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Understanding Pathways to Successful Aging: Behavioral and Social Factors Related to Alzheimer's Disease

Proceedings of a Workshop—in Brief

A strong body of research demonstrates associations between the incidence of Alzheimer's disease and individuals' personality characteristics, level of social engagement, and educational attainment. To advance understanding of the causal pathways leading to Alzheimer's, the Board on Behavioral, Cognitive, and Sensory Sciences (BBCSS), with support from the Division of Behavioral and Social Research at the National Institute on Aging (NIA), convened a workshop in June 2017. This workshop was designed to build on a 2015 workshop that focused on the importance of delineating causal relationships underlying associations between behavioral, social, and biological factors and long-term health.¹

NIA asked BBCSS to focus the current workshop on three objectives:

1. examine how personality has been convincingly associated with Alzheimer's disease, particularly with evidence of an association between the personality facets of conscientiousness and neuroticism and the risk of the disease;
2. follow up on the suggestion that a socially integrated and engaged life-style has been associated with slower cognitive decline and a reduced incidence of Alzheimer's disease; and
3. examine the role of educational attainment, which is considered to be the most replicated association of a social or behavioral factor and Alzheimer's disease.

Personality, social engagement, and educational attainment are of specific relevance to NIA and have high potential to generate intervention or prevention strategies for Alzheimer's disease that would be developed by NIA.

This document summarizes the presentations and discussion. More information about the project and the workshop (including presentation slides) can be found at www.nas.edu/UnderstandingPathwaystoAlzheimers.

SETTING THE STAGE

Lisbeth Nielsen (Division of Behavioral and Social Research [BSR] at NIA) set the context by describing the division's mission, noting that BSR supports research on aging as a process over the life course. The division is particularly interested in furthering understanding of the causal pathways through which behavioral and social factors affect trajectories of aging.

Jonathan King (director, cognitive aging program related to Alzheimer's disease, BSR) elaborated on the research issues that motivated the workshop, stressing that the next area of research that is needed is elucidating the pathways through which various factors affect the prevalence of the disease. He noted that this workshop was designed to help NIA identify future directions for this work.

¹National Academies of Sciences, Engineering, and Medicine. (2015). *Understanding Pathways to Successful Aging: How Social and Behavioral Factors Affect Health at Older Ages—Workshop in Brief*. Washington, DC: The National Academies Press. Available: <https://www.nap.edu/read/21815/chapter/1> [August 2017].

METHODOLOGICAL APPROACHES FOR UNDERSTANDING PATHWAYS TO ALZHEIMER'S DISEASE

The first set of presentations focused on various study designs and methods for understanding pathways to Alzheimer's disease.

OBSERVATIONAL APPROACHES

Roger Dixon (Faculty of Science/Psychology, University of Alberta) focused on how longitudinal data can be used not only to chart normal cognitive aging or transitions to Alzheimer's disease but also to explore alternative pathways and predictors that may reflect possible mechanisms to more successful outcomes. He illustrated what might be possible in this area by discussing findings from data collected through the Victoria Longitudinal Study,² a large longitudinal study that began collecting data in the late 1980s and includes multiple measures from key domains of the risk of Alzheimer's, including cognition, health, demographics, and life-style.

Dixon stated that to fully capitalize on such datasets, it is necessary to look beyond group mean changes and consider individual trajectories and stratified data, demonstrating this point with the example of the effect of pulse pressure (an indicator of vascular health) on episodic memory, which is a cardinal marker of Alzheimer's disease. Stratifying results on the basis of variation in the ApoE gene reveals differential effects of vascular health on episodic memory, depending on which of three main clusters of ApoE genotypes individuals have.

Dixon noted that although longitudinal databases do not afford experimental control, they offer the opportunity for precision risk assessment across multiple interacting factors, as well as precision recommendations for preventing Alzheimer's disease. He added that focusing on the individual level is not feasible, but looking at clusters of people based on stratification techniques may be fruitful.

RANDOMIZED CONTROLLED TRIALS

Arthur Kramer (workshop chair; senior vice provost for research and graduate education, Northwestern University) discussed considerations for using randomized controlled trials (RCTs). He began by noting that one of the advantages of RCTs is that randomization makes it possible to define causal pathways, which is not easily done with observational studies. However, RCTs tend to be more limited than observational studies in terms of representing the population and usually are limited to small samples due to cost, which restricts opportunities for stratification.

Kramer noted the importance of having an appropriate control group in an RCT. Many RCTs use no-contact control groups, and often the main finding of such studies

²See <https://sites.ualberta.ca/~vlslab/> [August 2017].

is that doing something is better than doing nothing. Though studies that use an active control group can be more difficult to design, they often yield more meaningful results. In thinking about how to design an active control group, he stated that, ideally, conditions in the control group would include everything from the experimental group, except for the "secret sauce" (the variable—often not obvious—having the greatest effect on outcomes), but it is very difficult to determine how to achieve this ideal. Other suggestions Kramer offered included accounting for expectancy or placebo effects and augmenting the measures and statistical techniques that are typically used with other techniques to increase generalizability, such as multivariate regression, machine learning, neuroscience measures, measures of brain structure and function, and biomarkers with psychosocial measures.

COMMUNITY-BASED INTERVENTIONS

Michelle Carlson (Bloomberg School of Public Health, Johns Hopkins University) discussed considerations for moving from observational trials to community-based interventions. She focused on findings from Experience Corps,³ a national community-based program now led by AARP, in which individuals aged 60 and older are recruited to volunteer to work with children in local elementary schools.

Carlson advised that messaging is very important. Given the strong evidence base demonstrating how important exercise is for maintaining or improving health, Carlson and her colleagues viewed any increase in physical activity as positive, which was one outcome with Experience Corps volunteers, who typically walked between their homes and the schools in which they volunteered. However, she learned during the recruitment process for Experience Corps that having a message relating to exercising for personal health benefit is not as appealing to people as asking them to participate in social engagement with a purpose.

