NIA Expert Meeting on Pathways and Mechanisms Linking Behavioral and Social Factors to Health

Board on Behavioral, Cognitive, and Sensory Sciences (BBCSS)
National Research Council (NRC)

In 2013, the Division of Behavioral and Social Research (BSR) underwent a review by the National Advisory Council on Aging (NACA) to evaluate the overall impact of research supported by the Division and make recommendations for future investments. A key recommendation was that BSR leverage both its data resources and new study designs to gain mechanistic insights on the pathways linking behavioral and social factors to health and mortality. BSR contracted with The National Academy of Sciences Board on Behavioral, Cognitive and Sensory Sciences to conduct an expert meeting in Washington, DC, on May 30, 2014 to explore this topic, including opportunities for using BSR-supported biosocial surveys to advance this agenda. This report provides a summary of discussions at that meeting.

Framework for the Meeting

The Division of Behavioral and Social Research has invested heavily in large scale survey research as well as in longitudinal studies that have tracked individuals from childhood to midlife, to old age and to the end of life. A number of striking findings have emerged from these studies. Discussions at this meeting were stimulated by consideration of a small set of papers that provided examples of observed associations between an antecedent—severe stress, behavioral self-control and the broader domain of conscientiousness— and a range of consequent findings on adjustment, emotional self-regulation, general health and longevity. Four key reports of these results were provided to invited meeting participants for review prior to the meeting to focus discussion (Moffitt et al., 2011; Raio et al., 2013; Javaras et al., 2012; Kern et al., 2012)

These exemplar findings are not isolated but rather exemplify a broad set of reports of associations between social, psychological, economic, and behavioral factors and health outcomes in middle-aged and older adults. They collectively serve as a case study for how BSR might best proceed to identify optimal strategies for illuminating the pathways and mechanisms through which these factors affect health in middle-aged and older adults. The goal of this meeting was to determine how BSR might support the next stage of research to deepen our mechanistic understanding of these findings and those like them. Of special interest was identifying targets that are amenable to change, leading to improvements in the health and well-being of older adults in the U.S.

Turning to the papers, Kern et al. (2012) illustrate the use of data harmonization to pool data from two very long-term studies of adult health that began in childhood. They focus on the long-term association between childhood conscientiousness and adult health and longevity. Their analyses suggest two potential but partial mediators of this antecedent and consequent relationship: educational attainment and possibly alcohol abuse. Moffitt et al. (2011) illustrate a

dose-response relationship between measures of childhood self-control and a broad range of health and economic indices in adulthood. They too identified a partial mediator of this effect: adolescent problem behavior or "snares." Their use of a second data set with siblings addresses between-family confounding variables. In a third paper, Javaras et al. (2012) use a subsample of a major BSR-supported study: MIDUS (Midlife in the United States). Here, the subsample size used in this analysis is small enough for a practical laboratory study that exposes subjects to standard, emotionally laden stimuli to test the effect of individual differences in conscientiousness on recovery from exposure to a negative stimulus. Finally, a BSR-supported project under the Science of Behavior Change Common Fund Initiative by Raio et al. (2013), demonstrates experimentally that exposure to acute stress impairs individuals' ability to regulate their affective responses, raising questions about the effectiveness of certain self-regulatory approaches under stressful conditions.

One example, among many tempting mechanistic syntheses of these findings, might be that enhanced recovery from the negative affect (as modeled in the lab setting) is a "mechanism" that accounts for how high conscientiousness achieves its protective effect from addiction, from early school leaving and falling prey to "adolescent snares." With reference to Raio et al. (2013), we might further speculate that neural mechanisms not yet identified, that are associated with conscientiousness, provide relative protection of cognitive control of emotions under conditions of sustained or stress. Alternately, Raio et al. (2013) might account for the erosion of this protective function under enduring stress. We are seeking a much more rigorous approach to proceeding forward from findings such as these. This might allow us to specify contextual and individual difference variables that account for aging trajectories characterized by greater or lesser affective and behavioral self-control and link these to aging outcomes.

For example, we must recognize that in the longitudinal data sets in our examples, a causal relationship between behavioral self-control and conscientiousness and both health and economic outcomes is far from proven, although the sibling control method in Moffitt et al. (2011) rules out a least one set of counterfactuals. Further, we are uncertain about the equivalence of the Kern and Moffitt childhood measures. Even when the causal status of the childhood variables is established, we need a rigorous approach to identify both mediators and moderators. What further steps need to be taken to establish more firmly that adolescent snares, addiction, low educational attainment and other acute or chronic stressors might truly lie on the causal path? Many data sets in our aging portfolio pose the problem of very long stretches of time between antecedent and consequence. We seek advice on the approaches to "filling in" these long gaps. Framing all of these questions is a persistent interest in using contemporary approaches to mechanistic analysis from social neuroscience, genomics and econometrics; as well as sub-sampling and more precise deployment of biomarkers in population based surveys; and capitalizing on natural experiments ranging from sharp economic upturns and downturns, to hurricanes, to the those inherent in twinning and adoption.

The expert meeting was centered on five questions that provide a framework for the meeting summary. Exerts explored these questions in presentations and discussions.

- *Question 1: Integrating Existing Data*. What are effective strategies for pooling, integrating or harmonizing existing data sets to form plausible hypotheses about the major pathways that link a significant antecedent to an important consequent variable?
- *Question 2: Causal Analyses of Antecedent and Consequent Variables*. Even before pathways are fully delineated, what research strategies, both analytic techniques and design innovations, are most suited to establish that the antecedent variable is causally related to the consequence variable rather simply an actuarial predictor of the consequence?
- *Question 3: Testing for Mediation and Moderation*. How can we improve and apply criteria we have already developed to securely identify important mediating process on the pathway from the antecedent to the consequent variable? How can interventions or experimental procedures be introduced into large-scale survey research or major longitudinal studies to improve certainty about putative mediating variables and their malleability? Can we develop criteria for identifying moderating variables that are as explicit as those for mediation?
- *Question 4: Temporal Considerations*. Some of our major findings concern relative short temporal distances between antecedent and consequent variables whereas as others involve temporal distance of many decades. Particularly for the latter, what approaches have been successful in other domains of study, and how might they be applied to understand the links between factors apparent in childhood and patterns of successful aging?
- *Question 5: Methods as Tools for Analysis of Pathways*. Are there methods and approaches that are now available for enhancing mechanistic understanding of some of our major findings? BSR has supported a broad range of studies in behavioral genetics and more recently the genotyping of large cohort studies including the HRS and WLS, as well as studies that have include measures of gene expression changes associated with psychosocial factors. Are these approaches useful for integrating into mechanistic analyses of principal findings? The same is true of our increasing support of brain imaging studies of processes involved in social, affective, and economic behavior. Where might work of this kind be most useful in pushing further our understanding? Closely related are design tactics such as systematic subsampling of population-based survey subjects for more fine-grained laboratory study and/or theory-testing interventions.

