However, funding for the interventions may not be available when the trial concludes. Academic researchers should also consider how to address participants' negative

perceptions, particularly those that impact their motivation to join a study. Some participants have reported being hesitant to join trials because of concerns that a university will begin an intervention trial, gather the necessary information, and then abandon the participants. One possibility to prevent negative perceptions is to build a maintenance plan into the study design to support participants after the intervention ends.

Addressing Different Levels of Alzheimer's Disease Risk

Trials should include all levels of risk because current studies cannot access everyone. Therefore, it might be necessary to phenotype the interventions and carefully assess non-responsivity to interventions. This approach would allow researchers to select participants who require more intensive interventions. Another consideration is multi-stage design, where participants start with a low-intensity intervention and then gradually increase intensity as necessary. Oncology clinical trials often adapt intervention models in a multi-stage manner (e.g., begin with a universal intervention and then personalize). Gaming provides the opportunity to meet people where they are, both cognitively and physically.

Professional Partnerships

Promoting long-term change will require establishing sustainable partnerships (e.g., workplace, insurance companies, higher education, churches, foundations, YMCA) and educating those partners on the importance of proposed interventions. In particular, if researchers can encourage workplace communities to align with research goals, participants may be more successful with long-term adherence. Scientists should teach their students (e.g., graduate students, postdocs) about the importance of engaging community stakeholders.

Intervention group leaders could be transferred to locations outside the academic institution (e.g., community centers) to maintain lifestyle changes. However, moving an intervention to an outside partner (e.g., YMCA) may require individual payment, which could be a barrier to participation. The Mental Activity and Exercise (MAX) trial partnered with the YMCA immediately, so participants became comfortable with the facility. Once the trial ended, the YMCA provided discounts to study participants to help maintain life-long changes. The POINTER trial is developing a similar partnership with the YMCA, whereby patients can receive a prescription for YMCA protocols.

Many small businesses are excited about the mechanisms of behavior change approach and seek help in developing ways to promote behavioral changes. Although incentives for academics (e.g., funding for lab, promotion) may be minimal, in the long-term developing strategies to address AD prevention will help the community and the population. The concept of multiple revenue streams is necessary to move the field of behavior change forward. Technology companies often see great value in partnering with researchers, as a way to introduce their technology to new consumer and investor groups.

Collaboration and Funding

Presentation: Mechanisms of Behavior Change as Drivers of Collaborative Impact: The NIH Science of Behavior Change Program

Donald Edmondson, Columbia University

The overlap between crucial targets in cognitive health and cardiovascular health creates many opportunities for collaboration among cognitive, cardiovascular, and behavioral researchers. The SOBC program offers a unique framework for guiding such collaborations. Few interventions reliably produce lasting behavior change for large numbers of people. A future goal of the SOBC program is to identify how to maintain behavioral change in diverse populations. The experimental medicine approach aims to identify mechanisms underlying behavior change to develop targeted interventions to influence those mechanisms (moving beyond the biological mechanisms mediating AD prevention or treatment). NIH funding opportunities, including those for research on behavior change, regularly require use of the experimental medicine approach, and collaborative efforts are necessary to ensure long-lasting behavior change.

As part of the NIH Common Fund, the SOBC program combines basic and applied research aimed at shifting the focus of behavior change science to the underlying neural, cognitive, affective, interpersonal, and environmental mechanisms by which interventions can cause behavior change. The keys to progress in behavior change include (1) uniting basic and applied researchers, (2) focusing on mechanisms of change, (3) developing and applying a common scientific method, and (4) optimizing interventions to promote effectiveness. The SOBC Program has created exciting tools to assess behavior change that are available free to the public.¹³ The SOBC Measures Repository provides experimentally identified measures of potential mechanisms of behavior change. Researchers can download the detailed measures directly and incorporate them into their own studies (Open Science Framework). The next version of the Repository will include Google scholar-related articles to assess frequency of use. Further, the SOBC program is working with the Busara Center for Behavioral Economics to develop a site for all scientists with university affiliations to upload and download measures and to discuss measurement properties and outcomes (e.g., how to code Fitbit movement) for simple transfer into IRB protocols.

