Understanding the Role of the Exposome in Brain Aging, Alzheimer's Disease (AD) and AD-Related Dementias (ADRD)

NIA Virtual Workshop

Division of Neuroscience

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Acronym Definitions

AD	Alzheimer's disease
ADRD	Alzheimer's disease-related dementia
ADI	area deprivation index
BMI	body mass index
DoN	National Institute on Aging Division of Neuroscience
FDA	U.S. Food and Drug Administration
fMRI	functional magnetic resonance imaging
ICE	index of concentration at the extremes
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NASEM	National Academies of Sciences, Engineering, and Medicine
NDVI	normalized difference vegetation index
NIMH	National Institute of Mental Health Data Archive
NIEHS	National Institute of Environmental Health Sciences
NIA	National Institute on Aging
PXS	Poly eXposure Score
PM	particulate matter
RNA	ribonucleic acid
SES	socioeconomic status

Executive Summary

Fifteen years after the concept of the exposome was introduced, charting the diverse range of exposures that can impact human health remains a challenge and an opportunity. To survey advances made in understanding exposomic effects on the risk of Alzheimer's disease (AD) and related dementias (ADRD), the NIA Division of Neuroscience held a virtual workshop on December 2-3, 2020. Researchers convened to discuss the breadth of the exposome and how it can impact risks related to cognitive impairment. Four major themes related to AD/ADRD risk research emerged: (1) technological advancements to assess AD/ADRD risks, (2) impact of the exposome across the lifecourse, (3) lifestyle and environmental impacts, and (4) the importance of integrating data across multiple fields and scales to generate policy-actionable outcomes.

The first theme of technological advancement highlighted many opportunities for researchers to make novel connections and discoveries related to exposomic risk factors. Geocoding technology has allowed researchers to evaluate associations between geographic location and individual activity levels, greenspace, air pollution, and structural disadvantage; machine learning technologies have enabled researchers to analyze large, complex datasets to predict ADRD risk; and novel methods of DNA sequencing have been developed that support exploration of the impact of exposures on the epigenome and gene expression.

The second theme addressed the effects of the exposome across the individual lifecourse. Participants presented findings on AD/ADRD risk factors that range from gestational exposure to metals to years of childhood education to late-life experiences of extreme temperatures. Toxic exposures across the lifecourse were associated with increased AD/ADRD risk, and epigenomic changes occurring across the lifecourse—whether stochastic or expected—can alter gene expression and influence an individual's risk, as well.

The third theme considered the scope of lifestyle and environmental factors within the exposome. The genotype, lifestyle choices such as diet, and local environmental differences have all been shown to affect the human gut microbiome, for example. Cultural differences between populations are associated with prevalence of cognitive impairment. For example, the Tsimane people, living in an active and communal agricultural society, experience different patterns of inflammation and lower levels of cognitive decline compared to United States or European populations. Years of schooling, literacy, and access to health information are also associated with social disparities in cognitive decline and with protection against it.

Building on these rich array of findings, the fourth theme focused on the importance of integrating data to facilitate future research. Many of the advances described during the meeting were achieved through multi-disciplinary efforts—for example, collaborations between environmental scientists and social scientists have fostered studies of air pollution as a risk factor for cognitive health. Further research integration across disciplines, scales, and data sources can facilitate policy-actionable efforts that can reduce risk of AD/ADRD.

Welcome and Introduction

Welcome and Opening Remarks

Suzana Petanceska, Director, Office for Strategic Development and Partnerships, Division of Neuroscience

The exposome remains an outstanding research challenge and opportunity. Technological advancements have laid the foundation to improve understanding of the broad potential impacts of ecosystems, individual lifestyle, social factors, and physical-chemical exposures on AD/ADRD.

Recent public funding for Alzheimer's disease research has led to an enhanced research enterprise encompassing epidemiology, population studies, research on health disparities, genetics and genomic sciences, big data infrastructure, and the development of translational research programs built on open science principles.

The field is now capable of advancing toward an understanding of the role of the exposome in brain aging and neurodegeneration across multiple scales, from the cellular to population levels. This timely effort is necessary to realize the goals of precision medicine and to develop effective disease prevention strategies.

Plenary Lectures

Quantifying the Exposome in Complex Traits and AD/ADRD

Chirag J. Patel, Harvard Medical School

The exposome is a complex array of environmental exposures humans encounter from birth to death (Wild, 2005) that can be quantified and linked to complex phenotypic traits. such as AD and ADRD, through the equation *phenome (P) = genetic variants (G) + the exposome (E)*. Studies of the exposome and genome are aided by a shift toward repurposing existing large observational cohorts and real-world datasets (e.g., biobanks and insurance claims data).

Three kinds of exposures make up the exposome: general external factors, which include education (a hypothesized factor for AD/ADRD), financial & social status, and climate; specific external factors, including environmental pollutants, lifestyle factors, and medical interventions; and internal factors, which are exemplified by metabolism, physical activity, and gut microflora. These categories are shared (e.g., levels of small particles found in polluted air) and non-shared (e.g., nutrient levels based on individual dietary choices). Shared exposomic factors have been well measured and may account for geographic clustering of AD/ADRD prevalence, similarly to cancer. Partitioning the precise role of the exposome is complicated. It requires an environmental correlate of genetic heritability (h^2), which exposome researchers

refer to as c^2: the range of phenotypic variability attributed to a shared household or geographic location that does not include genetic factors.

Dr. Patel's research group has considered insurance claims data as a tool to help document the role of genetics and the exposome in patient phenotypes. By geocoding claims data about twins' and other siblings' medical care and conditions (i.e., hypertension, Type II diabetes), influences of the shared exposome and shared genome can be partitioned. The combination of air pollution, climate, and geographical socioeconomic status (SES) are significant but modest factors of the total shared exposome as shown by Lakhani et al, 2019.

Telomere lengths have been published as a causal factor for late-onset AD. Specific environmental contributions like dietary indicators and VO2 max are associated with lengthened telomeres, and those who have the shortest telomeres are associated with cigarette smoking and cadmium exposures as well as risks for AD. Additional data are needed to further understand these relationships, which can be done with better measurement of exposomic factors. Broadening the scale of exposomic measurements have been hindered by integration and analysis challenges. High-resolution mass spectrometry is a promising area of expanding research and hopes that costs will decrease as technology advances.

The exposome is a promising tool to develop better clinical screening tools. For example, a preliminary machine learning technology is currently used by Dr. Patel's research group to validate and test a Poly eXposure Score (PXS) that could predict risk of Type II diabetes. While sex and age generate a 0.67 C-statistic and a genetically based risk score would achieve a .709 C-statistic, a risk score based on environmental and behavioral exposures achieves 0.762. The exposome may also help identify risk factors for complications among individuals with AD/ADRD. For example, researchers are considering how and by what magnitude extreme heat or cold could immediately influence hospitalization and mortality for individuals with AD/ADRD and the long-term outcomes for individuals with these exposures.

As the field moves forward, there is great promise in new hierarchical and geographical data linkages and in the potential for understanding differences between shared and non-shared environment. These efforts must grapple with complications, however, including the potential bias in real-world convenience samples, the modest ability of associations to explain variance, and the difficulty of distinguishing signal and noise with large datasets. However, Dr. Patel sees promise in mapping epidemiological cohorts with novel measurements of exposomic indicators.