The meeting was chaired by Dr. John Cacioppo, Chair of the Board on Behavioral, Cognitive, and Sensory Sciences (BBCSS), and began with a keynote presentation by BBCSS member Janice Kiecolt-Glaser and an update from BSR staff members on the NIH Science of Behavior Change (SOBC) Common Fund Initiative. SOBC seeks to leverage advances in basic behavioral and social science to improve the design of behavior al interventions change, with the goal of advancing a more mechanistically informed science of behavior change.

Keynote Presentation: Stress, Immune Function, and Health: Causal Relationships and Underlying Mechanisms
Janice Kiecolt-Glaser, Ph.D. Ohio State University College of Medicine

Dr. Janice Kiecolt-Glaser discussed behavioral pathways to health, reviewing research from her team focused primarily on the impact of stress on immune function, telomeres, and health behaviors, illustrating a range of approaches for elucidating psychological and biological mechanisms accounting for health consequences of psychosocial stress.

Immune Function

Early studies of caregivers showed that caregivers experience high levels of stress and differ from well-matched controls on multiple health measures. Caregivers have poorer functioning across a spectrum of biological responses compared to controls, i.e., poor blastogenic responses to mitogens and HSV-1, lower percentages of IL-2, and lower growth hormone mRNA. Vaccination studies shed some light on these differences. In a study of influenza vaccination, caregivers' antibody responses to the vaccine were substantially poorer than matched non-caregivers (Kiecolt-Glaser et al., 1996). Another study assessing pneumococcal antibodies among caregivers, former caregivers, and controls found that former caregivers respond as effectively to vaccination as the controls, compared with the current caregivers (Glaser et al., 2000). Vaccine responses provide a proxy for responses to infectious disease in order to study the effects of stress. Multiple labs have shown stress-related alterations in antibody and T-cell responses to viral and bacterial vaccines including hepatitis B, influenza virus, pneumococcal pneumonia, rubella, meningitis C conjugate, and tetanus. Unfortunately, in studies of caregivers, it is sometimes hard to show a stress relation to infectious illness since caregivers are usually more socially isolated and less likely to contract infections.

Stress has also been shown to slow wound healing. For example, in a study that measured wound healing through a biopsy punch, caregiver participants took on average 24% longer than matched controls to heal the same standardized wound (Kiecolt-Glaser et al., 1995). Similar outcomes are seen in oral wound healing studies. In a separate study, dental students were recruited and served as their own control by getting a punch biopsy on the hard palate either during exam week or summer vacation. None of the students healed as rapidly during exams, with the average student taking 40% (3 days) longer to heal (Marucha, Kiecolt-Glaser, and Favagehi, 1998).

The suction blister wound protocol has also been used to study local inflammatory processes. It serves as a model for studying immune responses central to the early stages of wound repair in vivo. These studies gather key data on the development of early sequential changes in the local inflammatory response and measure cytokines and leukocytes at wound sites. In a marital study design involving 42 married couples, subjects were admitted twice to a hospital research center. During their first admission, couples went through structured social support interactions and during the second admission, they experienced a structured conflict interaction (e.g., finances, in-laws, etc.). Blister wounds were administered before each interaction and healing was assessed daily after each admission. Results showed lower cytokine production in blister chamber wells following either interaction, showing that even mild stressors can slow the healing process. But,

after a structural conflict interaction, healing took a day longer compared to the social support visit. For couples that were hostile in both conditions, blister wounds healed two days slower (Kiecolt-Glaser et al., 2005).

Infection and trauma can trigger the inflammatory response system. These mechanisms are critical in resolving infections and repairing tissue damage. Pro-inflammatory cytokines attract immune cells to sites of infection or injury and activate the cells to respond to the insult.   In a non-stressed individual, one would encounter a virus, activating the production of pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-alpha), clearing the infection before returning to baseline cytokines level. However, in a chronically stressed individual, stress hormones stimulate white blood cells to continue to produce high levels of pro-inflammatory cytokines resulting in inflammatory reactions.

Pro-inflammatory cytokines are related to age-associated diseases including: arthritis, osteoporosis, Type 2 diabetes, cardiovascular disease, cancer, periodontal disease, Alzheimer's disease, etc. IL-6 rises at an accelerated rate after age 50 and age-related diseases become more prevalent. A chronic infectious process, such as periodontal disease, urinary tract infections, chronic pulmonary disease, etc., may provoke low levels of persistent inflammation.

Stress and depression further exacerbate the pro-inflammatory response. Immune dysregulation due to stress and depression leads to an enhanced risk of infection, prolonged infections, and delayed wound healing; causing further increased pro-inflammatory cytokine production. In a study of 138 healthy adults, stress induced using the Trier Social Stress Test caused individuals with more depressive symptoms to produce a higher amount of IL-6 in response to the stressor (Fagundes et al., 2013).

Chronic stress has shown similar outcomes. A longitudinal study followed 225 subjects, caregivers and non-caregivers, for six years. Caregivers' average rate of increase in IL-6 was found to be about four times as large as non-caregivers (Kiecolt-Glaser et al., 2003). Other studies also supported these findings. Compared to non-caregivers, men and women who provide care to a spouse with a stroke or dementia are at a greater risk of developing diabetes, coronary heart disease (CHD), metabolic syndromes, and becoming hypertensive (Lee et al., 2003; Shaw et al., 1999; Vitaliano et al., 1996, 2002). Another large population-based study of the elderly drawn from a random, stratified sample showed that the relative risk for all-cause mortality among strained caregivers was 63% higher than non-caregiving controls (Schulz and Beach, 1999).

Telomeres

Telomeres are bits of DNA on the ends of chromosomes that promote chromosomal stability and regulate cells' lifespan. Each time a cell divides, it loses some of its DNA at these ends. The more often that cells divide, the more DNA is lost, subsequently resulting in cell senescence. Inflammation triggers T-cell proliferation, enhancing leukocyte turnover rates; hence, this causes telomere shortening. Shortened telomeres are linked to health behaviors such as obesity, as well as aging, age-related diseases, and mortality. But recently, it has been found that caregivers have

shorter telomeres than their non-caregiving counterparts (Epel et al., 2004; Damjanovic et al., 2007).