Carlson noted that the hippocampus is an important target region for memory changes and as a biomarker for Alzheimer's disease. She and her colleagues were interested in exploring whether social stimulation and navigating complex environments in day-to-day life is related to cognitive and brain benefits in the same way as aerobic exercise. They found a selective association between increased levels of low-intensity physical activity and the subiculum of the hippocampus, which is mechanistically related to spatial navigation.

Carlson and her Experience Corps colleagues were hoping merely to forestall decline in hippocampal volume. Both genders saw gains in hippocampal volume, but gains

³The AARP Foundation Experience Corps is an intergenerational, volunteer-based tutoring program that engages adults aged 50 and older as literacy tutors for struggling students in public schools.

were seen earlier and were more pronounced for males than for females. By comparison, individuals in the control group (assigned to a low-activity condition) experienced an expected age-related reduction in hippocampal volume. Increases in hippocampal volume were behaviorally related to improvements in memory, Carlson reported. Experience Corps participation was also related to changes in the amygdala, which is an important region for socially salient information and another biomarker for Alzheimer's risk. These changes were behaviorally related to increases in feelings of generativity, a potentially important motivator for sustaining physical and social activity.

In terms of facilitating individuals' physical activity, Carlson noted the importance of making communities more walkable and ensuring safe access to areas for exercise. She added that people are drawn to novelty and fun, so spaces designed to encourage physical activity should include novel and fun elements.

Carlson identified several questions for future study. Her team is interested in exploring whether individuals' expectations regarding aging is a factor in aging outcomes and whether how an individual feels about his or her value or worth influences both adherence to and effects of interventions. Another question they have identified is whether socially salient pathways operate differently than, and therefore complement, learning pathways.

PERSONALITY

The second set of presentations provided a framing of what is known about the role of personality in the development of risk factors for cognitive decline, potential mediators of the relationship between personality and Alzheimer's disease, and what happens to personality pre- and postdiagnosis of the disease.

PERSONALITY AND THE RISK OF DEMENTIA AND ALZHEIMER'S DISEASE

Angelina Sutin (College of Medicine, Florida State University) discussed moderators and mechanisms of the relationship between personality and Alzheimer's disease. Data from the Baltimore Longitudinal Study of Aging (BLSA),⁴ which followed participants for over 20 years, and a meta-analysis, show there is a very consistent relationship between aspects of personality, particularly neuroticism and conscientiousness, and the risk of Alzheimer's. Individuals who score high in neuroticism are at increased risk of developing the disease relative to those who score low in neuroticism; individuals who score high in conscientiousness are at lower risk of developing it relative to those who score low in conscientiousness. In order to better understand the relationship, she discussed findings related to the association between various facets of conscientious-

ness and incidence of dementia, based on data from both the BLSA and the Health and Retirement Study (HRS).⁵ Of the eight facets examined across both datasets, three were found to have consistent relationships with incidence of dementia and Alzheimer's disease: self-discipline/self-control, order, and dutifulness/responsibility.

Sutin noted that people who score high on the facets of self-discipline/self-control and order tend to create very stable and predictable environments for themselves. Such environments are associated with lower stress levels, which in turn supports healthier brain aging and affords advantages when an individual begins to experience difficulties in cognition. Having a stable and predictable environment can help maintain functionality, enabling an individual experiencing cognitive decline to remain longer in her or his known environment. The facet of dutifulness/responsibility is the only facet that has an interpersonal component to it, Sutin explained, as it involves the propensity to be reliable for other people; this accountability is protective independent of other aspects of conscientiousness.

In looking at whether there was variation in associations between personality facets in relation to demographic or genetic characteristics, Sutin said that her research has not found differences based on gender, ApoE allele, or race, though the facet of traditionalism appears to be protective against dementia for Hispanics.

Sutin identified several strategies and directions for future research. She suggested that there needs to be further examination of how the processes associated with personality translate into biological factors that affect the brain. She also suggested that data from social media avenues like Facebook could provide opportunities to look at individuals' activities and interests over their lifespans. In addition, ecological momentary assessment can provide more frequent assessments of both personality and mechanisms, and they could be combined with more frequent biological measures.

LIFESPAN MODELS OF PERSONALITY AND HEALTH

Grant Edmonds (Oregon Research Institute) focused on applying lifespan models of personality and health to enhance research on cognitive resilience. He noted that if studies show that conscientiousness predicts mortality, one should be able to detect associations between intervening health states and identify plausible pathways linking personality to health.

Edmonds discussed a hypothetical causal model for how childhood conscientiousness might be related to health in older age and mortality, showing pathways through adult conscientiousness, modifiable health behaviors, social environmental factors, and cognitive ability. He then described efforts to identify pathways using data from the

⁴See <https://www.blsa.nih.gov/> [August 2017].

⁵See <http://hrsonline.isr.umich.edu/> [August 2017].

Hawaii Longitudinal Study of Personality and Health.⁶ He noted that personality is not perfectly stable: the Hawaii study has yielded an average stability coefficient of about 0.25. Therefore, it is important to measure personality at various points across the lifespan.

Edmonds described gender similarities and differences in the mediating pathways between childhood conscientiousness and physiological dysregulation. For men and women, lower educational attainment and negative health behaviors, including smoking and low physical activity, were associated with higher incidence of physiological dysregulation, though educational attainment appears to be a more important mediator for men. For women, adult cognitive ability was also found to be a mediator.

Childhood openness is another personality factor that Edmonds suggested might be important for cognitive aging because it is consistently related to cognitive ability in cross-sectional studies, and it is also related to cognitive engagement across the lifespan. His data suggest two possible intervening pathways from childhood openness to performance on the Mini-Cog assessment of cognitive impairment⁷—a pathway operating through grip strength, and a pathway operating through educational attainment and body mass index.