Embedding Mobile Health and Deep Learning into Prospective Cohort Studies to Study the Exposome

Peter James, Harvard Medical School and Harvard Pilgrim Health Care Institute

The ecosocial model of health argues that contextual influences (e.g., access to healthy food, exposure to noise) combine with individual choices (e.g., physical activity, sleep) to shape health outcomes, including brain health and Alzheimer's risk. Contextual factors are modifiable and have long-lasting effects, making them prime targets for analysis and intervention. This

analysis can be conducted by synthesizing geographic, deep learning, and mobile health data within prospective cohort studies to measure links between factors such as driving distances to nearest fast food, full-service restaurants, supermarkets, and convenience stores or air pollution models and cohort health data. Dr. James' research focuses primarily on the contextual factor of human exposure to nature. Based in part on the theory of *biophilia* which suggests that humans have an evolved affinity for nature, researchers have shown that exposure to nature can facilitate health-related processes such as stress reduction. Exposure to nature has been linked to cognitive health, in particular—for example, reduction of neural activity is linked to psychiatric disorders[1], which has been shown to affect cognitive functionand cognitive decline in the elderly[2]. James's research explores the specific mechanistic pathways through which exposure to green space may impact cognitive function–including pathways such as physical activity, social engagement, depression, and air pollution

To study these pathways on a nation-wide scale, Dr. James has combined satellite data from the Normalized Difference Vegetation Index (NDVI)—provided by MODIS satellite—with data from the Nurses' Health Study. Using a participant's address, researchers can use NDVI data to determine the level of green space in their neighborhood. This approach has shown that nurses living in the top quintile of greenness exposure had a 12 percent lower mortality rate after accounting for other factors (i.e., age, race/ethnicity, education, smoking status, income).

Dr. James's research group has used the Nurses' Health Study II, Health Professionals Follow-Up Study, and Project Viva Cohort to conduct similar geocoded analyses. The Project Viva Cohort, for example, showed links between childhood greenspace exposure and improved non-verbal intelligence and visual memory at age 3, but not at age eight. The results underline the importance of time-windows of susceptibility and long-term studies through the life course.

These spatial epidemiologic approaches have important limitations, however they do not measure a participant's *level of engagement* with nature and they focus on residential neighborhoods where researchers have found that people spend less than 50 percent of their time. To address these issues, Dr. James is piloting the use of smartphone applications and consumer wearable devices in the Nurses' Health Study 3. These tools can track metrics such as steps, heart rate, and sleep on one-minute intervals for seven-day sample periods at multiple times throughout the year and can record participant GPS data that can be overlayed with satellite-based green space data to understand time spent and activity engagement in a participant's actual environment.

Geocoded street-level images, like Google Street View, can be utilized to provide further insight into specific spatial features from a ground-level perspective and better account for the quality of spatial exposure. Deep learning technologies can be used in conjunction with such tools to classify specific components of images for analysis and model ground-level greenness as a

[1] Bratman GN, Hamilton JP, Hahn KS, et al. Nature experience reduces rumination and subgenual prefrontal cortex activation. *Proceedings of the National Academy of Sciences* 2015;112(28): 8567. https://doi.org/10.1073/pnas.1510459112; Kühn S, Düzel S, Eibich P, et al. In search of features that constitute an "enriched environment" in humans: Associations between geographical properties and brain structure. *Scientific Reports* 2017;7:11920. https://doi.org/10.1038/s41598-017-12046-7

[2] Beddington J, Cooper C, Field J., et al. The mental wealth of nations. *Nature* 2008;455:1057-1060. https://doi.org/10.1038/4551057a

participant would see it. This range of tools can provide specific, objective, and fine scale spatio-temporal resolution data for health behaviors, spatial factors, and cognitive function, delivering relevant and actionable information that can help urban planners and policymakers design cities that optimize human health and healthy aging.

Discussion

Operationalizing the Exposome

Dr. Weuve asked Dr. Patel to clarify the meaning of "real-world data," which Dr. Patel defined as data generated as health care is disseminated (i.e., electronic health records, claims data).

Dr. Kaufman asked both Drs. Patel and James to discuss the relationship between their different approaches to operationalizing the exposome. Dr. James stated that Dr. Patel's work addresses the three environments that comprise the exposome (i.e., specific external, general external, and internal), while Dr. James's own work mostly relates to the general external environment. Dr. Patel agreed that their work is highly complementary.

Prenatal Exposures

Dr. Ma asked whether prenatal exposure, including to stress and alcohol, is part of the exposome. Dr. Patel described disagreement in the field over the exact definition of the exposome: Wild considers stress to be a part of the exposome, but Dr. Patel considers it to be a complex phenotypic trait influenced by genetics and the environment. Dr. Balshaw added that stress is an exposure but is measured by an individual's phenotypic response to stress. Dr. Ma asked Dr. James about his collection of prenatal exposure data in his studies. James suggested that some studies, such as the Nurses' Health Study 3, have a prenatal health set of questions. Metrics of exposure can be created for prenatal data in this latest cohort study; there have been more than 1,000 births so far. A new cohort, the Growing Up Study, is composed of the children of participants from the Nurses' Health Study 2. James' research group has begun investigating potential associations between green space and depression for this cohort.

Geography and Social Inequality

Dr. Weuve asked how Dr. James has approached the co-location of accessible and usable natural spaces with neighborhood safety and socioeconomic capital within the United States. Dr. James cited the theory of equigenesis, which suggests that the health benefits of green spaces are strongest for individuals at the lowest socioeconomic level. The distribution of green space and SES also varies throughout the United States; for example, the high SES areas of New York City have low green space, but the opposite is true for a city like Atlanta.

Dr. Leikauf asked how racism is included in the geographic analysis of the exposome. Noting that this question is very complicated, Dr. James described a partnership with Columbia University researchers that is investigating redlining, a historic housing practice that segregated neighborhoods by race. Dr. James also noted that spatial data that include ICE data can measure the level of segregation or polarity within a census tract. Dr. James' group is investigating factors related to racism but does not currently have the capability to investigate an individual's perceived experiences of racism at a spatial level. The spatial data are, however,

capable of displaying factors that can be related to health outcomes and their connection to race, for instance location of fast-food restaurants is more closely related to race versus income.

Genetics and the Exposome

Dr. Finch asked whether either of the panelists investigated a method to define the levels of stochasticity present in twin studies, where gene expression varies. Dr. Patel explained his assumption that a significant portion of variance in gene expression could be attributed to randomness. Increasing measurements of exposomic factors will provide explicit values and further explain non-genetic factors.

Dr. Cory-Slechta noted that environmental, genetic, and other risk factors may have overlapping and synergistic effects, and thus asked whether separating these data creates a misleading analysis. Dr. James agreed that the interactions between different exposomic factors should not be investigated separately. Dr. Patel believes the ADRD risk attributable to these factors can be properly assessed when all exposomic factors are measured simultaneously; overlapping effects are expected and should not be discouraged.

Dr. Huang asked whether epigenetics could explain variations in the P = G + E model. Dr. Patel stated that the epigenome can be defined in many ways; if epigenetics is defined as the regulation of gene expression, then the epigenome can explain genetic variance.

Session I: Translational Epidemiology

A Lifespan Approach to Understanding AD Risk and Resilience

Rachel Whitmer, University of California, Davis

Rachel Whitmer presented on lifecourse epidemiology, which considers an individual's threshold and directionality for AD risk over many decades. Most data regarding lifespan AD risk and resilience focus on mid-life stages, but increasingly studies are investigating younger individuals based on snapshot exposures. While these snapshots capture specific moments in the lifecourse (e.g., birth, adolescence, early old age), the collective set of snapshots can be leveraged with cohort study data to explore additional factors, such as air pollution, toxic chemical exposure, crime data, food density, and weather patterns.

Research on early stages of the lifecourse are often linked to the Barker hypothesis, which describes fetal programming and its association with adult-onset disease, has led to a large body of research that found an association between birth weight and risk of chronic diseases (e.g., cardiovascular disease, hypertension). In accordance with the Barker hypothesis and the thrifty phenotype hypothesis, data from the Swedish Twin Registry found an association between low birth weight and head size and increased risk of dementia. Additional studies found a correlation between incidence of dementia and birth in geographic areas with high stroke mortality or incidence. Recently published data found associations between adverse childhood experiences and a significantly higher risk of dementia.