Critical periods in an individual's lifespan have a maximal health impact from stressors. Those critical periods include infancy and old age where immature immune and endocrine responses or age-related immune senescence increases risk, respectively. Early life stress results in longer-term risks. Adults who have experienced neglect as children, compared to those who did not, show an enhanced emotional sensitivity to stress and neuroendocrine stress response sensitization. When confronting stressors, like depression, these adults are more likely to develop psychiatric disorders. Furthermore, childhood maltreatment and adversities have been tied to elevated C-reactive protein (CRP) in young adults (Danese et al., 2007), increased risk for autoimmune diseases (Dube et al., 2009), and shorter telomeres in young adults (Tyrka et al., 2010).

Most of our evidence on health consequences of childhood maltreatment comes from young or middle-aged adults. Poorer health outcomes are more obvious in older samples. As a result, data from younger cohorts may underestimate effect sizes if consequences persist late in life. Therefore Kiecolt-Glaser's group studied the effects of childhood maltreatment on inflammation and cell aging in a group of older dementia family caregivers and controls (the mean age was approximately 70 years). Findings show that with an increase in numbers of childhood adversities, IL-6 production increased as well. Telomere differences between individuals reporting no adversities and those reporting multiple adversities could thus translate into a 7 to 15 year difference in one's lifespan (Kiecolt-Glaser et al., 2011). Childhood adversities have long-lasting, measurable consequences later in life, namely with older adults.

Health Behaviors

Stress promotes poor health behaviors, such as eating high-saturated fat and calorically dense foods, less exercise, poor sleep, and smoking. These behaviors enhance pro-inflammatory cytokine production. This, in turn, promotes further depressive symptoms, fatigue, pain, and cognitive problems.

Kiecolt-Glaser and colleagues conducted a randomized clinical trial among cancer patients to interrupt this feedback loop associated with experiencing stress and depression. Two hundred breast cancer survivors were enrolled in a twelve-week Hatha Yoga intervention. Yoga reduced inflammation and fatigue in the subjects. At the 3-month follow-up, the geometric means for IL-6, TNF-α, and IL-1β were 15%, 13%, and 20% lower, respectively, for yoga participants compared to controls (Kiecolt-Glaser et al., 2014).

Stress is closely linked to individuals' diet as well. A Western diet has shown to have pro-inflammatory components with high intake in red and processed meats and refined grains. A Mediterranean diet, which is high in cereals, vegetables, fruits and nuts, legumes, fish, a high dietary ratio of monounsaturated to saturated fatty acids (as reflected by high olive oil consumption), and moderate alcohol consumption, is associated with lower inflammation and lower IL-6. Adherence to the Mediterranean diet was found to be inversely associated with circulating Interleukin 6 (IL-6) among middle-aged men in a twin study (Dai et al., 2008).

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In a double blind, randomized study known as the FOOD Study, 58 women (38 breast cancer survivors and 20 controls) were observed after eating a meal high in saturated fat versus high oleic sunflower oil on two separate days. Serial blood draws in the next 7 to 8 hours measuring inflammation, lipids, glucose, and insulin showed no difference between the two high fat diets on these outcomes. However, when taking into account the stress level of subjects (measured using the Daily Inventory of Stressful Events, or DISE) there was a cumulative 6-hour difference in the resting energy expenditure equaling to 104 kcal after high-fat meals in individuals who experienced at least one prior day stressor compared to those with no stressors. Recent stressors lowered fat oxidation after high-fat meals. In addition, women with a history of depression who had more recent stressors had higher peaks of triglyceride responses after high-fat meals, a biological mechanism that is highly correlated with progression of atherosclerosis. Perhaps, individuals may actually have been metabolizing high-fat foods differently (Kiecolt-Glaser, in press). Multiple studies have found similar results: depressed individuals have a 58% increased risk of becoming obese (Luppino et al., 2010), gain visceral fat (Vogelzangs et al., 2008), and accelerate the development of the metabolic syndrome, of which obesity is its cornerstone (Troxel et al., 2005; Chandola, Brunner, and Marmot, 2006). Connecting back to the original discussion of inflammation, Kiecolt-Glaser noted that weight change is important for inflammation is those with higher BMI have higher levels of IL-6.

Discussion

Participants discussed differences in males and females regarding stress processes. Kiecolt-Glaser noted that there are age-related discrepancies between men and women but they are hard to decipher among caregivers since two-thirds of caregivers are females. After bereavement, men are more disadvantaged, as their primary confidant is usually their wife. With regards to marital data women tend to have a larger response to marital stress. Kiecolt-Glaser clarified how single versus multiple stressors were measured using the DISE. This daily diary instrument can identify days that are stress-free versus those that are not, including determining how stress is embedded in daily life structure. Kiecolt-Glaser also looked at the number of stressors but was unable to determine types of stressors due to limited sample size.

Regarding the study on early life circumstances, participants wondered to what extent factors such as employment and education mitigated effects of early childhood issues. There was no definite answer since employment status was not controlled for in the study. Studying individuals with high vulnerabilities, including caretakers, depressed persons, and significantly maltreated persons offer an enormous lever for examining biological mechanisms linking various forms of environmental and social adversity to health. A major source of potential resilience lies in a good marriage and strong social support systems. Dr. David Reiss encouraged the group to consider how researchers can leverage this data when thinking about public health interventions and strategies.

Science of Behavior Change: Increasing Precision in Causal Analyses

Jonathan W. King, Ph.D. and Lisbeth Nielsen, Ph.D., Division of Behavioral and Social Research (BSR), National Institute on Aging (NIA)

The Science of Behavior Change (SOBC) Initiative began in 2008, with funds from the NIH Common Fund (then Roadmap) program. It sought to confront the balkanization in the field of behavior change intervention development and within the basic science domains that support these more translational efforts. The program aims to create a unified science of behavior change by transforming the current approach to intervention development and therefore help reduce the substantial behavioral contributions to morbidity and mortality across a wide range of health and disease targets that are central to the mission of the NIH.

It is now widely acknowledged that poor health behaviors (smoking, drinking, poor diet, lack of exercise, failures of adherence to medical regimens) account for a substantial proportion of disease burden in the U.S. Based on data from 1993, we know that behavioral patterns make a substantial contribution to premature death (McGinnis and Foege, 1993). More recently, BSR commissioned an NAS effort to investigate whether there had been any change in the contribution of behavioral patterns. Although the overall analysis of these effects is not yet complete, the burden attributable to behavioral factors has, if anything, increased over the past 20 years, with approximately fifty percent of the burden of premature death attributable to behavioral risk factors.