Edmonds suggested that lifespan research relating personality to cognitive aging can be accelerated in two ways—by defining surrogate endpoints that predict declines in cognitive functioning and by capitalizing on other existing data resources. Datasets that include a measure of childhood personality and that can be linked to still-living individuals who can be located and followed up are particularly useful. He also suggested that it would be very valuable to have a new longitudinal study that included personality assessment across the lifespan along with health behaviors and a battery of biomarkers predictive of morbidity and mortality.

PERSONALITY CHANGE AND DEMENTIA

Antonio Terracciano (College of Medicine, Florida State University) focused his remarks on examining changes in personality in relation to dementia, which can yield insights about the risk factors for developing Alzheimer's. He shared a graphic prepared by NIA that presents a "decision tree" of possible explanations for the relationship of personality to the disease: see Figure, page 5.

Terracciano stated that from the earliest known observation of Alzheimer's disease, personality change has been among the factors noted in manifestation of the condition. The current diagnostic guidelines include change in

personality, behavior, or comportsment as one of five domains that clinicians should consider.

Terracciano reported that data from retrospective studies in which those in caregiving roles for individuals with dementia are asked to describe both the current personality of the individual for whom they are providing care and the personality prior to the onset of dementia. These studies showed large increases in neuroticism and declines in extraversion, openness, agreeableness, and conscientiousness.

Noting that retrospective studies are most likely to capture changes that occur with and after the onset of the disease, Terracciano then addressed the questions of whether changes in personality begin during the preclinical phase of Alzheimer's disease and whether reverse causality may explain the association between personality and risk of dementia. Using data from the BLSA that span up to 36 years, he found no difference in personality trajectories prior to the onset of dementia: this finding suggests that personality traits are risk factors and not a preclinical early sign of dementia.

One additional line of investigation Terracciano described involved examination of autopsy data for individuals in the BLSA. The autopsies revealed that some individuals who had normal cognition when they died had amyloid- β and tau levels that met the criteria for Alzheimer's disease (the ASYMAD group). Consistent with the idea that a resilient personality can be protective and help postpone the onset of clinical dementia, Terracciano reported that the ASYMAD group tended to be lower in neuroticism and higher in conscientiousness than people who had been diagnosed with dementia.

Terracciano suggested one avenue for future research is to examine neuropathy using cerebrospinal fluid (CSF) and positron emission topography imaging biomarkers to test whether findings from the autopsy study he described would be replicated with in vivo data. Another line of work that might yield beneficial knowledge is examination of the role of personality in behavioral symptoms of Alzheimer's disease and related dementias. Finally, he suggested that efforts to leverage knowledge about individuals' personality traits, preferences, and other characteristics could contribute to more tailored interventions.

In response to these presentations, participants raised the topic of interventions to change personality. Sutin noted that there is consistent evidence that people who are more physically active show greater declines in neuroticism and greater increases in conscientiousness over time, though whether that is due to individuals with those traits being more likely to maintain exercise routines needs to be investigated. She also noted that therapeutic interventions targeting depression and anxiety appear to decrease neuroticism. Edmonds added that there is some evidence that education influences personality development, though research is needed to determine the mechanisms involved.

⁶See http://www.ori.org/research/detail/personality_and_health_a_longitudinal_study [August 2017].

⁷The Mini-Cog test is a 3-minute instrument to screen for cognitive impairment in older adults that is used in primary care settings.

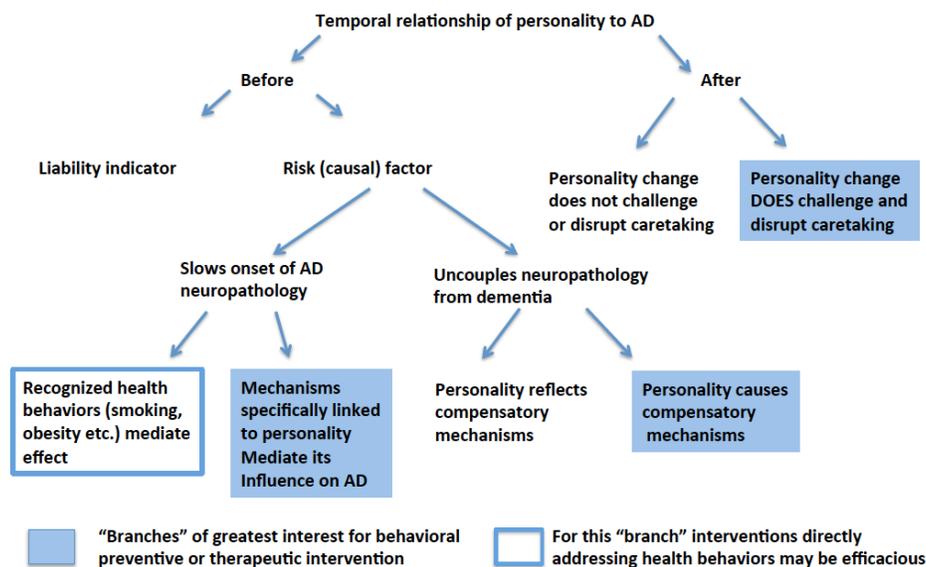


Figure The relationship of personality to Alzheimer’s disease: A “decision tree” of possible explanations.

Source: National Institute on Aging, U.S. Department of Health and Human Services. (2017). *Follow-up on Understanding Pathways to Successful Aging: Behavioral and Social Factors Related to Alzheimer’s Disease*. Background discussion prepared for the Workshop Planning Committee.

SOCIAL AND COGNITIVE ENGAGEMENT

Presentations in this session focused on what is known about the role of social and cognitive engagement in the development of Alzheimer’s disease and whether it is possible to tease apart these conceptually distinct areas.

SOCIAL ENGAGEMENT AND COGNITIVE FUNCTION

Deborah Barnes (School of Medicine, University of California, San Francisco) presented data from observational studies, intervention studies, and multidomain interventions that looked at connections among social engagement, cognitive function, and Alzheimer’s disease. A recent systematic review and meta-analysis of longitudinal cohort studies examining the relationship between social relationship and dementia risk⁸ found that low social participation, less frequent social contact, and high loneliness are consistently associated with an increased risk of developing dementia. However, Barnes noted, such studies leave the “chicken or egg” question remaining: Is social engagement truly protective, or is there a decline in social engagement during the preclinical period?