Physical well-being, specifically maintaining a healthy weight, is also connected to ADRD risk. For example, previous studies have concluded that higher body mass index levels in midlife are associated with dementia, and more recent data shed light on associations between obesity in an individual's 20s and 30s and longer-term dementia risk. Whitmer highlighted research that focuses on modifiable vascular risk factors to predict dementia risk. Early results suggest that vascular risk factors in early adulthood and potentially adolescence can have a cumulative effect on dementia risk or cognitive decline.[3] While certain health factors in people under age 30 can pose a risk, Whitmer noted results from the 90+ Study that suggest individuals with hypertension, high cholesterol, and coronary artery disease had a decreased risk of dementia. One cannot assume that risk factors over the lifecourse operate in the same manner and the same direction, nor that the factors mean the same thing in different populations. For example, changes in lifecourse SES (financial, cultural, and social capital) can affect late-life cognition, with those who move from a high childhood SES to a low adulthood SES experiencing the greatest cognitive decline.

All previously mentioned factors are also impacted by individual factors, as well as interpersonal, community, and public policy influences that occur over the lifecourse. A conceptual view of individuals and susceptibility, their unique susceptibility to the exposome changes over time even if the individual remains at the same residential address.

Discussion

Dr. Whitmer explained that future research will investigate the effects of migration out of a high stroke incidence area. This research will include additional information on migration age as well as educational attainment.

Assessing Factors Contributing to Cognitive Decline and AD Risk and Resilience Across Diverse Cohorts

Lisa Barnes and David Bennett, Rush University

Drs. Barnes and Bennett discussed general findings over a broad range of potential exposomic risk factors for AD/ADRD, including early-life cognitive activity, literacy, perceived stressors, and acculturation. However, they emphasized that racially and ethnically diverse cohorts are critical for understanding how these factors differ across the entire population. Dr. Barnes presented findings from a range of diverse cohorts, including the Religious Orders Study, Rush Memory and Aging Project (MAP), Minority Aging Research Study (MARS), Rush ADCC African American Clinical Core, and Rush ADCC Latino Core cohorts.

Using longitudinal data, Dr. Bennet began by linking exposures to the epigenome, transcriptome, proteome, and metabolome, as well as to brain imaging and additional phenotype data. Dr. Bennett hypothesized that exposomic risk factors—such as early-life exposures—should demonstrate effects in the brain. For example, depressive symptoms have been related to cognitive decline across multiple studies, and neural findings suggest that an

[3] Kivipelto M, Ngandu T, Laatikainen T, et al. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurology*. 2006 Sep;5(9):735-741. doi:10.1016/S1474-4422(06)70537-3. PMID:16914401.

abundance of the IGFPB-5 protein and some microRNAs increase the effect of depressive symptoms on cognitive decline. Bennett explained that molecular network analysis, paired with Bayesian modeling, can identify specific genes and proteins through which the exposome may contribute to the pathology and cognitive decline associated with AD/ADRD.

Dr. Barnes focused on environmental exposures related to cognitive activity, resource access, and decision making and considered evidence exclusively from cohorts who identify as Black or Latino (e.g., MARS, ADCC African American and Latino Cores) . Black participants from the MARS and MAP cohorts had lower literacy scores, but once literacy was controlled for, racial differences in decision making were non-significant. This finding suggests that racial differences in decision making are due, in part, to a lack of access to decision-making resources.

Two distinct constructs related to psycho-social stress also emerged among Black participants: perceived stress and experienced discrimination. Participants who experienced higher levels of experienced discrimination tested lower on multiple cognitive measures (global cognition, episodic memory, and perceptual speed), while those with higher perceived stressors experienced a faster rate of cognitive decline. Factors including larger social networks, life spaces, and cognition were associated with lower perceived stress. Cognitive performance was also lower for cohort members born or living, at age 12. in southern states compared to those in northern states and this effect was exacerbated for Black cohort members.[4] In cohorts made up of Latino populations, a positive association emerged between cognition and acculturation and a negative association between cognition and contextual factors (discrimination, social isolation).

Future diverse cohort research will: examine disadvantaged neighborhoods, air pollution, and exposures along with AD risk; l allow whole genome sequencing, RNA sequencing, and proteomics; and, add diet measures to questionnaires to allow comparison with traditionally sampled cohorts for whom this information is already collected.

Discussion

Cohorts and Assessments

Dr. Anderson asked whether the Latino cohort consisted mostly of Mexican-Americans or sampled different groups. Dr. Barnes explained that future research aims to diversify the sampling of Rush University cohorts, particularly the Latino cohort. The current Latino cohort does not disaggregate into country of origin because the sample size is too small for comparative analysis. Seven countries are currently represented with a majority of participants from Mexico. Cohorts are predominately women, and recruitment of more males to the study is a major priority.

Dr. Bennett clarified that his use of annual assessments, as compared with studies that assess participants every 3 to 5 years, aims to capture non-linear cognitive decline, and the potential

[4] Lamar M, Lerner AJ, James BD, et al. Relationship of early-life residence and educational experience to level and change in cognitive functioning: Results of the Minority Aging Research Study. *The Journals of Gerontology: Series B* 20202;75(7):e81-e92. https://doi.org/10.1093/geronb/gbz031

in some participants for rapid decline. The final years of life are very complicated for individuals with ADRD, and more granular data can effectively capture cognitive changes.

Lifestyle

Dr. Anderson also asked Dr. Barnes to clarify the impact of "life space" on AD/ADRD risk. Dr. Barnes replied that an individual's life space—or the geographic zones they experience—is related to stress: as life space grows, perceived stress levels decrease. As one's life space restricts, an association with ADRD risk increases across all examined racial groups.

Lifecourse Pathways Linking Educational Experience to Cognitive Decline and AD

Jennifer Manly, Columbia University

The link between early life conditions and adult illness is known, but the precise mechanisms of that link are complex. Dr. Manly aims to discover potential mechanisms of the relationship between the complex construct of *educational experience* and AD/ADRD risk in later life. These links may lie anywhere from the individual to the family to the community level; for example, at the community level, education may enhance the ability to organize politically and thus improve broader conditions that affect aging. Several methodologies can help establish the precise nature of education's link to AD/ADRD, including policy studies (which have shown that compulsory increases in the number of years of schooling has a positive impact on late-life memory and executive function[5]) and assessments of school quality (which can be measured through length of school year and student-teacher ratio).

Dr. Manly's research with the Project Talent cohort revealed an association between higher school quality and better cognitive test scores, but that relationship was not consistent across all racial groups; for example, the effect was strongest for white women, but was not reliably different from zero for Black men. Racial disparities in schooling investment exist for primary school students and are exacerbated by geographic location; disparities increased for students residing in southern states. Research from the REGARDS cohort found increased investment in elementary education was associated with reduced risk of cognitive impairment—except in the case of Black men, for whom racism in the labor market appears to eliminate the benefits of schooling.

Additional racial disparities persist concerning cognitive reserve in later life. Based on MRI imaging data, number of years of schooling contributes to cognitive reserve in whites, but not in Black or Hispanic participants. Through buildup of cognitive reserve, education may serve as a moderator of the effect of neuropathology on cognition and may indirectly affect risk of ADRD through economic, behavioral, and social mediators.

[5] Vonk JMJ, Arce Rentería M, Avila JF, Schupf N, Noble JM, Mayeux R, Brickman AM, Manly JJ. Secular trends in cognitive trajectories of diverse older adults. Alzheimers Dement. 2019 Dec;15(12):1576-1587. doi: 10.1016/j.jalz.2019.06.4944. Epub 2019 Oct 28. PMID: 31672483; PMCID: PMC6925643.

Supporting education policies supports brain health in later life, but additional research is needed to understand mechanisms. To effectively capture racially patterned early life educational experiences, mechanism studies should be nationally representative, oversample populations burdened with brain health disparities, and include population level biomarkers and residential history. All studies should avoid highly selective samples (e.g., UK Biobank), because even at large sample sizes, they will not help elucidate pathways.

Discussion

Dr. Manly explained that improving overall brain health in later life will require a nationwide social investment in equity-promoting educational practices. Dr. Barnes added that scientists will need explain the impact of early life measures to advocates and policy makers outside of academia. Community-wide investment and opportunity will be key for areas where formal education is not available. To improve policy, all future studies should include historical residential data, particularly to address the effects of migration.