Measured in terms of its impact on disease burden, health care costs, and preventable deaths, behavior change represents a public health challenge of tremendous scope. Despite widespread awareness that improvements in health behaviors are essential for health promotion, as well as disease prevention and management, it remains exceptionally difficult for most people to initiate and maintain behavioral change. Dr. King shared a few examples of successes in this domain and addressed what needs to be done in the future.

The SOBC team goal is to develop a more effective and unified science of behavior change which will lay the foundation for effective and scalable interventions. Over time, it has become clear that there are at least three different scientific divides that have thwarted the development of a more unified science of behavior change:

1) Insights from basic science, including newly emerging mechanistic insights from transdisciplinary domains of behavioral science, are often not applied to search for intervention targets for behavior change.
2) Though the NIH supports basic work on behavioral and biobehavioral mechanisms, every problem behavior has its own clinical endpoint, institute, and research community. This leads to researchers who study closely related endpoints or problem behaviors to work independently of each other, limiting the prospects for generalization on the clinical science side.
3) There remains an artificial separation between basic science, where mechanistic intervention targets can be identified, and clinical science, which seeks to modify those targets to affect clinical endpoints. Closer communication between the two approaches will be crucial for the development of more effective behavioral interventions.

SOBC has sought to bridge all three divides. The program aimed to capitalize on emerging basic science in order to accelerate the study of common mechanisms of behavior change. It supported lab and field studies to delineate what the common behavior change mechanisms are and how they are engaged in different contexts. Perhaps most importantly, SOBC annual grantees' meetings have helped to break down disciplinary boundaries, start collaborations, and expand perspectives on the mechanisms of behavior and behavior change in the laboratory and the field.

Intervention Development Pipeline

SOBC has proposed to implement an intervention development pipeline for behavior change interventions similar to the experimental medicine approach for drug/device development. In the drug development world, intervention development ideally follows a series of well-defined procedural steps. These steps include: the identification of appropriate intervention targets and the development of ways to engage those targets, lead (compound) optimization, and pre-clinical studies in animal models as well as obtaining an Investigational New Drug (IND) certification from the Food and Drug Administration (FDA), followed by the sequential of Phase 1, 2, and 3 for clinical trials. Following successful Phase 3 clinical trials and FDA approval, additional trials may be conducted to assess the effectiveness of treatment in the real world.

This pipeline approach contrasts notably with the process of intervention development in the social and behavioral sciences, which does not spend as much effort on the development and testing of mechanistic targets but instead relies on the development of complex (albeit sometimes efficacious) "package" intervention that are not tested with respect to specific mechanisms of action, which makes it difficult to identify and target the "active ingredient" to optimize or personalize the intervention.

Moreover, many behavioral interventions that are found to be highly efficacious are not implemented in the real world. For example, the Diabetes Prevention Program (DPP) Research Group (2002) findings showed that lifestyle changes were more effective in reducing the risk of conversion to Type 2 diabetes in insulin-insensitive individuals than was the drug metformin, especially in older adults. The DPP approach, however, has not been implemented widely in everyday practice.

A preliminary portfolio analysis of the NIH behavioral interventions suggested that tests of mechanism of action are present in only 44% of behavior intervention development projects, compared to 56% of efficacy projects, which is striking in that the former have the explicit goal of developing new ways to change behavior, and really should be assessing whether the they are affecting the intended target. In an effort to incorporate mechanistic approaches into ongoing clinical interventions research, SOBC also sought to implement Pasteur's notion of "use-inspired basic research," providing supplements to incorporate studies of mechanisms of change in ongoing clinical trials, taking advantage of innovative measures and methods from the basic sciences. This approach has the potential to advance understanding of behavioral mechanisms of change and hasten the translation of basic science within clinical settings.

The 2013 SOBC's [Harnessing Neuroplasticity for Behavior Change](#) meeting was motivated by questions regarding the utility of neurological approaches for advancing research on behavior

change. The meeting converged on issues related to the use of neurobiological targets for causal inference and clarified when neurobiological (NB) findings could be "assays" or intermediate biomarkers. Research across diverse behavioral conditions demonstrates that neurological variables and measures hold potential as biomarkers or signatures for successful behavior change. They can also serve as indicators or predictors for *who* will respond to interventions. They can serve as potential targets for behavioral interventions, in cases where known substrates and circuits have been identified.

This meeting was framed in terms of a continuum of research on neurobiological variables in behavior change research, with higher levels of evidence for causality at each successive stage:

1) A NB substrate, activation, or pattern is correlated with a behavior.
2) A change in a NB substrate, activation, or pattern is correlated with a change in behavior.
3) Only those who show behavior change show change in a NB measure, and that change predicts treatment response.
4) Those randomly assigned to the intervention show a NB change that is associated with (later) behavior change
5) Direct manipulation of the putative NB variable induces the (desired) behavior change.

Recent studies on treatment for depression exemplify the value of this model for in intervention studies. It has been known for some time that both behavioral and drug therapies can be effective in the treatment of depression, but only in the last decade has there been a more systematic effort to determine whether the two therapies lead to the same kinds of changes in the structure or function of the central nervous system. Beginning with work by Helen Mayberg and her colleagues (e.g., Goldapple et al., 2004) we now have evidence that these treatment modalities may have very different effects on (e.g.) resting glucose metabolism, suggesting different mechanisms of action and potentially differential efficacy of these treatments in different groups of patients.

Building on its initial accomplishments, SOBC 2 seeks to transform behavior change interventions through implementation of an experimental medicine approach to behavior changes. The approach would include:

1) Identifying the most promising targets whose engagement drives behavior change, such as "self-control" or "self-regulation;"
2) Developing the appropriate assays for measurement with better-defined targets that will be sensitive enough to induce change leading to reliable indicators of target engagement;
3) Validating assumed targets, given the complexity of behavior, in both lab and clinical settings; and
4) Systematically improving behavioral trial designs to include measures of target engagement throughout the "intervention-target-clinical" pathway.