Future SOBC program tools include empirical and visual ontologies (e.g., Poldrack/Marsch), automated visualized systematic review, and experimental medicine guidelines and manuscript templates. In addition, the SOBC program is developing a Triad Tool to perform rapid automated systematic review to identify what is currently known and next steps for the field. The overarching goal is to use the SOBC Measures Repository to provide details for the Triad Tool, which will in turn determine the tailored measures that a researcher could include in a study plan (Figure 2) and will help researchers to report the experimental medicine approach. Successful change requires behavior scientists to change their behaviors in ways that may not benefit them personally but will make a difference in the overall field.

¹³ For additional information, see <https://scienceofbehaviorchange.org/>.

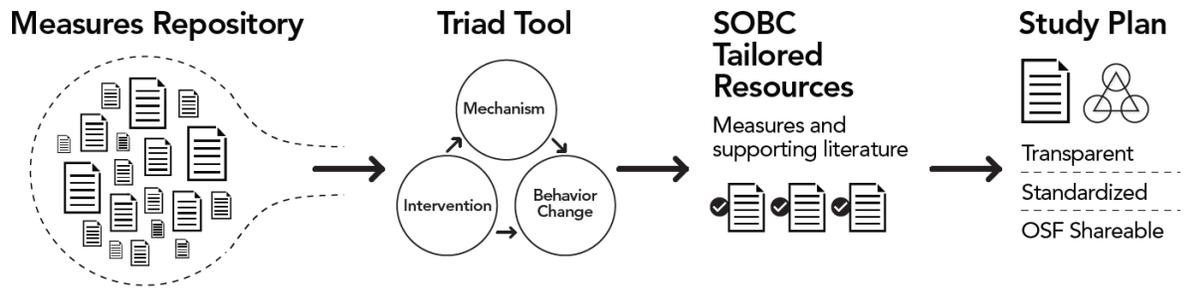


Figure 2. Future SOBC Workflow

Discussion

The Measures Repository was developed with the goal to provide an opportunity to determine whether a measure or mechanism did or did not work, ensuring that even negative results are reported. There are also plans for links to other repositories. The SOBC program wants to ensure that researchers use the tool perpetually. The NIH Common Fund prefers researchers to develop deliverables that incorporate basic science and validation. Transparency is key, and providing measures alongside effect sizes (i.e., how tightly measures are linked to outcomes) will strengthen the usefulness of the measure.

Concerns were raised about reliability and validity in the SOBC Repository, especially for scientists who are new to this research area. One way to address this concern is to require researchers to provide their name in association with the measures to promote collaboration and validation. Establishing the Repository will include a labor-intensive curation process, involving experts who are invested in the program’s success. The SOBC program will provide sufficient information about each measure’s population and validity. The program is also developing ways for researchers to receive academic credit for uploading information to the Repository (e.g., CV line items). Other potential features include a variation of academic Reddit for researchers to provide feedback and opinions and “office hours” for researchers to consult with each other.

The SOBC program is developing plans to address the nuances of the Measures Repository and possible intellectual property concerns. Copyrighted measures are currently not included in the Repository. The need for better digital sharing policies also exists. The SOBC program could utilize a technology that matches collaborators (e.g., “researchmatch.org”), especially for early career scientists or researchers from underrepresented universities or less intense research environments. Major paradigm shifts will occur if academic researchers collaborate with people outside the field (e.g., Dream Challenges by Sage Bionetworks).

Many researchers are not aware of the complexity of measurement issues for the Repository. For example, leaders in the field were quick to reject invitations to work on a project to bring together neuropsychiatric measures for obesity and diabetes trials. Further, test-retest protocols (i.e., basic psychometrics) are difficult to find. However, if the SOBC program can build a more predictive science, researchers could determine individual differences across diverse populations.

The involvement of the U.S. Centers for Disease Control and Prevention (CDC) or the Food and Drug Administration (FDA) may be required to help researchers influence the public agenda.

Closing Comments

Lis Nielsen, NIA, Michael Otto, Boston University

SOBC strives to bring together unusual suspects in the same room, and this meeting has been an example of taking that approach. Connecting basic behavioral and psychological scientists with researchers conducting interventions in the field (e.g., economic, mental and cardiovascular health, age-related cognitive impairment) can inspire conversations about how the study of basic behavioral mechanisms, in the context of disease-focused behavior change interventions, can accelerate progress and break down silos in the field.

Dr. Otto thanked the committee members and speakers for participating in the workshop.