Quantifying the Socioeconomic Impact on Brain Health—The Neighborhood Atlas

Amy J.H. Kind, University of Wisconsin

The United States has profound health disparities among its residents, but a health disparities research framework exists and use of a mechanistic vantage point could lead to cures for disease across the nation. Implementation science, which focuses on the barriers to implementing research findings systematically, can shine a light on pathways to influence policy action and decrease disparities.

To better understand which geographic areas are most likely to experience difficulty engaging in healthy behaviors, the Area Deprivation Index (ADI)—originally created by Health Resources and Services Administration (HRSA) and updated by researchers at the University of Wisconsin—can be used. Its *Neighborhood Atlas* allows users to visualize neighborhood disadvantage with geospatial metrics. *Neighborhood Atlas* users should be aware that although the tool is policy-actionable, application and interpretation of this tool must be informed by the lens of health disparities theory.

Dr. Kind investigated neighborhood level social determinants of health, and how contextual factors might be associated with elements of brain health, such as amygdala-prefrontal connectivity, brain volume, and AD-related pathology. For example, her findings suggest neighborhood disadvantage can be linked to total brain volume but remains independent of individual socioeconomics, with further research needed. Recent work determined a socio-biological phenotyping lens can feasibly be brought to neuropathology, and early work suggests living in disadvantaged area increases odds of AD neuropathology, but sample size low.

She recommends that exposome researchers (1) embrace the principles of implementation sciences and allow research to broadly translate into action more rapidly, (2) measure and apply the complex socioeconomic factors with a clear understanding of health disparities

theory, and (3) embrace data democratization and open science as critical components that lead to solutions.

Discussion

Dr. Manly asked Dr. Kind to comment on the use of the ADI in studies that have used ADI as a marker for neighborhood SES and as a mediator for race. Dr. Kind emphasized that any use of mediation models must be informed by sound theory. There are multiple levels of interweaving that exist between race and neighborhood disadvantage, particularly in urban areas and with Native American populations.

Researchers must proceed with caution because an oversimplification of factors can quickly become problematic. Dr. Kind added causal inference must be considered carefully among both contextual and individual perspective across the lifecourse. Models used must consider the structural inequities present in the United States. Responsibility for knowing when to use certain types of metrics will fall to the researchers.

What the Tsimane Tribe is Teaching us About the Environmental Impact on Chronic Diseases of Aging

Hillard Kaplan, Chapman University

The Tsimane tribe, an indigenous population in Bolivia, helps shed light on population-level differences in aging. The Tsimane tribe's lifestyle is very different from contemporary Western lifestyles: the tribe practices slash and burn agriculture, forage farming, and fishing. The tribe's exposome includes high physical work effort (on average double the daily steps compared to U.S. populations), highly social living with large families leading to high amounts of food sharing, high infectious disease transmission (stemming in large part from untreated water and sewage), and exposure to a large amount of wood smoke. Although the tribe's exposome is rapidly changing, with the adoption of commercial activity, including food purchases, and motorized transportation, it still offers an instructive counterpoint to Western patterns of aging.

The Tsimane generally have low levels of adiposity, circulating LDL, triglycerides, and glucose, which all impact arterial health. The population experiences low levels of coronary heart disease, diabetes, and recently low mortality rates from COVID-19. The arterial health of the population allows for a slower rate of brain volume loss, and a decreased prevalence of dementia and AD compared to U.S. and European populations. Prevalence of Mild Cognitive Impairment (MCI) was nearly the same for both the Tsimane and U.S. populations. However, for those diagnosed with dementia, most did not conform to the typical AD symptoms, and most MCI cases are non-amnestic.

The different pattern of cognitive decline in Tsimane and U.S. populations suggest that different sources of inflammation over the lifecourse have different cognitive effects: infection-driven inflammation experienced by the Tsimane appear to pose lower cognitive risks than the metabolically driven inflammation more frequently seen in United States or European

populations. The Tsimane exposome could also contribute to low mortality rates experienced from SARS CoV-2, potentially due to their high infectious disease exposure. Kaplan's future work will center around the relationship between viral exposure, cognitive decline, and brain pathology. His work will also expand the use of intensive vascular imaging analyses and include blood markers for ADRD in the Tsimane population. He will continue investigating the effects of lifestyle change on chronic disease outcomes.

Discussion

Dr. Anderson asked about reasons for the low COVID-19 mortality rate among the Tsimane. Dr. Kaplan speculates that the previously high prevalence of infectious diseases among the population has likely exposed the tribe to a coronavirus-like virus prior to SARS CoV-2.

Dr. Kaplan described childhood mortality and patterns of disease seen within the Tsimane tribe. The age structure of the population pyramid is broad at the bottom and narrow at the top, because of higher mortality rates in infancy and childhood. Childhood mortality rates create a selection effect for adulthood: more robust individuals may be surviving into older age, which may alter population-level late-life cognitive performance.

Session II: Overview of NIH Initiatives

The Adolescent Brain Cognitive Development (ABCD) Study

Gaya Dowling, National Institute on Drug Abuse (NIDA)

ABCD is a longitudinal study designed to follow more than 10,000 demographically representative children ages 9-10 years through their adolescence and into adulthood. The aim is to assess various factors that influence brain development trajectories and functional outcomes. During in-person and telephone visits, the study measures physical health and activity, pubertal development, mental health, substance use, and culture and environment (e.g., ethnic identity, acculturation, neighborhood safety), and—prior to COVID-19—conducted structural and functional MRI scans, neurocognitive task assessments (e.g., language, attention, behavioral inhibition), and biospecimen collection. During the pandemic, monthly online questionnaires have been disseminated to all participants to understand the impact of the pandemic and the extent to which exposures and family factors mitigate or exacerbate neurobiological, cognitive, and affective outcomes. ABCD is committed to an open science framework and releases data through the NIMH data archive. Data releases result in a proliferation of related publications.

Dr. Dowling highlighted a publication that investigates the associations between cognitive test scores and risk of lead exposure. The study concluded that children living in areas with higher risk for lead exposure scored lower in cognitive assessments and had decreased brain volume. This analysis is an example of how ABCD data can link brain metrics, behavior, and environmental exposures in an integrated framework. This unique data set avoids "modeling

life factors in isolation" and thereby missing "the importance of the wider context in which [those factors] occur."[6]

Discussion

Data Accessibility
Studies based on ABCD data have the advantage of using a wide range of variables, from genomics to environmental factors based on geo-coded data. The breadth of variables allows researchers to investigate potential interactions and associations.

Dr. Petanceska asked whether bio sampling data are collected and whether there is any way to enhance molecular profiling. Dr. Dowling stated that blood and serum are currently banked but have not been collected for the entire cohort. The bio sampling data should become available to other researchers within the next year. ABCD also plans to sequence the whole genome of the cohort, and these data will also be available in the future.

Extended Sampling
Dr. Patel asked whether the ABCD cohort can be followed beyond ages 19-20 as currently planned. Continued data collection of the cohort would depend on funding opportunities, and Dr. Dowling would support continuation.

Overview of the NIEHS Exposome/Exposure Programs and Resources

David Balshaw, National Institute of Environmental Health Sciences (NIEHS)

To investigate the complexity of the exposome, NIEHS has prioritized measurements on the individual level from two angles—at the point of contact (i.e., through sensors worn or used by the individual) and through archival biological samples. Tools used for point of contact data collection must accurately and reliably measure desired variables, be used by participants with minimal burden, and provide valuable data to the field.

Previous research to understand exposure effects throughout the lifecourse attempted to investigate a single exposure and control for all other factors not directly related to the hypothesis. However, researchers have increasingly begun to measure multiple stressors and aspects of the environment.