⁸Kuiper, J.S., Zuidersma, M., Oude Voshaar, R.C., Zuidema, S.U., van den Heuvel, E.R., Stolk, R.P., and Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Review*, 22, 39-57. doi: <https://www.ncbi.nlm.nih.gov/pubmed/19223606>. Available: <https://www.ncbi.nlm.nih.gov/pubmed/25956016> [August 2017]

One study that has attempted to address this question is the Honolulu-Asia Aging Study.⁹ Results showed that the level of social engagement at midlife was not associated with dementia risk, but decline in social engagement from midlife to later life was associated increased risk of dementia, so this change could be part of the prodromal period. She added that she believes the relationship between social activity and Alzheimer’s risk is bidirectional or circular: social activity is likely a protective factor, and as individuals develop preclinical disease, social engagement begins to decline.

Barnes then turned to discussing intervention studies, which often look at cognitive change because of the difficulty of conducting an

intervention long enough in duration to examine dementia risk. She noted that it is difficult to separate the social component from other aspects of an intervention because social activity usually also involves cognitive and language stimulation through interaction with others (or with physical activity in some conditions), but some intervention studies suggest that social activity improves cognitive function in lonely elderly people.¹⁰ Another study found that a social activity intervention increased brain volume in Shanghai elders.¹¹ Multidomain interventions that have social engagement as a motivator, such as the MAX (Mental Activity and Exercise) Trial¹² and the PLIÉ (Preventing

⁹See <http://www.kuakini.org/wps/portal/kuakini-research/research-home/kuakini-research-programs/kuakini-honolulu-asia-aging-study> [August 2017].

¹⁰See, for example, Pitkala, K.H., Routasalo, P., Kautiainen, H., and Tilvis, R.S. (2009). Effects of psychosocial group rehabilitation on health, use of health care services, and mortality of older persons suffering from loneliness: A randomized, controlled trial. *Journal of Gerontology: Biological Sciences*, 64(7), 792-800. doi: 10.1093/gerona/glp011. Available: <https://www.ncbi.nlm.nih.gov/pubmed/19223606> [August 2017].

¹¹See Mortimer, J.A., Ding, D., Borenstein, A.R., DeCarli, C., Guo, Q., Wu, Y., Zhao, Q., and Chu, S. (2012). Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *Journal of Alzheimer’s Disease*, 30(4), 757-766. doi: 10.3233/JAD-2012-120079. Available: <https://www.ncbi.nlm.nih.gov/pubmed/22451320> [August 2017].

¹²See Barnes, D.E., Santos-Modesitt, W., Kramer, A.F., Castro, C., Middleton, L.E., and Yaffe, K. (2013). The Mental Activity and eExercise (MAX) Trial: A randomized controlled trial to enhance cognitive function in older adults. *JAMA Internal Medicine*, 173(9), 797-804. doi: 10.1001/jamainternmed.2013.189. <http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1673747> [August 2017].

Loss of Independence through Exercise) Program,¹³ also show cognitive improvement. Although neither of these studies focused on social activity as an experimental variable, the experimental conditions included social components, and, for the PLIÉ program, the social aspect of the program is what fostered participation.

In terms of next steps, Barnes asserted that multidomain interventions have potential to make a positive difference. Noting the challenge of separating effects of various components, she asked whether this is a question that the field should care about, stating: “Is it important to know what the secret in the sauce is, or do we just want to know that it’s delicious?” She said that she is not convinced social engagement is a direct mechanism; rather, she believes, social engagement may help people do other things that have a more direct effect on cognitive function. Social activity might also reduce stress, which could have a more direct effect on Alzheimer’s risk. Barnes added that pragmatic trials are needed to address the question of what works in terms of helping people who are affected by Alzheimer’s and related dementias, not just strategies for prevention.

ENGAGEMENT AND COGNITIVE RESILIENCE

Elizabeth A.L. Stine-Morrow (College of Education and Beckman Institute, University of Illinois at Urbana-Champaign) defined three types of engagement. Activity engagement, which is typically measured through retrospective self-report, is investment over time in particular types of behaviors, either in an individual or social context. Dispositional engagement, which is also measured through self-report, refers to attitudes, beliefs, values, and interests. Attentional engagement, which is usually measured through timing or accuracy data or using functional magnetic resonance imaging (fMRI), is an investment of attention or processing resources.

Stine-Morrow then described several mechanisms that might contribute to the relationship between social engagement and cognitive resilience, some of which focus specifically on activity engagement. First, social engagement involves cognitive stimulation: “There is a dance in social interactions; people are complex stimuli and they require responses at a pretty good tempo in order to maintain that interaction,” she said. Second, social interactions usually require conversation, which exercises language and therefore engages executive control networks in the brain.

Stine-Morrow noted that as they usually involve some type of activity, not simply sitting with other people, social interactions could be a mediator or even a proxy for activ-

ity engagement. Social interactions can also provide emotional support to buffer the damaging effects of stress. In addition, there may be a motivational component, she said, as individuals might cultivate conscientiousness to maintain social support. Having a social network could encourage continued activity engagement even when alone, as in the case of individuals practicing or reading a book to improve skills in an activity they engage in with others, such as chess, Stine-Morrow noted.

Stine-Morrow described findings from a study that supports the concept of environmental fit. Participants were assigned to one of three conditions: a team-based creative problem-solving activity (Senior Odyssey¹⁴), home-based inductive reasoning training (adapted from the ACTIVE¹⁵ trial), or a control group. The Senior Odyssey group improved in divergent thinking, the key skill exercised in the program, but Stine-Morrow noted that there were several apparent moderators for this affect, including social network size: individuals who had large social networks showed much larger gains in divergent thinking than those with small social networks. One possible explanation for this difference, she suggested, is that individuals with large social networks are likely to be “social experts” and thus better able to navigate and gain from the complex social environment involved in Odyssey.