The point concerning the intervention-target-behavior pathway is important in that interventions almost never directly cause a change in behavior but rather change the activity of a putative target that is being manipulated, with the hypothesis that the target is connected causally to the behavior to be changed. In order to determine causality, it is necessary to have assays that validly measure changes in target *activity* (i.e., a change in the target will cause a change in the

assay). These assays could take the form of behavioral tests, neuroimaging data, an endocrine assay such as cortisol or alpha amylase, or gene expression. Once assays are in place, researchers can verify whether or not the manipulation engages the target. If the manipulation does engage the target, researchers will be able to determine whether the target was valid for the desired behavior change.

The key targets for behavior change as identified by SOBC grantees include:

1) **Self-regulation (within-person)**: Any failure here can lead to decisions that essentially ignore longer-term consequences.
2) **Stress resilience and stress reactivity**: Something more external impinging on a person can enhance impulsivity.
3) **Interpersonal and social processes**: Social partners and networks are very powerful as they influence and continually reinforce behavioral patterns.
4) **Environmental factors**: Included moderators (i.e., variables that affect strength of any relation between "X" and "Y") where effects of interventions differ across individuals that can induce/suppress behavior; the target is the environment.

King provided examples of SOBC projects that illustrate the utility of studying targets and mechanisms of behavior change in the future. Dr. Kevin Ochsner, a recipient of a SOBC grant, demonstrated differential blood flow to a specific region of prefrontal cortex in an fMRI experiment when studying attention and self-regulation. The study provided evidence that adolescents found it more difficult to regulate negative emotions compared to young adults. Young adults were far more successful at the task of emotional self-regulation, which appeared to require the engagement of a particular region of prefrontal cortex to aid in deflecting attention away from the negative stimuli (McRae et al., 2012). Dr. Ian Gotlib, in work supported by an administrative supplement awarded by SOBC, demonstrated that the manipulation of attentional processes could provide a way to intervene where emotional regulation itself might be ineffective in his study of daughters of women with recurrent major depression (who are therefore at unusually high risk of depression). Gotlib used an attentional training task to help shift attention away from negative stimuli, which was the default mode of attention in these participants. Attentional Bias Training (ABT) was successful in shifting attention away from negative and toward positive emotional stimuli in this group of individuals. This change in attention had an effect on the processing of negative emotional stimuli in relevant brain structures as well.

Discussion

Concerning the key targets proposed by SOBC, it was noted that many behavioral interventions are effective due to group characteristics and the influences of social relationships and networks, and that these influences may vary as a function of age. It is therefore important that researchers have proper measurement strategies that inform whether the effects were due to the social aspect or other variables of the intervention. Some of the social processes that may influence interventions include norms, being part of a group, loneliness, feelings of rejections, etc. It can be challenging to convince our biomedical colleagues of the importance of social and interpersonal processes as targets for behavior change.

Dr. David Almeida asked to what extent the SOBC initiative would focus on the fidelity of behavior change and study the conditions under which people will enact change. Individuals have more time during certain ages and might not adopt behavior changes during demanding life periods. King agreed that behavior change would not necessarily be consistently obtainable at every stages in the lifecourse, and, moreover, it was not clear from current data how long individual are able to maintain the changes they do make. This is another reason why it is important to determine whether it is the extra time or opportunity for change that individuals have in certain ages, age-related aspects of conscientiousness, or the effects of other factors that brings about behavior change. Almeida also noted that with new data collection technology, researchers have an increased ability to collect information on environmental effects, which may shed some light on individuals' decision to maintain certain health behaviors.

Cacioppo inquired about the importance of lesion and animal models and how they can contribute to mechanistic studies. Experts confirmed that animal models including lesion studies have been effective in studying the reward system and its role in appetitive behavior generally and mapping out the brain circuitry responsible for behavior and change at lower levels, but that in many cases appropriate animal models had not yet been developed for other important areas of human behavior.

Framing and Discussion of the Five Readings and Questions
Lis Nielsen, Ph.D. and David Reiss, M.D. & Consultant BSR, NIA

Within BSR, psychological, biobehavioral, and biosocial science focuses on function, health, and well-being of midlife and older adults, and is not exclusively focused on disease. We are focused on the process of aging over the full life course, not solely on the unique problems of the aged. This includes research on midlife transitions and life-span psychological development. Understanding these processes is facilitated by a substantial focus on biobehavioral and biosocial sciences and on links between psychology and economics.

In 2013, the National Advisory Council on Aging conducted an extensive review of the BSR portfolio and made recommendations for future research investments. Key research questions recommended for current and future study include:

1) How can we identify the pathways by which social, psychological, economic, and behavioral factors affect health in middle aged and older adults?
2) How do we identify the mechanisms that can ameliorate the effects of disadvantage?
3) How do we modify organizational/individual behaviors associated with health-related aging outcomes?
4) How does population aging impact well-being of individuals as well as societies?

Answering these questions requires identifying key psychological, behavioral, and social factors on the causal pathways to adverse or good health. It also requires the identification of critical periods for reversing the effects of adversity (timing of interventions) and an understanding of social environments and how they promote or inhibit adaptive aging. This requires science that examines how behavior and biology mediate the links between stress and disease.

One important tool for advancing this effort is a set of harmonized national and international studies containing measures of behavioral, psychological, social, environmental predictors and outcomes. The Health and Retirement Study (HRS) family of studies, including the English Longitudinal Study of Ageing (ELSA) and the Survey of Health, Ageing, and Retirement in Europe (SHARE) and a growing number of sister studies around the world, is the cornerstone of BSR's investments in this area. The Midlife in the United States (MIDUS) Survey is BSR's second largest project; it takes a more psychologically-oriented approach to examining life course influences on aging. MIDUS includes detailed information on sociodemographic and genetic factors, life challenges, health behaviors, and neurobiological mechanisms in order to obtain a better understanding of trajectories of health and well-being from midlife into aging. BSR also supports harmonization activities including development of meta-data for the HRS and its sister studies. Harmonization of data on subjective well-being, psychological constructs such as cognition and dementia assessment, life histories, and physical activity are areas of high interest for BSR.

Harmonized biosocial surveys with links to lab science allow investigators to answer mechanistic questions such as: How does work impact cognitive aging? What are the pathways through which psychosocial stress and adversity get under the skin? What are the links between conscientiousness or self-control and healthy aging?

For this meeting, BSR is seeking discussion by experts on approaches we should take in the coming years to address the following issues:

1) How can we identify the pathways by which social, psychological, economic, and behavioral factors affect health in middle and older adults?
2) How can we identify the mechanisms that can ameliorate the effects of disadvantage?