Balshaw presented three models for measuring exposures to multiple stressors: targeted, which includes bio- and environmental monitoring; semi-targeted, where suspect screening based on broadly defined hypotheses occurs; and untargeted, which is largely discovery driven. In the third model, researchers measure large sets of analytes simultaneously to allow data-driven, "hypothesis-free" associations between exposure and biological response. In this model,

[6] Amirhossein M, Janiri D, Doucet GE, Reichenberg A, Frangou S. Multivariate patterns of brain-behavior-environment associations in the adolescent brain and cognitive development study. *Biological Psychiatry*. Accessed January 2, 2021. https://doi.org/10.1016/j.biopsych.2020.08.014

the exposome can be used as a tool for discovery, provided researchers embrace complexity and are open to unexpected associations between environment and health.

The Human Health Exposure Analysis Resource (HHEAR) provides access to specialized and comprehensive exposure assessments. HHEAR laboratories have added environmental samples collected through targeted and untargeted methods to their biological sampling databases. Each sample can be leveraged with new technologies and measurements to provide specialized and comprehensive exposure assessments.

Discussion

NIEHS Resources

Brian Fulton-Howard asked whether a biological responses repository or an infrastructure program like Biobank would qualify for analysis by NIEHS. Dr. Balshaw highlighted the potential value and challenges that repositories hold but noted that increased use of electronic health data increases the feasibility of analyses. The prospective repository must be structured in a compatible manner.

Dr. Petanceska asked about investigator access to the HHEAR database. To gain access to the data, individuals must be validated based on their institutional affiliation. All validated individuals have access to online analysis tools and all data is downloadable.

Future Research

Dr. Kaplan asked about ongoing NIH support for research on the widespread use of mercury for gold-panning in the Amazonian rivers. Dr. Cory-Slechta noted a few publications in this area, but further research would be interesting because local differences in culture and exposures exist.

Highlights from the NASEM Environmental Neuroscience Workshop

David Jett, National Institute of Neurological Disorders and Stroke (NINDS)

Dr. Jett delivered highlights of the June 2020 National Academies of Science, Engineering and Medicine (NASEM) workshop *Environmental Neuroscience: Advancing the Understanding of How Chemical Exposures Impact Brain Health and Disease*. The workshop considered one underexamined element of the exposome—the risk of neurotoxicant exposure to human health—with a focus on its effects on specific neurological diseases and disorders (e.g., idiopathic Parkinson's disease, AD). This NASEM workshop also addressed SES and racial disparities as well as differential sex-based effects that require further epidemiological studies.

A 1999-2000 NHANES survey found evidence of pesticides in urine of 50-95 percent of the U.S. population, revealing the widespread nature of neurotoxicant exposure. The impact and risk of collective chemical exposures, particularly from air pollution, are significant for aging and neurodegeneration. The workshop participants shared a concern that heavy metals and pesticides might contribute to neurodevelopmental problems, although they did not reach consensus on this point.

Further, the effects of early-life chemical exposures on specific neurological diseases and disorders were confirmed by another study that reported increased vulnerability to late-life neurological insults; for example, traffic-related air pollution led to an increased risk of Parkinson's disease for individuals carrying interleukin-1β. In addition, studies discussed by the workshop presenters pointed to the microbiome as a likely contributor to the risk of neurological diseases.

There is a need to generate more mechanistic data on biological processes, particularly using an adverse outcome pathway approach to investigate clinically relevant exposures. Future investigations should explore potential high-dose exposures during critical periods (e.g., pregnancy), critical effects of a short and remote but high human exposure, and chronic effects of low, long-term exposure. A new research framework that includes multidisciplinary collaborations among environmental scientists, social scientists, and toxicologists will benefit the research field. An increase in collaborations with data scientists can be useful for re-packaging and utilizing existing data sets.

Discussion

Dr. Reddy asked whether any information is available on the toxic effect of natural gas, particularly near rigging sites. Dr. Jett was unaware of any specific studies. Dr. Cory-Slechta stressed the difficulty of studying natural gas effects because the gas formulations are generally proprietary, so the full structure of the exposure is unknown.

Session III: From Clinical Research to Molecular Mechanisms (Part 1)

Environmental Epigenomics/Mechanisms of Transgenerational Inheritance of Risk and Resilience

Environmental & Nutritional Epigenomics: Using Animal Models to Understand Mechanisms of Environmental Factors

Dana Dolinoy, University of Michigan

Epigenetics is broadly defined as heritable changes in gene expression that do not alter the underlying DNA sequence. Environmental epigenomics, or toxic epigenetics, studies the ways that environmental factors may cause negative epigenetic changes, while nutritional epigenetics studies the ways that food may affect patterns of gene regulation. Dr. Dolinoy is interested in how toxicoepigenetic researchers can identify exposures and which individuals within a population are at risk. She shared results from a mouse study that successfully employed a multi-omics approach to investigate environmental exposure and tissue-level methylation and another mouse study that investigated perinatal exposure to BPA (bisphenol A) and its effect on a variety of genes.

Translating results from mice to humans remains a challenge that is exacerbated when studies must be conducted with surrogate tissue because data from target tissue are unavailable (e.g., blood samples taken as a substitute for liver tissue). Dolinoy highlighted a human study investigating BPA exposure in young girls using DNA from saliva; exposure effects overlapped with those of mouse liver, including an increase in genes that are associated with both immune response and metabolism, as well as in genes positionally located on the X-chromosome.

Changes in the epigenome through time involve two processes: epigenetic drift and age-related methylation. The former includes stochastic and bi-directional changes in epigenetic variability with age, and the latter involves predictable unidirectional changes that are expected as individuals age (i.e., promoter genes increase in methylation with age whereas repetitive genomic content decreases with age). Successful research into the aging epigenome will require longitudinal animal model and human cohort studies because exposures can occur throughout the lifecourse.

Ultimately, environmental epigenetics explores the possibility of reversing epigenetic changes due to environmental exposure. Dr. Dolinoy's research group has developed the technique of using piRNA, a short, non-coding RNA, to perform epigenome editing and influence gene expression. For example, a piRNA injection successfully reversed a single epigenetic change at a mouse's agouti locus, increasing DNA methylation to produce a change in coat color. This example shows promise for the potential to reverse environmental impacts on the epigenome to prevent disease development.

Discussion

Epigenomic Divergence

Dr. Dolinoy confirmed Dr. Cory-Slechta's sense that the stochastic drift seen in twins could be caused by differences in environment and lifestyle choice that result in epigenomic divergence. Predictable changes in DNA methylation may also be affected by "environmental deflection." Exposures in utero could reset the programming of genes that undergo age-related change, preventing them from reaching the critical epigenetic levels that cause age-related decreases. This phenomenon can be analogized to shooting a bow and arrow into a windy environment; even if aimed properly, the arrow will likely miss its target.

Mouse Models

Ms. Tarver asked about additional effects from the single mouse injected with piRNA. Dr. Dolinoy responded that the mouse also experienced decreased body weight, further signaling an effect on DNA methylation. However, no additional phenotyping was conducted. Additional collaboration with Dr. Pini Perera, who has developed a method to continue investigations in vitro, will facilitate this type of study. Additional phenotyping data should be available in the future.

Dr. Patel asked about setting mouse dosage and exposure levels for relevance to human outcomes. Dolinoy ensures all studies with mice are conducted at human-relevant exposure levels and collects blood samples to determine relevancy. Studies described today use mouse

mothers (dams) with blood lead levels higher than what is currently seen in humans (30 micrograms per deciliter) but similar levels were observed in the 1970s.

Impact of Heavy Metals Exposure on the Risk of Dementia: From Environmental Epidemiology to Molecular Mechanisms

Kelly Bakulski, University of Michigan

The United States is the global leader in the production of a variety of chemicals, with only a minority fully assessed for risk by the Environmental Protection Agency (EPA). Metal exposure is widespread but varies across the United States, with some due to geographic region and others due to anthropogenic causes. Many of these metals, such as lead, cadmium, manganese, arsenic, methylmercury, and tributyltin, exhibit neurotoxicity at different points of the lifespan.

The timing of a chemical exposure within the lifecourse is an important factor because exposure at certain life stages can have detrimental effects, particularly if it occurs during a window of susceptibility. For instance, a study of macaques exposed to low levels of lead in early life showed elevated beta amyloid levels and phosphorylated tau (known factors for AD/ADRD) in adulthood. Metal exposure can cause a general neural toxicity that includes oxidative stress, disrupted iron levels, and altered calcium levels.