Appendix A: Workshop Agenda

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

DIVISION OF BEHAVIORAL AND SOCIAL SCIENCES AND EDUCATION
Board on Behavioral, Cognitive, and Sensory Sciences

Incorporating the Experimental Medicine Approach in the Development of Primary Prevention Trials for Alzheimer's Disease: A Workshop

October 10-11, 2019

Keck Center of the National Academies
500 Fifth Street, NW, Room 103
Washington, DC 20001

DAY ONE: THURSDAY, OCTOBER 10, 2019

Please note: Coffee and water will be provided by the National Academies starting in the morning. However, no food will be provided. Please purchase food items in the cafeteria on the 3rd floor (breakfast, lunch, snacks) and save receipts for reimbursement.

9:00 a.m. WELCOME AND OVERVIEW OF MEETING

- Michael Otto, Boston University, Planning Committee Chair
- Adrienne Stith Butler, BBCSS Associate Board Director
- Julie Schuck, BBCSS Program Officer

SPONSOR'S WELCOME

- Lis Nielsen, National Institute on Aging
- Jonathan King, National Institute on Aging
- Lisa Onken, National Institute on Aging

9:30 a.m. COHORT CONCERNS: THE WHO, WHAT, WHEN FOR INTERVENTIONS AND RISK OUTCOMES

- Deborah Barnes, University of California, San Francisco
 - Cohort Concerns: The Who, What, & When for Alzheimer's Prevention

Trials 9:45 a.m. Questions and discussion

9:55 a.m. EARLY OUTCOME ASSESSMENTS FOR AD TRAJECTORY

- Rhoda Au, Boston University
 - The Path to Zero is One: Accelerating Innovation and Discovery for AD through a Precision Brain Health Approach
- Stephen Salloway, Brown University Medical School and Butler Hospital
 - Our Experience with Recruitment of At-Risk Participants for Alzheimer's Prevention Trials

10:25 a.m. Questions and discussion

10:45 a.m. BREAK

MECHANISM TARGETS FOR INTERVENTIONS MORNING

- 11:00 a.m. EXERCISE
- Kirk Erickson, University of Pittsburgh, Planning Committee Member
 - Moderators and Mediators of Exercise Effects on Brain and Cognition
- 11:15 a.m. Questions and discussion
- 11:25 a.m. CARDIOVASCULAR DISEASE RISK REDUCTION
- Jeff Williamson, Wake Forest Baptist Health
 - Mechanistic Targets and Moderators for the Effects of Cardiovascular Disease Risk Reduction on AD
- 11:40 a.m. Questions and discussion

11:50 p.m. LUNCH BREAK (Lunch available for purchase on 3rd floor)

- 1:00 p.m. RETURN FROM LUNCH
- 1:00 p.m. COGNITIVE TRAINING
- Michelle Voss, University of Iowa
 - Mechanistic Targets and Moderators for Cognitive Training and Exercise: Similarities, Differences, Potential for Synergy
 - George Rebok, Johns Hopkins University
 - Preventing Cognitive Decline and Alzheimer's Disease Dementia: Evidence for Cognitive Training
- 1:30 p.m. Questions and discussion
- 1:50 p.m. MULTIMODAL INTERVENTIONS
- Judy Pa, University of Southern California, Planning Committee Member
 - Combined interventions, coupling physical and cognitive activities into a single design; digital interventions and devices used for combined interventions
 - Michelle Carlson, John Hopkins University, Planning Committee Member
 - Interventions that combine cognitive and physical activities in social contexts; social engagement as a motivator of activity; use of technology in multimodal interventions
- 2:20 p.m. Questions and discussion

ADHERENCE AFTERNOON

- 2:40 p.m. GENERAL ADHERENCE ISSUES
- Neha Gothe, University of Illinois at Urbana-Champaign
 - Cognitive Behavioral Strategies to Increase Intervention

Adherence 2:55 p.m. Questions and discussion

3:05 p.m. BREAK

3:20 p.m. TARGETS FOR EXERCISE ADHERENCE AND WAYS TO INCREASE ENGAGEMENT IN EXERCISE

- Panteleimon (Paddy) Ekkekakis, Iowa State University
 - Targets for Exercise Adherence and Ways to Increase Exercise