Currently, BSR is endeavoring to develop more systematic approaches to examining pathways and mechanisms, and would like feedback on both the best approaches and strategies for pursuing this agenda. BSR has invested in large-scale longitudinal studies that include population-based longitudinal surveys to assure generalizability (e.g., HRS, MIDUS). The Division has also funded longitudinal studies extending from childhood to old age (e.g., Terman and Hawaii Studies) to explore the childhood "origins" of patterns of aging. Current work in this area includes studies of the impact of early personality and severe childhood adversity on aging, and studies that combine population sampling and assessments in childhood (e.g., Dunedin, Add Health, British cohort studies). It is possible that BSR has underutilized certain methods, approaches, techniques, or recent data that would be very valuable. Experts were encouraged to provide feedback on these areas.

Question 1: *Integrating Existing Data. What are effective strategies for pooling, integrating or harmonizing existing data sets to form plausible hypotheses about the major pathways that link a significant antecedent to an important consequent variable?*

Integrating Existing Data
Teresa Seeman, Ph.D., Schools of Medicine and Public Health, University of California, Los Angeles

Dr. Teresa Seeman gave a brief overview regarding the richness of available data, specifically in areas where harmonization and replication work can be achieved as it relates to pathways and shared findings that highlighted the potential uses of these datasets.

Using data from the MIDUS and the 1958 U.K. Birth Cohort, Seeman and Dr. Chris Powers illustrated areas of harmonized data relating to early life influences in childhood and later life outcomes in adulthood. The U.K. Birth Cohort and MIDUS have a number of similar or identical measures allowing comparison between the groups. Although the two surveys' data collection methodology varies, the U.K. study being prospective and MIDUS being retrospective, their outcome measures are reported in a similar fashion. Both surveys collect biological data, though it is limited in the 1958 U.K. Birth Cohort. MIDUS includes sociodemographic factors, genetic factors, and rich cognitive assessments and in-depth measures within a subset of the sample.

Seeman discussed the possibility of building on findings from Moffitt (2011) and Raio's (2013) publications on self-control and conscientiousness. The variables in that study, i.e., stress, health, and economic well-being, parallel the measures collected in MIDUS, including: adult personality measures, inclusion of twins and siblings, a variety of adult health measures, daily stress processes, etc. Seeman also discussed opportunities to link these existing datasets to CMS data, especially for individuals over the age of 65.

MIDUS DNA samples will allow for future genome-wide association studies (GWAS) as well as gene-expression analyses for the MIDUS Refresher Cohort. The team is currently collecting venous blood and freezing it for future genetic studies (pending funds), though there are IRB limitations on the amount of blood that can be stored. The HRS and the Wisconsin Longitudinal Study (WLS) have full GWAS and would be valuable to harmonize.

Seeman described the constant struggle that arises in determining which items to keep and which ones to remove from large longitudinal-national surveys. On the one hand it is beneficial to keep items on a survey long enough to see changes in key outcomes. On the other hand, it is crucial to incorporate new items associated with new outcomes or predictor of interest. This is complicated further by funding constraints. MIDUS investigators have conducted crosswalks between old and new information in order to preserve data that was collected previously. Moving to a new measurement should not be considered "uninformative." Reiss added that investigators could utilize third samples to harmonize across studies and use samples within studies to test for equivalence.

An increasing number of population-based studies have biological protocols, collecting information on cortisol, norepinephrine, epinephrine, blood pressure, pulse, heart rate variability, cholesterol, etc. This growing number of biomarker collection makes it even more imperative to harmonize data. Aside from biomarkers, a range of population-based studies have other constructs that could be harmonized or used in comparative analyses. For example, MIDUS, HRS, National Social Life, Health and Aging (NSHAP), and several NHLBI-funded projects, including the Multi-Ethnic Study of Atherosclerosis (MESA), Coronary Artery Risk Development in Young Adults (CARDIA), and Cardiovascular Health Study (CHS), all overlap in pertinent constructs such as financial strain, work-family stress, loneliness, chronic burden, perceived stress scale, etc.

Using the studies and surveys mentioned above, Seeman's participated in a "stress measurement" initiative supported by NIA, for which they identified studies that measure stress and determined which ones used identical measures. For instance, the perceived stress scale was used in MIDUS, HRS, and NSHAP for 10, 4, and 4 measurements, respectively. Chronic burden was used in the same way within HRS, CARDIA, and MESA. Discrimination was measured similarly in MIDUS, HRS, CARDIA, and MESA. These are areas where one can harmonize the analyses across studies measuring the same constructs. This provides a better measurement of the outcome and offers opportunities for replication. Harmonization among these studies would be beneficial since these datasets offer different kinds of information. This includes varying birth cohorts and differing age ranges, representations of multiple ethnic groups, and variety in strength of measurements such as psychosocial factors, biological pathways, or health outcomes.

Strategically, adding new items to studies would augment harmonization. This includes adding in-depth protocols and assessments, as in the MIDUS study, on a subset of the sample. Finally, researchers need to ensure the documentation and archiving of relevant and high-quality data in order to move the field forward.

Discussion

Participants discussed a range of issues related to reproducibility, replication, and generalizability. Cacioppo cautioned against deducing "failure to replicate" with differing effect sizes across studies.   Participants suggested various reasons for the lack of replicability in studies. This included demographic differences in the sample (i.e., socioeconomic status, or SES), making it imperative that investigators assess the study approach before analyzing the data. One must first look at the quality of measures when a study fails to replicate. Participants agreed that investigators should determine whether an alternative theoretical explanation would apply, and if the theory can be replicated. Framing the question(s) is an important aspect when comparing across studies.

Reiss concurred with the need to replicate and provide comparisons across studies, but posed a series of questions regarding harmonization to the group: When do we actually combine data from several studies using harmonization? To what extent does this produce a better-delineated theory? To what extent should we pool data? It is important to pay attention to the notion of the "subsample," but at what point is a population-based subsample crucial? When could we combine samples into a mega-sample?

Dr. Jennifer Harris advised that there is no universal approach to harmonization; the approach needs to match the question being addressed. If harmonized data exists that allows you to pull out subsamples (e.g., biological profile stratifying), then one would need smaller samples to test research questions. The Behavioral and Social Sciences should think of harmonization within a larger framework, rather than just looking to measure the same content in all studies. One needs to keep in mind how the data be "mined," particularly as genomic data gets involved. How can one use the appropriate tools? How can we build data so that there is enough interoperability to find the pathways via measures that are reliable? These questions will be answered based on how the data are organized.