Stine-Morrow offered another example of how the match between an activity and social integration might affect cognition, based on “flow,” an individual’s experience of being pleasurably immersed in an activity in which the level of challenge is well balanced with his or her skill level. At younger ages, flow is experienced more strongly in activities that are engaged in for one’s own purpose than for communal purposes, but as individuals age, the increase in flow is greater for communal activities.

Stine-Morrow suggested several directions for efforts to increase understanding of the mechanisms by which social engagement influences cognitive aging. Work is needed to develop a better definition and understanding of social integration. In terms of cognition, focus is typically on transfer as a unitary point of assessment, but this approach misses the mutual effects of experience. Efforts are needed to develop dynamic measures of activity and dispositional engagement over time, such as incorporating reports from others close to an individual and incorporating data from technologies like electronic diaries. Other potentially fruitful approaches, Stine-Morrow said, are experimental designs that look at mechanisms, as well as successive-experience paradigms.

¹⁴See <https://www.seniorodyssey.org/about.html> [August 2017].

¹⁵See Tennstedt, S.L., and Unverzagt, F.W. (2014). The ACTIVE study: Study overview and major findings. *Journal of Aging and Health*, 25(8_suppl), 3S-20S. doi: 10.1177/0898264313518133. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3934012/> [August 2017].

¹³See Barnes, D.E., Mehling, W., Wu, E., Beristianos, M., Yaffe, K., Skultety, K., and Chesney, M.A. (2015). Preventing Loss of Independence through Exercise (PLIÉ): A pilot clinical trial in older adults with dementia. *PLoS One*, 11(2). doi: 10.1371/journal.pone.0113367. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0113367> [August 2017].

ENGAGEMENT ENHANCEMENT AND COGNITION: SOME THOUGHTS ON MECHANISMS

Denise Park (Center for Vital Longevity, University of Texas, Dallas) described four elements needed for any activity intended to foster social engagement. First, the activity should be doable by most people and also very motivating to the subjects. It should be fun, so that subjects look forward to participating in the activity, and it is even better if subjects find the activity a bit addictive. Second, the activity should be done in a social context. Because humans are highly social, this element promotes staying in the study and engaging in meaningful relationships. This element also increases the processing demands because individuals are meeting new people at the same time they are learning new things. Third, the activity should be infinitely complex yet permit beginning at a very basic level. In other words, there should be no ceiling for how much a person can learn. Fourth, the activity should be at least somewhat novel for the participant. Novelty adds to the mental effort required and promotes new neural pathways and neural scaffolding, Park noted.

Park then discussed findings from the Synapse Project.¹⁶ The project, which included over 200 subjects, involved assignment to one of six conditions for 3 months. Three were high-effort conditions involving active learning (quilting, digital photography, or both) in a social group. Park noted that quilting and digital photography both possess all four of the elements she described as necessary for an activity to foster social engagement. The other three conditions were a moderate mental effort condition involving engaging in activities not involving active learning in a social group; a placebo group that worked at home on word knowledge tasks, rather than learning new things; and a no-treatment control group. The high-effort groups had a space for their activity with quilting and digital photography classrooms, and the moderate mental effort group had a separate group space.

Park reported that the high-effort groups showed greater improvements in episodic memory than the other treatment two groups, and that some of these improvements were maintained 1 year later. Data from the fMRI scans showed that modulatory capacity (the ability to calibrate brain function to task difficulty) also improved for participants in the high-effort conditions.

Looking at directions for future work, Park echoed others' suggestions for developing technology-based approaches for assessing cognition and everyday behaviors in naturalistic settings. She also proposed brain research to explore whether engagement changes brain structure, brain function, or both; how long changes last following an intervention; and to what extent brain changes relate to behavioral changes. Finally, Park suggested it would be

beneficial to follow individuals after the conclusion of an intervention to determine whether they continue to pursue the skill they were trained in during the intervention, engage in new learning, and maintain social networks formed during the intervention.

EDUCATION

Presentations during this session focused on what is known about years of education and educational experiences as modifiable risk factors and the potential mechanisms through which education influences cognitive function and the incidence of Alzheimer's disease.

PATHWAYS LINKING EDUCATION TO ALZHEIMER'S DISEASE

Jennifer Manly (Columbia University Medical Center) began by discussing education in the context of the concept of social determinants of health.¹⁷ This concept suggests that the window to intervene to reduce incidence of diseases like Alzheimer's and to improve general health outcomes opens in early life. Therefore, a life-course model of these diseases and of health disparities is needed. It also suggests that economic and social policy is health policy.

Manly identified eight challenges in elucidating the pathways involved in the relationship between educational attainment and Alzheimer's risk: (1) the difficulty of distinguishing selection into higher education from the causal effects of education; (2) the gap between education exposure, which is generally early in life, and later life outcomes; (3) changes in cognitive outcomes may be nonlinear; (4) critical periods are difficult to capture; (5) the possible presence of selection, survival, and measurement bias; (6) cognitive tests may be biased against individuals without a lot of schooling; (7) other factors besides education, such as parenting practices, can exacerbate an individual's initial intellectual endowment; and (8) differentiating biological from behavioral responses can be difficult because individual behavior can buffer or magnify biological embedding of early life experiences, and different early life conditions may act through different pathways.

In spite of these challenges, there is evidence for a causal relationship between education and Alzheimer's disease from a number of sources, Manly reported. These include birth cohort studies, effects of historical school policy changes, and observational data. As an example, Manly described results of an analysis of the effects of changes in compulsory schooling laws in locations where an increase in the minimum number of years children must attend school was mandated. States where such policy changes were enacted in a manner such that there was only 1 year in age difference between the children who were subject

¹⁶<http://agingmind.utdallas.edu/learn-about-our-work/the-synapse-project/> [August 2017].