Engagement 3:35 p.m. Questions and discussion

3:45 p.m. TARGETS FOR ADHERENCE TO REDUCING RISK OF CVD INTERVENTIONS AND WAYS TO INCREASE ENGAGEMENT IN CVD RISK REDUCING INTERVENTIONS

- Patrick Smith, Duke University
 - Cerebrovascular Risk Factor Reduction: Movement, Metabolism, and Body Morphology

4:00 p.m. Questions and discussion

4:10 p.m. USE OF PROXY TREATMENT TARGETS TO INFLUENCE MOTIVATION/ADHERENCE

- Michael Otto, Boston University, Planning Committee Chair
 - Cohorts, Motivations, Proximal

Targets 4:25 p.m. Questions and discussion

4:35 p.m. DAY 1 WRAP-UP

- Michael Otto, Planning Committee Chair
 - Summary of Day 1; Overview of Day 2

4:45 p.m. CONCLUDE DAY ONE

DAY TWO: FRIDAY, OCTOBER 11, 2019

9:00 a.m. WELCOME

- Michael Otto, Planning Committee Chair
 - Review of Day 1; Overview of

Day 2 9:15 a.m. DEVELOPMENT OF PRIMARY

PREVENTION TRIALS

- Erin Abner, University of Kentucky
 - Considerations for Designing AD Primary Prevention

Trials 9:30 a.m. Questions and discussion

ADDRESSING RESEARCH GAPS BREAK OUT GROUPS

9:45 a.m. STUDY DESIGN: COHORTS in K102

- Planning Committee and Speakers
 - Given the material discussed yesterday, please work to summarize responses to the following questions: What is the right cohort for intervention (specifically, what are the costs vs. benefits of selecting specific risk cohorts, and how do these selection factors change based on age)? What is the right time for initiating the intervention and what is the right time to begin assessing AD or related proxy outcomes given the interventions being considered?

STUDY DESIGN: MECHANISM ISSUES in K103

- Planning Committee and Speakers
 - Given the material discussed yesterday, please work to summarize responses to the following questions: What are the core mechanistic targets associated with the role of exercise, cardiac factors, and cognitive training interventions for ameliorating AD risk? Are there recommendations about the range of interventions that should be tested, given what is and what is not known about the ability of these interventions to engage the putative mechanistic targets? What are additional theoretically-derived mechanistic targets that should be assessed in addition to core variables already discussed? What are the known moderators for these mechanisms?

STUDY DESIGN: ADHERENCE in K104

- Planning Committee and Speakers
 - Given the material discussed yesterday, please summarize some of the appropriate mechanistic targets to be considered for the task of improving adherence (using, as a core example, the difficult task of initiating and maintaining exercise interventions across years). Please link empirically-supported adherence strategies to appropriate

mechanistic targets, and consider targets at family/community levels in addition to person-level interventions. Discussion of technology-assisted strategies is encouraged, but the mechanistic target of such strategies should also be noted. Finally, please consider additional strategies that are relevant to participant age, degree of AD risk, or other moderators of adherence strategies.

10:45 a.m. BREAK

- 11:00 a.m. GROUP DISCUSSION OF BREAK OUT SESSIONS STUDY DESIGN: COHORTS (15 minutes)
- Michael Otto, Planning Committee Member
- STUDY DESIGN: MECHANISM ISSUES (15 minutes)
- Kirk Erickson, Planning Committee Member
- STUDY DESIGN: ADHERENCE (15 minutes)
- Michelle Carlson, Planning Committee Member
- GENERAL DISCUSSION (15 minutes)

12:00 p.m. BREAK FOR LUNCH (Available for purchase on 3rd Floor)

- 1:00 p.m. COLLABORATION AND FUNDING
- Donald Edmondson, Columbia University
 - Mechanisms of Behavior Change in Primary Prevention Trials: The NIH Science of Behavior Change Program
 - Planning Committee Members
 - What are novel collaborative methods and funding strategies for a study like this? In the absence of a long trial, what are some things we can learn from other studies or short-term goals/studies that piggy back on other studies?
- 1:45 p.m. CLOSING COMMENTS
- Michael Otto, Planning Committee Chair

2:00 p.m. ADJOURN

Please note: Coffee and water will be provided by the National Academies starting in the morning. However, no food will be provided. Please purchase food items in the cafeteria on the 3rd floor (breakfast, lunch, snacks) and save receipts for reimbursement.