To understand how exposure affects the body, researchers typically collect tissue samples, but these samples often consist of different cell type structures. This kind of sampling will not capture the cell-specific effects that metal exposure can exert on cell-specific epigenetic patterns. Without cell type differentiation, a researcher could not successfully identify direct effects, vulnerable cell types, or cell type heterogeneity. Dr. Bakulski employs single cell RNA sequencing to uniquely code individual cells, and the data structure allows inclusion of several genes based on the cells within the sample.

Discussion

Dr. Niu asked whether changes in specific proteins and receptors, such as glutamate receptors have been investigated, and Dr. Bakulski confirmed that toxicology studies conducted by other researchers have reported that lead significantly impacts glutamate excitotoxicity cortical neurons and inhibits an MDA receptor. The Singapore Pediatric Institute also describes lead inhibiting other glutamate receptors. There is additional evidence for lead's direct impact on neural signaling in neural pathways.

NIEHS TaRGET and FRAMED Programs

Fred Tyson, NIEHS

Both the Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET) and Functional RNA Modifications Environment and Disease (FRAMED) programs study how epigenetic modifiers respond to environmental exposures and how the impact of environmental exposures can perturb the epigenome or modify functional RNA. TaRGET I focuses on DNA methylation and chromatin accessibility, Target II focuses on

generation of epigenomic signatures from chemical exposures generate epigenomic signatures, and FRAMED focuses on RNA.

TaRGET I investigated multiple exposures across the lifecourse of mice (gestation through 10 months) to explore their potential impact on adverse outcomes. TaRGET II characterized epigenetic changes induced by environmental exposure in tissues, with sample collection of brain, lung, liver, skin, and blood tissue followed by epigenomic and transcriptomic assay analysis for both DNA and RNA.

To ensure that the resulting data remain available to the public, the TaRGET II data coordination center provides data quality assurance and accessibility through the TaRGET Data Portal. The nearly 2,000 data sets submitted by TaRGET investigators cover a range of exposures, with associated findings that highlighted a need for additional research with RNA, leading to establishment of FRAMED.

FRAMED currently supports five R01 and four R21 grants. The epitranscriptomics grant portfolio investigates four epitranscriptome modifications, reader, writer, and eraser proteins, a variety of exposures, and health outcomes. PIs use cutting-edge technologies to answer questions regarding toxicant exposure, mechanisms that alter the transcriptome, what characteristics of mis-localized RNA are associated with disease, and how RNA methylation may be associated with neurodegenerative disorders.

Future research includes the completion of TaRGET II analysis and the possibility of a TaRGET III, depending on funding. The current programs (TaRGET and FRAMED) have shown significant crosstalk between the epigenome and the epitranscriptome. Work related to this junction would open research opportunities to identify how exposures may perturb epigenome and epitranscriptomic communications.

Discussion

Extended Sampling

Dr. Petanceska asked whether TaRGET II will include mice of older ages. Although there is a desire to include mice older than 10 months who have had *in utero* exposures, current resources do not support extended aging of the animals. If extended ages are included, then an additional cohort will be necessary.

Cognitive Impairment Factors

Dr. Mollayeva raised a concern that some animals may be inherently able to recover from exposures or infections that lead to cognitive impairment. Dr. Tyson noted that, to explain individual differences in response to toxic exposures that may cause cognitive impairment, TaRGET II investigates an individual's underlying genetic sequence, differences in which could explain variance in susceptibility and part of brain plasticity. Dr. Bakulski added that several genetic polymorphisms can increase likelihood of AD or alter metabolism.

Dr. Mollayeva further asked whether any behavioral adjustments are known to be protective across the lifecourse. Dr. Bakulski described evidence that physical activity reduces risk of dementia and that intake of leafy green vegetables decreases rate of cognitive decline. Studying the exposome, instead a single exposure, could reveal the totality of factors that together could increase an individual's risk.

Session III: From Clinical Research to Molecular Mechanisms (Part 2)

Microbiome and Lifestyle Factors

MODEL-AD – Model Organism Development and Evaluation for Late-Onset AD

Gareth Howell, Jackson Laboratory

Clinical trials of AD have not been successful, and the lack of success has been attributed to the efficacy and translatability of mouse models. To overcome previous challenges, the field set out to develop the next generation of *in vivo* mouse models, standardize processes, make results rapidly available for preclinical drug development, align pathophysiological features of AD models with corresponding stages of clinical disease using translatable biomarkers, and to establish guidelines for rigorous preclinical testing in animal models.

The goal of these efforts is to design the best models for late onset AD and to assess them based on translational phenotypes ('omics, neuropathology, neuroimaging) so that the models can be used for preclinical testing of potential novel AD-related compounds. To create appropriate models, the MODEL-AD effort aims to introduce strong risk variants (e.g., APOE4), humanize AD genes (e.g., amyloid pathology), introduce precise AD risk variants (e.g., ABCA7), account for environmental risk (e.g., high fat diet), and account for the influence of genetic diversity. Additional research considers how the same diet can be linked to alterations in microbiome diversity for mice with different AD gene pathologies. Alterations in microbiome diversity were shown to be laboratory site and cage specific, suggesting the impact of environmental differences.

MODEL-AD is focused on investigating genetic manipulations that generate disease relevant pathologies in an age-dependent manner. For success, mouse models for late-onset AD need to reflect the human condition as much as possible, which includes a need for genetic variation. Molecular profiling approaches are used to better align mouse models to the human condition. Additionally, MODEL-AD aims to define AD on the molecular level, which could identify targets for therapeutics. Mouse models carrying human genetic risk factors (in the absence of strong amyloid and tau drivers) are ideal for investigating the interactions between genome and exposome.

Discussion

Dr. Mollayeva asked for comment comparing the sex differences observed in Preuss et al. (2020) and the results of AD-relevant phenotypes on a high-fat diet. Dr. Howell clarified that MODEL-AD studies include equal numbers of males and females to accurately identify any sex differences. Sex differences were seen in Preuss et al. and caution must be taken, because the transgenes that drive amyloid deposition are accelerated in female mice. To mitigate these sex differences, future research will focus less on transgenes and more on manipulating the endogenous locus. Additional sex differences depend on strain and genotype. Though sex-specific transcriptomics are not yet completely tracked, Dr. Howell expects to see differences in age and high fat diet.

Understanding the Role of the Microbiome in Brain Aging and AD/ADRD

Rima Kaddurah-Daouk, Duke University and Rob Knight, University of California, San Diego

A combination of big data and precision science has allowed scientific investigation into vulnerability to disease and the unique trajectories of disease observed in individuals to help shed light on the exposome. Dr. Kaddurah-Daouk presented the metabolome as a way of analyzing the combined influences of the genome, gut, microbiome, and exposome. The bacteria of the gut and its processes are critical for molecules that impact human health. The gut microbiome completes human metabolism, an element of the internal exposome, and pulls together a network of connected processes and pathways.

The metabolomics consortium aims to map the biochemical trajectory and changes in AD from pre-symptomatic stages through the complete trajectory of the disease. This effort is achieved by connecting changes in blood and brain imaging to cognitive disfunction. Current research examines the association between the gut microbiome and AD phenotypes. By identifying metabolic signatures (e.g., membrane structure remodeling, beta oxidation dysfunction) that are associated with AD phenotypes and examining the mechanistic links between gut microbiome activity and AD pathogens, researchers can understand changes in the gut microbiome, its relation to the metabolome, and their connections to clinical measures, such as brain imaging changes. Dr. Kaddurah-Daouk has partnered with Dr. Knight and 40 other researchers in the Alzheimer's Gut Microbiome Initiative to understand how changes in the microbiome are related to ADRD.