¹⁷See <https://www.cdc.gov/socialdeterminants/> [August 2017].

to the new law and those who were not provided conditions for a natural experiment. HRS data show higher cognition scores for the individuals who had more schooling as a result of enforcement of these laws. Manly noted that racial disparities in enforcement of compulsory schooling laws resulted in African Americans not gaining the same benefit from the policy changes as whites. She added that HRS data also show that racial disparities in Alzheimer's risk related to education may also be attributable to differences in quality of education, not just to differences in years of education.

Manly suggested that leveraging studies involving randomized assignment to education conditions, such as the Perry Preschool Project¹⁸ and Project STAR,¹⁹ could better delineate the causal relationship between education and Alzheimer's disease, but health outcomes have not been a focus of these studies. Other directions for future work include developing better measures of qualities of education that may be important, such as the social environment and the provision of knowledge, skills, resources, and the qualities that select for higher educational attainment. Larger sample sizes are also needed to help identify moderators, as well as collecting more imaging data and CSF biomarkers. Manly also called for measures of pathology at midlife and studies with biological aging data, particularly epigenetic and inflammatory markers, measured across the life course. She added that midlife data are needed to understand trajectories, particularly data from individuals with low education levels, because later in life selection bias and survival bias come into the fore.

PATHWAYS LINKING EDUCATION TO MIDLIFE CORRELATES OF ALZHEIMER'S DISEASE

Chandra Muller (Department of Sociology and Population Research Center, University of Texas at Austin) echoed Manly's statement about the importance of teasing out school effects from selection effects. One mechanism through which schools act is improving human capital by teaching skills, imparting knowledge and information, and providing social networks, which all then carry through the life course. Muller added that schools also position individuals to engage other formal institutions in society, most notably work, so that they can continue to learn throughout their lives.

Building on the idea of school quality that Manly introduced, Muller listed several features that contribute to the overall quality of a school or quality of an individual's experience in a school: academic rigor, developmentally appropriate curriculum, social climate (which influences

motivation and engagement), peer effects (e.g., having classmates with higher socioeconomic status [SES] contributes to an academically richer learning environment), and the quality of teachers and other school personnel.

Muller briefly discussed school organization, noting that as students progress through school, curriculum becomes more complex and more demanding; social relationships become more complex; class size increases; teachers' demands of students increase; judgment, grading, and pressure increase; and stratification within schools increases. She noted that coursework trajectories diverge in high school; students take different courses, some of which serve as college preparatory work and some of which lead only to precarious occupations. Although the share of students taking higher-level coursework has increased during the past 35 years, the proportion of students who take advanced college preparatory courses is still limited: about one-quarter of high school students are not preparing for higher education.

Muller noted that different elements of academic achievement, such as test scores, grades, and coursework, can all be linked to different outcomes in early adulthood. She added that effects are heterogeneous: the largest effects of schooling are for lower SES students, so those who are the least likely to attend high-quality schools benefit the most from them when they do.

Muller reported that mathematics coursework, more than any other subject, seems to predict adult labor force outcomes, and Algebra 1 and Geometry appear to be the courses that make the largest difference. She added that these courses are the first point in the mathematics curriculum where students learn abstract thinking skills, and they are the foundation for science courses. Data from the High School and Beyond Study²⁰ enable examination of coursework patterns and midlife outcomes and suggest that advanced mathematics and, to a lesser extent, science coursework predicts positive occupational outcomes and protect against having low-wage occupations or occupations with high rates of unemployment.

GENETIC AND ENVIRONMENTAL FACTORS

William Kremen (Department of Psychiatry, University of California, San Diego) discussed genetic and environmental influences on cognitive ability and implications for thinking about the relationship between education and dementia or Alzheimer's risk. He explained that children from families with limited financial resources have smaller frontal, temporal and hippocampal volumes and poorer cognitive performance and academic achievement than children from higher SES families. Since lower hippocampal volume is a risk for Alzheimer's in aging populations, he said, education and risk reduction for Alzheimer's disease may need to begin in childhood. These developmen-

¹⁸See <http://evidencebasedprograms.org/1366-2/65-2> [August 2017].

¹⁹Steps to Achieving Resilience was a 3-year research project (1999-2003) with preschoolers in a [Head Start](#) program to increase literacy skills of at-risk children by improving their learning environments.

²⁰See <https://nces.ed.gov/surveys/hsb/> [August 2017].

tal brain differences account for as much as 20 percent of the academic achievement deficits, which are then associated with occupational attainment later in life. Kremen reported that most of this effect is accounted for by the poorest households, which fits with the “good-enough environments” theory that reasonable brain development does not require a tremendous amount of resources, but if resources are very scarce, brain development will be affected, which in turn will affect educational attainment and Alzheimer’s risk.

Measures presumed to be environmental are often partly heritable, Kremen stated. Moreover, disentangling cause and effect can be difficult because particular environments may be passively received, but they can also be actively sought out or selected. In this context, he explained the phenomenon of gene-environment (G-E) correlation, in which individuals with a genetic propensity for some trait live in an environment that supports the expression of that trait. He illustrated three forms of G-E correlation using the example of children whose parents have passed on genes that predispose them to high intellectual ability. (1) Passive G-E correlation: Parents provide an environment with a lot of intellectual stimulation that enhances the expression of the genes. (2) Active G-E correlation: The child seeks out environments and experiences, such as visiting the library or joining the debate club, that enhance the expression of the genes. (3) Evocative G-E correlation: Expression of the genetic propensities evokes responses from the environment that further enhance expression of those genes, such as a teacher recognizing a child’s intellectual ability and encouraging her to join the math club.