Additional questions arose as part of the harmonization discussion: What is the best method to harmonize across studies? Who gets ownership of the data? Who will be responsible for keeping track of this data? Furthermore, if the system of journal articles were well established, as investigators increasingly work together on the data, how would that be tracked? When should two studies be kept separate?

The group was in agreement that the theoretical basis and contextual background is imperative and investigators must ensure that context is not lost when harmonizing data. It is important to not lump datasets from different cultures together. For example, with the comparison of telomere lengths within the HRS and the Netherlands Study, early adversity in childhood is associated with shorter telomere length in adulthood. But, this correlation is seen only amongst HRS subjects, not in the Netherlands, possibly due to a better "social fabric" (i.e., social collaboration

and social buffer). Testing for social buffers would be worthwhile in the HRS. While we can measure toxic exposures, this is more of an opportunity to learn about social buffers. When testing main effects, one should never assume an answer is the final answer.

Question 2: *Causal Analyses of Antecedent and Consequent Variables. Even before pathways are fully delineated, what research strategies, both analytic techniques and design innovations, are most suited to establish that the antecedent variable is causally related to the consequence variable rather simply an actuarial predictor of the consequence?*

Causal Analyses of Antecedent and Consequent Variables
Gregory A. Miller, Ph.D., Department of Psychology and Psychiatry and Biobehavioral Sciences, University of California, Los Angeles

Establishing causality includes covariance, temporal precedence, and the presence of internal validity, where there is not a third variable driving both X and Y. Generally, researchers prefer clear distinctions between independent variables (IVs), dependent variables (DVs), and manipulation check variables. However, numbers are not inherently IV or DV, especially when one factors time into the equation. Choices about the role each variable plays in the analysis will affect the evidence in favor of particular causal relationships.

It is common that predictors are correlated. When establishing variables of interest, challenges to causal interpretation may arise from several sources:

1) It is useful to determine in advance how much the stipulated predictors correlate. When predictors correlate, it is tempting to use statistical means of attempting to "control for" such correlations. There is no single, broadly satisfactory way to achieve such statistical control, such as analysis of covariance or hierarchical multiple regression. When examining correlated predicts within a single group, it may be straightforward to decide to which predictor to assign any shared variance. The problem is more difficult when one or more predictors correlate with a grouping variable. This is often described as the groups differing on a (potential) covariate. Especially, group assignment has not been done randomly, and the groups turn out to differ on the covariate; merely removing from the grouping variable the variance shared with the covariate does not yield a satisfactory solution. Such an analysis alters the grouping variable itself, often in non-obvious ways. It may nevertheless be fruitful to examine the dataset, both with and without removing the covariate, to see what difference it makes. If it makes a difference, it may be worth treating the covariate not as a nuisance or confound to be removed, but a substantive variable to be understood. Thus, rather than "controlling for" shared variance, we can try to understand it. A particularly important and complex example would be groups with cultural differences. One is probably not going to get rid of those with a statistical maneuver. One can still study the role of such factors, acknowledging that they may be substantially and importantly intertwined with other factors that we conceive of and attempt to measure separately.

2) If researchers employ factorial designs as part of their analyses, with equal or proportional Ns (i.e., number of subjects), IVs do not correlate simply as a function of the experimental design. When designing a study, one may want to sample groups in such a way that the Ns are comparable, to avoid confounded IVs. This can be done even if the IVs correlate in the population. An alternative option is to sample randomly from the population, accepting the interpretive problem of correlated IVs in exchange for the sample better representing what is truly present in the population. Miller's take-home message was that there is no single "right thing" to do. For example, in looking gender and income (i.e., low vs. high income) as predictors of health status in a population in which one gender has higher income, choosing equal numbers of men and women in each group would avoid a confound of gender and income internal to the study but would reduce its external validity – its generalizability to the population under study. More information may be obtained by recruiting unequal numbers by gender and income, reflecting the population, and then exploring the correlations.

3) In circumstances where one is observing rare events, Miller maintained that it is worthwhile to understand the effect of extreme base rates on one's ability to find true causal effects. For instance, with dementia, studying the one individual truly *without* dementia in a unit of 100 persons all of whom are diagnosed with the disease may require different measures and inference methods than studying the one person *with* dementia in a sample of non-patients/persons all diagnosed as not having dementia. One has to mindful of the distinct sensitivity and specificity of available measures. When the primary goal is to validly detect a condition that is rare, it may be best to sacrifice some specificity in order to improve sensitivity. The point is that base rates of phenomena should be considered when selecting diagnostic methods and decision rules.

4) Beyond the challenge of measuring individually rare phenomena, rare patterns can be particularly difficult to detect. Often we take for granted that measures with high internal validity are desirable. In circumstances where researchers are observing rare configurations, that may be a mistake. We may need a scale that does not cohere – has low internal consistency – in the population, because we want to find the rare cases when the separate indicators all "hit." In this case, a set of individually rare events should have low reliability when assessed collectively. Rare configurations can consist of a very diverse set of indicators that one may want to take into account, including demographic, economic, psychological, and biological indicators.

After discussing these challenges to causal interpretations, Miller also addressed two recommendations to help fix these problems to identify causal relationships: (1) Multiple-IV Time-Series Analysis, and (2) Granger Causality.

Multiple-IV Time-Series Analysis

While acknowledging the interpretive challenge of using correlated IVs, there may be considerable added value in collecting data suitable for multiple-IV time-series analyses. The IVs may differ in temporal sampling density, time span, and causal relations. An example involved examining early childhood stress and its effects in early and later adulthood. Measures

may differ on numerous temporal and other dimensions. One need not, for example, use the sample temporal sampling density at different ages. Available data may differ, and in any case, the time course of contributing inputs may differ at different ages or in different environments.

Furthermore, a given subset of the data may be treated as "outcomes" at one stage, and the same data may serve as predictors of subsequent "outcomes." For example, data collected at T0 (say, age 3 to 5 years) may predict data collected at T1 (perhaps adolescent "mistakes" or "snares" that occur during that phase of life). In turn, T0 and T1 data may be examined in combination to predict "outcomes" at T2 (say, adults aged 30 or 60). Miller noted that this again raises the question of whether a given variable is an IV or DV. Depending on the conceptual and analytic approaches taken, there can be multiple roles for a given variable, without distinctions between IVs or DVs being inherent in the data.