Dr. Knight discussed the union of the microbiome and metabolome and their potential for integrating human and environmental microbiology, both of which are highly complex and can involve thousands of unique DNA barcodes. Technological advancement has made genetic sequencing technology more feasible and allows microbiomes from large cohorts to be analyzed and later visualized. For instance, researchers are now able to gain simultaneous insights from the lung of a cystic fibrosis patient and integrate the genetic sequences with river and air data and other complex microbiome sequencing.

A large percentage of the microbial genetic material in humans can be altered and can have an impact on health and the aging process. Additionally, environmental factors have a larger impact on shaping the microbiome than the genome. The American Gut Project, a citizen science initiative that collects American fecal samples, has provided a continually increasing dataset for investigation of the human gut microbiome. Dr. Knight described age and sleep duration as having a strong impact on the human microbiome, but diversity of plant species consumed by participants has the strongest effect. Though genes are fixed, their expression can be greatly modified by food.

Discussion

Diet Impacts

Dr. Voss asked whether breaks in eating (e.g., intermittent fasting) affect microbiome diversity. Dr. Knight stated that the role of intermittent fasting has not yet been investigated. Colleagues have found that intermittent fasting has a significant impact in mice, but the impacts in humans are less well understood and long-term diet interventions are more difficult to carry out in human studies.

Dr. Kaddurah-Daouk explained that NIST is conducting a study that compares fecal samples from vegetarians and non-vegetarians to explore impacts on the gut microbiome and metabolome, but study data are not yet available. Knight added that the American Gut Project found no association between veganism or vegetarianism and the microbiome overall, but diversity of plant sources consumed is positively associated with microbiome diversity.

Fecal Transplants

Ms. Tarver asked whether the U-19 Gut Project III will perform bi-directional fecal transplants between mice that are more obese and those that are more slender. Drs. Kaddurah-Daouk and Knight clarified that fecal transplants would occur only in subsequent years and only from humans to mice.

Session IV: The Impact of Air Pollution on the Etiology of AD

Air Pollution: Gerogen in the AD Exposome

Caleb Finch, University of Southern California

Recent data from several studies have pointed to moderate heritability of AD/ADRD accounting for 50 to 59 percent of variance in risk. However, gene environment interactions (GxE) remain largely undefined. A great deal of diversity exists in individual environmental exposures, and GxE interactions need to be studied over an individual's lifecourse to fully understand the AD exposome.

One major factor in understanding that exposome is the *gerogen,* defined as a toxin or stressor that accelerates aging processes (e.g., increased risk of AD or cardiovascular disease). Gerogens can be exogenous (i.e., air pollutants) or endogenous (i.e., fat depots) and can accelerate aging,

which leads to AD risk factors. For example, the presence of the ApoE4 allele is not only a risk factor for Alzheimer's, but also for increased vulnerability to air pollution, an exogenous gerogen.[7] Endogenous individual responses to air pollution have been shown to vary based on sex, suggesting additional research should be pursued to investigate differences in response to air pollution.

Exposure to air pollution has been shown to cause a major deficit in adult neural stem cells[8]. Loss of this population of neurons in the hippocampus and olfactory systems are critical for contextual memory and disorders related to Alzheimer's. Prenatal exposure to air pollution caused the loss of adult neural stem cells, increased fat deposits, and an increased intolerance for glucose. Finch hopes to expand research investigating ApoE in relation to neighboring genes, as some recent research finds[9] AD haplotypes that lead to genetic variation in adjacent genes, which includes a gene cluster with relevance for the pathophysiology (e.g., BMI, hypertension) for Alzheimer's risk factors. The future of healthy brain aging will depend on GxE interactions in the AD exposome and must consider the entire lifecourse.

Contribution of Air Pollution to Risk of AD/ADRD: The Epidemiologic Evidence

Jennifer Weuve, Boston University

Most ADRD cases occur with other (often cerebrovascular) pathologies. This complexity offers a framework for understanding the potential effects of air pollution on the aging brain. Air pollution may affect the brain directly, but it also may have pleiotropic effects. For example, animal and autopsy studies suggest that air pollution exposure increases oxidative stress, inflammation, cerebrovascular damage, and each of these may link air pollution to dementia.

Including epidemiologic research in the study of AD would help study potential risk factors such as air pollution. An epidemiologic approach can evaluate a range of exposure dosages, the mixtures and sources of air pollution, and the dimension and timing of exposure (age and duration). Epidemiological studies, by definition, consider human data and have outcomes that happen and matter to humans.

Current epidemiological studies of air pollution and cognition have investigated level of cognitive functioning, rate of cognitive decline, dementia incidence, and brain imaging. Most studies report estimated associations between air pollution and cognitive level or incidence of dementia, thought studies are not well represented in South America, Africa, nor Australia. Though publications in the field are increasing, concerns of bias and misclassification remain. Misclassification concerns arise for studies using *passive surveillance* and relying on medical

[7] Kulick ER, Elkind MSV, Boehme AK, et al. Long-term exposure to ambient air pollution, APOE-E4 status, and cognitive decline in a cohort of older adults in northern Manhattan. *Environment International* 2020;136: 105440. https://doi.org/10.1016/j.envint.2019.105440

[8] Moreno-Jiménez EP, Flor-García M, Terreros-Roncal, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nature Medicine* 2019;25:554-560. https://doi.org/10.1038/s41591-019-0375-9

[9] Haghani A, Thorwald M, Morgan TE, et al. The APOE gene cluster responds to air pollution factors in mice with coordinated expression of genes that differs by age in humans. *Alzheimer's & Dementia*. November 2020. doi:10.1002/alz.12230

records and insurance claims data; these studies may miss participants who have not received a dementia diagnosis from a medical professional. If diagnosed individuals are more likely to have experienced air pollution (e.g., because they are more likely to come into contact with physicians due to other air pollution-related pathologies), that would distort measurement of the relationship between air pollution and dementia. Selection bias may also occur, most frequently with high-burden protocols like brain imaging, because they are more likely to attract participants with a familial risk of AD. Adjusting for confounding factors can present an additional challenge: any non-causal pathways of the relationship between air pollution and ADRD (such as SES or smoking) should be eliminated.

Of 53 studies initially reviewed by Dr. Weuve, 29 were selected for further characterization based on their small number of methodological limitations. These studies found consistent associations between fine particulate matter ($PM_{2.5}$) and cognitive function/decline. The field can improve future studies of $PM_{2.5}$ and other elements of air pollution by incorporating standardized assessments of dementia, making note of potential biases (misclassification or selection), and setting realistic time scales that match the unfolding of dementia over years and decades. Further improvements could come from interdisciplinary collaborations and studies with diverse populations.

Discussion

Dr. Charles Hall asked whether individual-level measurements of air pollution are necessary given that particulate matter can vary over short distances. Dr. Weuve stated that individual-level measurements would be ideal and noted that, although current air pollution measurements are based on regional measures, the accuracy of air pollution measurement is continually improving. Individual-level measurements can lead to highly accurate estimates of short-term exposure but not long-term exposure data. Further, they are a high burden for participants.

Air Pollutant Exposure: Impact on Cardiovascular and Neurological Function

Loren Wold, Ohio State University

Environmental pollutants are well documented, but novel and self-induced pollutants have relatively recently been introduced. Air pollution—including gasses, liquid suspensions, and particulate matter (PM)—poses cardiovascular health risks. Fine scale $PM_{2.5}$ exposure, for example, is positively associated with myocardial infarction, atherosclerosis and vascular dysfunction, arrhythmias, increased blood pressure, hypertrophy, and thrombosis. PM exposure can have direct effects if particulates travel directly to the heart, as well as indirect effects through pulmonary inflammation and inflammatory mediators.

Dr. Wold conducted in vivo mouse studies of direct and in utero exposure to fine particulate matter, $PM_{2.5}$. Nine-month exposure periods cause contractile dysfunction by direct and indirect effects as well as a reduction in cardiac function. Regarding effects on the brain, findings suggest increases in brain amyloid beta 1-40 levels increased with no alterations of tau,

brain amyloid precursor protein (APP) levels were significantly reduced, and brain beta-site APPP cleaving enzyme (BACE) protein levels increased.