G-E correlation, particularly active G-E correlation, likely explains why genetic influences for cognitive ability increase from childhood to early adulthood, Kremen noted, and this is an important part of the question of educational attainment and Alzheimer’s risk. Exposure to education is only partly due to environmental factors; genes and G-E correlation likely play a larger role. For example, IQ, which is highly heritable, is a strong predictor of educational attainment. Higher lifetime educational attainment and greater midlife engagement in cognitive activities are associated with better late-midlife cognitive function. However, individuals are not randomly assigned to the amount of educational exposure they receive. Indeed, these associations are absent or greatly diminished after accounting for young adult general cognitive ability. Thus, the effect seems to be largely a function of the fact that people with higher intellectual ability tend to seek out more education and cognitive activities. These findings have implications for the design of studies to examine the effects of educational attainment on later life health outcomes.

REFLECTIONS ON DAY ONE

Kramer began the second day of the workshop with his reflections on salient points raised during the first day. He first noted the importance of individual differences, which may be moderators or mediators, depending on their relationship to other variables. Another point that arose from the discussion was the potential benefit of multi-modal trials; ideally, such trials would include a control condition for each unimodal condition, as well as combinations of unimodal conditions in order to determine important components. The benefit of stratifying data also came to the forefront. Kramer noted that carrying out such stratifications likely requires that studies be conducted in a city or in multiple sites to ensure sufficient populations to be able to stratify by factors known to be important, such as personality, education, and SES.

Another point from the first day’s discussions, Kramer stated, is that in order to elucidate whether particular interventions will scale up in situations in which experimental control is less than perfect, researchers need to move from lab settings to real-world settings. In addition, existing outcome measures are not always optimized for what researchers are trying to measure, and better measures are needed for phenomena that are not often measured, such as enjoyment and motivation. Kramer reported that the role of enjoyment and motivation arose multiple times during the first day’s discussion, and he noted that there may be lessons that researchers could learn from video game developers about how to engender enjoyment and motivation to encourage or maintain beneficial behaviors. The final point Kramer discussed was the need for more data collected from individuals in midlife; obtaining these data can be difficult because individuals in this stage of life tend to be too busy to commit to the time required to participate in studies involving multiple lab visits.

In response to this last point, Dana Plude (deputy director, BSR) suggested that researchers should consider alternative methods for collecting data on individuals in midlife, such as using passive detection systems available with cell phones and other technologies. Informed consent would still be required, but this strategy could dramatically reduce the number of hours participants would need to spend in a lab for testing.

Kramer noted the variation in intervention studies discussed during the presentations. Some of them were full randomized trials, and some allowed participants to choose the intervention that they preferred or thought might have the biggest effect. On this point, Kramer cautioned, the findings from video game training studies he and other researchers have conducted suggest that preferences do not always map to better performance or outcomes.

Kramer used examples from the exercise and cognition literature to illustrate the need for more focused research to inform intervention development. He noted that very little is known about whether there are critical periods, how to optimize intensity, and the most beneficial combinations of activities. Dixon followed up by stating that another area in which knowledge development is especially needed is the mechanisms linking social engagement to aging outcomes; for exercise and for cognition, there is better understanding of mechanistic links. He commented that it is also difficult to disentangle cognitive activity from social engagement.

Reflecting on Park's presentation and the finding that participants who engaged in both the photography and quilting activities showed lower cognitive benefits than those who participated in only one of the two activities, Nielsen suggested that this outcome might reflect that neuroplasticity is expensive for the body, so the capacity for growth in multiple areas simultaneously might be limited. An area for future investigation, Nielsen proposed, might be to examine how growing in one area affects the ability to grow in another area.

Kramer then raised the question of the extent to which it is possible to reduce neuroticism and increase conscientiousness in children. Manly commented that schooling itself is the biggest existing intervention to increase conscientiousness and noted that many schools are actively engaged in efforts to improve socioemotional skills. Returning to the topic of individual differences, she cautioned that attempts to influence noncognitive skills can be problematic because an approach that is successful for one group of people may be destructive for another group of people.

BREAKOUT GROUP DISCUSSIONS

To advance the workshop's objectives, workshop participants were divided into breakout groups to build on the presentations and discussions from the first day. Each group included two or three workshop presenters and an NIA staff person. This section summarizes those group discussions.

Deborah Barnes reported for the group in which she participated, which also included Roger Dixon, Grant Edmonds, Chandra Muller, and Dana Plude. She said that the group first considered strategies for enriching how education is measured, beyond simply measuring years of education. The group identified several measures that might yield more meaningful data: the highest level of mathematics completed in high school, the year of first enrollment in postsecondary education, name and location of higher educational institution (this measure would yield detail about the quality and selectivity of the institution and could be linked to existing databases), type of degree or certificate and year awarded (how long an in-

dividual takes to complete higher education could be an important marker), and field of study.

Others in the group noted that adult education is not captured well in many of studies and that it would be important to capture the above measures for individuals who pursue higher education later than the traditional period immediately following high school, but any new items should ask for information that people are likely to remember. The group also discussed the possibility of linking new data to existing datasets.

The group then turned to personality, Barnes reported, and identified the need for studies that capture personality at multiple points in time using a continuous measure across the lifespan. One particularly important time point for assessing personality is at the onset of Alzheimer's disease. The group discussed collecting observer ratings of personality from an individual's family members or friends in addition to an individual's self-ratings, which may enhance assessments of personality changes associated with Alzheimer's and related dementias. Another point raised in the group was that personality may affect and be affected by different risk factors at different points across a person's lifespan. Better understanding of these transactions might yield insight into mechanisms and targets for intervention and time points when interventions may be most effective.

Muller added that the group discussed whether Alzheimer's should also be thought of not just as a disorder of memory and cognition but also of personality. This conception might alert a broader field of Alzheimer's researchers to the importance of personality development and change as a crucial component of basic studies of Alzheimer's disease. The group also noted the possible benefit of using objective measures of behavioral manifestations of personality.

With regard to social engagement, Barnes reported, group participants underscored the point that although there is consistent evidence that loneliness and low social participation are risk factors for dementia and Alzheimer's disease, little is known about the mechanisms that lead to this association. One possible mechanism is that social engagement may lead people to make other healthy decisions, such as increasing cognitive or physical activity, both of which reduce Alzheimer's risk. Although social engagement nearly always involves cognitive activity, it may also offer stress reduction, another possible mechanism for reduced Alzheimer's risk. The group discussed the potential value of measuring stress indicators as a mediator or an intervention, looking at changes in reported stress levels or inflammatory markers.

Barnes reported that the discussion of stress led the group to identify another area for future research, the interaction between personality and social engagement. Indi-

viduals with risk factors in both areas may have a magnified risk and therefore be fruitful targets for interventions. The group also discussed the synergy between flow and the four activity elements that Park described—motivation, complexity, novelty, and social engagement—adding that combining focus on flow with understanding of an individual’s personality and educational background as related to aging health risks could provide both a theoretical model and help inform the design of tailored interventions.

William Kremen spoke for the group in which he participated, which also included Angelina Sutin, Elizabeth Stine-Morrow, and Jonathan King. He noted that the group discussed the need to develop a better understanding of the mechanisms through which personality is related to Alzheimer’s protection or risk. It might be productive to explore how personality relates to regulatory mechanisms such as the regulation of stress. The group discussed the need for a strategy to measure cognitive decline that can be captured in midlife, as midlife cognitive impairment may be a more appropriate initial target than Alzheimer’s disease itself. One possibility is to administer multiple cognitive assessments to people at midlife, rather than using screening instruments. The group also discussed possible strategies for measuring physiological phenomena that may be related to cognition and risk for cognitive impairment. One such strategy, pupillometry,²¹ can show the level of effort a person expends to complete a task. If one person has to expend more effort to achieve the same performance as another person, that person may be at greater risk for decline because he or she will reach the point at which compensation is no longer possible sooner than a person who requires less effort for performance. Therefore, a strategy like pupillometry may enable identification of deficits before performance declines are apparent. Kremen added that there is potential for the development of devices to monitor other physiological phenomena in real time.

Another area the group discussed, Kremen reported, is gaps in knowledge related to the effect of adult education, such as how benefits may differ on the basis of the age at which an adult pursues additional education. The group suggested there is a need to better understand the regulatory skills that education seems to confer, and to develop strategies for investigating this question. One hypothesis posed during the discussion was that education might have an advantage over narrow skill training (and activities like “brain training” games) because education involves the acquisition of content (i.e., knowledge) interwoven with the exercise of fluid cognitive processes, such as an attention, memory, and cognitive control.

²¹Pupillometry is the measurement of pupil size and reactivity, which is a key part of the clinical neurological examination for patients with a wide variety of neurological conditions or injuries.

The group discussed the need to develop more fine-grained measures to determine the number and quality of social ties; characteristics of social interactions, including individual behavior within the interaction; and individual responses to social interactions, such as the extent to which an individual is stressed during an interaction. The group also discussed the need to harmonize existing datasets. Data from social media outlets, such as Facebook, might yield insights related to people’s interests and what they find valuable, worthwhile, or purposeful. Two other areas the group discussed, Kremen reported, were the need for further understanding of how personality and social integration interface with reward pathways and whether it might be possible to use non-invasive wearable devices to examine physiological responses related to reward. The one caveat with wearable devices is that they generate enormous amounts of data, requiring significant resources for handling and analysis.

Michelle Carlson reported on the group in which she participated, which also included Jennifer Manly, Antonio Terracciano, and Lisbeth Nielsen. Although educational attainment is one of the most robust predictors of Alzheimer’s disease, the group suggested that work is needed to better measure confounders, such as context (e.g., historical factors such as segregation and the role of parents and grandparents in a particular cohort) and quality or characteristics of education (e.g., the degree to which a particular education setting prepares individuals for the changing landscape of the workplace).

Group participants noted that social interaction and social engagement are relatively difficult to measure, Carlson reported. In contrast to physical activity, for example, for which intensity can be rated as low, moderate, or high, quantifiable measures are lacking for social engagement. The group suggested two possible strategies to advance understanding in this area. One is to incorporate loneliness measures and self-report measures of purpose and mattering in studies and then examine the relationship to downstream cognitive outcomes. The other is to explore possibilities for using wearable technology to measure social engagement, which is difficult to measure using self-reports. Passively collected data might also yield information about the context in which people are functioning.

Carlson noted that the group discussed that one strategy for obtaining data from midlife individuals, who may be difficult to recruit for studies, is to capitalize on data from stakeholders, such as insurance companies and employers, who might be willing to work with researchers. Other sources of data that researchers might use are the U.S. Census and Patient-Centered Outcomes Research Institute; adding measures to newly funded child-based studies, such as the ECHO study;²² ongoing observational

²²See <https://www.nih.gov/echo> [August 2017].

studies such as the YCAP project;²³ and completed and ongoing interventions. The group also discussed the need to target underrepresented and at-risk individuals, such as those with one or more of the following characteristics: low SES, low engagement, loneliness, low physical activity, smoking, history of concussion, and low reading ability.

Carlson reported that the group discussed the importance of separating outcomes by midlife and later life and that they be informed by mechanism and critical windows or periods of exposure. Group participants suggested that outcomes may also need to be examined longitudinally and with enough frequency to determine rates of decline, rather than absolute differences.

FINAL REFLECTIONS

Kramer closed the workshop by commenting on four themes that emerged across the 2 days. First, he noted, many suggestions were provided over the course of the workshop for the mechanisms that might explain relationships between personality, social engagement, and educational attainment and the risk of Alzheimer's disease. Second, there were also many suggestions for research to test the hypothesized mechanisms: interdisciplinary work could improve existing measures, harmonize data across measures, and develop new approaches to measurement, such as through the use of wearable sensors. Third, some participants suggested the development of richer, more detailed measures in the context of a theoretical construct. Fourth, some participants suggested that better efforts are needed to recruit a more diverse participant base for studies and to go beyond the United States for some studies.

²³See <http://www.empowervate.org/overview-of-ycap/> [August 2017].

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