In a separate study, pregnant mice were exposed to $PM_{2.5}$ for their entire gestation with exposure ending upon birth. Exposure during development caused reduced cardiac function in adulthood and altered brain cytokines and working memory in adult male mice. These findings suggest that pre-birth exposures to air pollution can have significant long-term cardiovascular and neurological effects for male mice. More recent studies involve APP/DE9 mice that have been exposed to $PM_{2.5}$ for 6 months. Those exposed had decreased responses to the novel recognition test and increased hindlimb clasping, a marker of neurodegenerative disease.

Discussion

All of Dr. Wold's studies investigated both male and female mice, but the latter show either a tempered or no response specifically for cardiovascular assessments. These sex differences are attributed to the fact that ovariectomized mice are not currently in the sample.

Air Pollution, Metal Dyshomeostasis and Neurodegeneration

Deborah Cory-Slechta, University of Rochester

Human exposure to ultrafine particles (UFP), which have an elemental carbon core which often contain several contaminants, is widespread both in utero and after birth. Fetal susceptibility to UFP is direct (through the placenta) and indirect (through maternal inflammation), and after birth particles can directly enter the brain through the olfactory bulb and through the blood-brain barrier. Investigations of the effects of UFP could therefore offer insights into neurodegeneration.

Animal studies have found that male mice exposed to UFP matter during the final stages of brain development experienced an array of effects, including increased lateral ventricle size, microglial inflammation, and disrupted CC white matter development, while female mice experienced latent reductions (270 days after birth) in corpus callosum white matter occurring well after exposure ceased.[10] Additional studies of these exposed mice in adulthood suggest that exposures impaired short-term memory for both male and female mice, negatively affected learning behaviors, and altered temporal discrimination. Female mice may be particularly susceptible to the iron component in air pollution, which causes a reduction of neurons in the nucleus accumbens.

The induced changes in mice after PM exposure are consistent with the features and potential mechanisms of Alzheimer's disease in humans (reductions in white matter, alterations in brain connectivity, executive function deficits). In addition, the ultrafine particulate exposed mice to metals that have been previously associated at high concentrations with neurodegenerative

[10] Allen JL, Oberdorster G, Morris-Schaffer K, et al. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. *Neurotoxicology*. December 2015.

disease, such as iron. Brain metal dyshomeostasis also showed increased sulfur, aluminum, calcium, and copper levels, while manganese and zinc were decreased.

In addition to having potential mechanistic connections to AD/ADRD, air pollution also displays a geographic, seasonal, and temporal heterogeneity that could be related to the heterogenous expression of neurodegenerative disease. Individuals express AD/ADRD differently, with rates varying across the country, as does air pollution. Future research by Dr. Cory-Slechta will expand the metals investigated, move toward studies that may influence intervention strategies (i.e., regulation of air metal levels), and investigate the impacts of cumulative exposure in adults.

Discussion

Metal Removal

Dr. Opanashuk asked whether chelation therapy could be used to mitigate metal accumulation. Dr. Cory-Slechta confirmed that chelation is most frequently used for children who have been exposed to lead, but its benefits are limited. Chelators are not metal specific, so they also pull essential metals out of the body. Some exposures to metals through air pollution bypass the blood–brain barrier, and chelation cannot effectively remove this type of exposure.

Metal Prevalence in the Body

Researchers do not know whether pollution exposure leads to a predominant presence of all metals in the hippocampus. Evidence suggests that aluminum and copper have a high presence in the hippocampus, but metals can be found throughout the brain. Work to understand how metals influence the capacity for microglial phagocytosis has not begun.

Appendix A: Agenda

Understanding the Role of the Exposome in Brain Aging, Alzheimer's Disease (AD) and AD-Related Dementias

(All times listed are Eastern Standard Time)

Day 1	**December 2, 2020**
10:00 am – 10:15 am	**Welcome & Introductions - NIA**
	PLENARY LECTURES
10:15 am – 10:45 am	Quantifying the Impact of Gene and Environment Interactions on Health and Disease *Chirag Patel, Harvard Medical School*
10:45 am – 11:15 am	Embedding Mobile Health and Deep Learning into Prospective Cohort Studies to Study the Exposome *Peter James, Harvard Medical School and Harvard Pilgrim Health Care Institute*
11:15 am – 11:25 am	Q&A
	Session 1: Translational Epidemiology

11:25 am – 11:45 am	A Lifespan Approach to Understanding AD Risk and Resilience *Rachel Whitmer, University of California, Davis*
11:45 am – 12:15 pm	Assessing Factors Contributing to Cognitive Decline and AD Risk and Resilience Across Diverse Cohorts *Lisa Barnes, Rush University* *David Bennett, Rush University*
12:15 pm – 12:35 pm	Lifecourse Pathways Linking Educational Experience to Cognitive Decline and AD *Jennifer Manly, Columbia University*
12:35 pm – 12:55 pm	Q&A
12:55 pm -1:15 pm	**BREAK**
1:15 pm – 1:35 pm	Quantifying the Socioeconomic Impact on Brain Health – The Neighborhood Atlas *Amy JH Kind, University of Wisconsin*
1:35 pm – 1:55 pm	What the Tsimane Tribe is Teaching us About the Environmental Impact on Chronic Diseases of Aging *Hillard Kaplan, Chapman University*
1:55 pm – 2:05 pm	Q&A
	Session 2: Overview of NIH Initiatives
2:05 pm – 2:25 pm	The Adolescent Brain Cognitive Development (ABCD) Study *Gaya Dowling, NIDA*
2:25 pm – 2:45 pm	Overview of the NIEHS Exposome/Exposure Programs and Resources

	David Balshaw, NIEHS
2:45 pm – 2:55 pm	Highlights from the NASEM Environmental Neuroscience Workshop *David Jett, NINDS*
2:55 pm – 3:15 pm	Q&A
	Session 3: From Clinical Research to Molecular Mechanisms (part 1) Environmental Epigenomics/Mechanisms of Transgenerational Inheritance of Risk and Resilience
3:15 pm – 3:35 pm	Environmental Epigenomics and Nutritional Epigenetics Using Animal Models to Understand Mechanisms of Environmental Factors *Dana Dolinoy, University of Michigan*
3:35 pm – 3:55 pm	Impact of Heavy Metals Exposure on the Risk of Dementia: From Environmental Epidemiology to Molecular Mechanisms *Kelly Bakulski, University of Michigan*
3:55 pm – 4:15 pm	NIEHS TaRGET and FRAMED Programs *Fred Tyson, NIEHS*
4:15 pm – 4:35 pm	Q&A
4:35 pm	**End of Day 1**

Day 2	**December 3, 2020**
	Session 3: From Clinical Research to Molecular Mechanisms (part 2) Microbiome and Lifestyle Factors
10:00 am – 10:20 am	MODEL-AD – Modeling Environmental Influences in Transgenic Mouse Models of LOAD *Gareth Howell, Jackson Laboratory*

10:20 am – 10:50 am	Understanding the Role of the Microbiome in Brain Aging and AD/ADRD *Rima Kaddurah-Daouk, Duke University* *Rob Knight, University of California, San Diego*
10:50 am – 11:00 am	Q&A
	Session 4: The Impact of Air Pollution on the Etiology of AD
11:00 am – 11:20 am	Air Pollution: Gerogen in the AD-Exposome *Caleb Finch, University of Southern California*
11:20 am – 11:40 am	Contribution of Air Pollution to Risk of AD/ADRD: The Epidemiologic Evidence *Jennifer Weuve, Boston University*
11:40 am – 12:00 pm	Air Pollutant Exposure: Impact on Cardiovascular and Neurological Function *Loren Wold, Ohio State University*
12:00 pm – 12:20 pm	Air Pollution, Metal Dyshomeostasis and Neurodegeneration *Deborah Cory-Slechta, University of Rochester*
12:20 pm – 12:45 pm	Q&A
12:45 pm	**Wrap up - NIA**
1:00 pm	**Meeting Adjourns**

Appendix B: Participants List

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