Granger Causality (GC)

Granger causality is a statistical association model that is based on prediction; it is not really a "causal model" in a conventional sense. In other words, a GC analysis does not generally establish causality as traditionally conceived. It is a type of analysis predicting one time series from another, potentially offering an account of the relationships that is consistent with a specific causal relationship without establishing definitively that one variable controls another. Specifically, it uses a sequence of X values to predict Y in order to examine how much variance in Y is predictable using prior values of X. This concept is generalizable to large time lags, for example, with lifespan studies where early-life X events may influence late-life Y events. Additionally, GC is readily usable even with different sampling densities for X and Y. For example, dense experience sampling (X) can predict recovery from stroke that unfolds over a much longer time period and is adequately measured much less densely (Y).

Miller also noted that GC is not confined to temporal relationships. It is possible to generalize to any two series of ordered observations. These features are evident in measures of variables such as friendship networks and travel distance to jobs. Despite typically being temporally directional, it need not involve (measured) time. GC is not mechanistic, in that, although it can establish correlative relationships over time, it does not identify the substance of the causal arrows relating the variables, which is necessary to understand causal mechanisms. Even when it

Finally, Miller noted how the third-variable problem can affect GC analysis. GC results may or may not be insensitive to third variables. One may observe X and Y as they naturally vary and assess the correlation between them and how that varies at different temporal lags, modeling such relationships with GC methods. If one can then systematically manipulate X without affecting Y, then there is strong evidence that the originally observed XY correlation is due to a third variable. If manipulating X does affect Y, this is evidence against a third-variable confound. The bottom line is that GC can contribute to causal analyses even though, in general, when used in isolation, it cannot establish causality.

Causality in Brain-Behavior Relationships

Researchers want to establish causality and identify its mechanisms. Miller concretized some challenges in determining causal relationships by introducing the question of causal relationships between psychosocial and biological phenomena. In particular, he emphasized the question of how we determine (and what we assume about) the directions of such causal relationships. Typically, we assume that the causal arrows are such that biology drives psychology and not the other way around. However, at least in the present state of the field, as the sole premise, this is untenable.

Psychological terms cannot be reduced trivially to biological phenomena. A psychological construct has meaning independent of any biological implementation, known or hypothetical. For instance, concepts of memory, depression, and attention are fundamentally psychological phenomena, not biological. Certainly, biological features go awry in dementia or depression. But it does not follow from that the biological aberrations cause the psychological aberrations, or vice versa. Miller noted that psychological and biological phenomena can each be changed via either psychological or biological interventions.

In this area of work, Miller maintains that there is no evidence of a single case where all the causal mechanisms have been identified from biology to psychology. There are biological or psychological changes for which we are inclined to infer causation, but not a single "causal chain" between biology and psychology has not been worked out fully. This is not just a matter of us not yet knowing enough to flesh out the story. Arguments in the literature about whether causation between biology and psychology is even possible, on logical grounds, are unresolved.

Miller commented on how the NIH has evolved over the years in how they address the relationship of biological and psychological phenomena. In the 1990s, NIH leadership claimed that mental illnesses such as depression and schizophrenia are real, treatable "brain disorders" – wholly biological entities. These statements marginalized psychological phenomena and the relevance of psychology, which has major implications for grant-funding priorities. In what he called the second Decade of the Brain (e.g., 2003), mental disorders were referred to as "brain disorders" again. In what he called the third Decade of the Brain, the NIH is beginning to emerge from this native biological reductionism. For example, the RDoC initiative at the NIMH casts biological and psychological phenomena and mechanisms as peers. This is a most welcome development.

Miller criticized the now-common goal of localization of psychological events in the brain. As an example, memory is a psychological construct that does not have a location – it is not located anywhere. Important neurochemistry occurs in specific brain areas, but the neurochemistry is not the memory. Again, a psychological construct has meaning independent of any biological implementation. Nevertheless, although we do not know whether biology "underlies" psychology or vice-versa, researchers can employ biological measures to study psychological phenomena, and psychological measures to study biological phenomena. Reductionism, such as

pursuit of the biological "basis" of psychological phenomena or mental disorder is not a feasible goal.

Discussion

With Miller's presentation of GC, discussion ensued about its validity and whether it was a true "causality" measure. Cacioppo provided an example where in one condition where there are distant measures of outcome(s) of interest, and others that are proximal measures. One may find that a condition associated with more proximal measures is a better predictor. This would have nothing to do with differences in conditions, but instead with the proximity to the outcome in predictions. There was also discussion of Miller's contention that we are not now and may never be able to fully reduce psychological phenomena to biological phenomena.

Question 3: *Testing for Mediation and Moderation. How can we improve and apply criteria we have already developed to securely identify important mediating process on the pathway from the antecedent to the consequent variable? How can interventions or experimental procedures be introduced into large-scale survey research or major longitudinal studies to improve certainty about putative mediating variables and their malleability? Can we develop criteria for identifying moderating variables that are as explicit as those for mediation?*

Testing for Mediation and Moderation
Angela Duckworth, Ph.D., Department of Psychology, University of Pennsylvania

Duckworth began with the question, "What part of the lifespan puzzle does one take on with this subject?" She started answering this question by addressing the personality trait "conscientiousness." Literature elucidates that conscientiousness is an established personality trait that "predicts healthy behaviors, healthy social relationships, and physical health and longevity" (Friedman et al., 2014). However, the causal links among these behaviors are complex. The Friedman et al. paper (2014) for the Special Section of *Developmental Psychology* on Conscientiousness and Healthy Aging pooled data to clarify temporal relationships among conscientiousness, hypothesized mediators and outcomes.

However, pooling data across these studies and across broad spans of time presented methodological threats to the validity of results obtained. Duckworth and colleagues recognized this as a potential first step in identifying early conscientiousness in life mechanisms given they can result to important outcomes later in life. In that same journal issue, Eisenberg et al. (2014) sought to identify mediators linking early childhood behavior to adult conscientiousness. They asked whether analogues of assessed conscientiousness could be identified in childhood and adolescence. While there was no direct "causal arrow" going from early self-regulatory behaviors to another set of life outcomes, Duckworth and her collaborators concluded that conscientiousness did in fact appear and develop in childhood, with a distinctive focus on links between self-regulation and academic motivation as well as "internalized compliance" with standards and norms. Essentially, self-regulation cultivated conscientiousness in later in life.

The map provided by Eisenberg et al. lent importance to the study of self-control and impulsivity in childhood; for example consider the study of impulsivity and neighborhood context on offending by Lynam et al. (2000). Here, they examined the relations between impulsivity, neighborhood context, and antisocial behavior in young males in Pittsburgh. In this study, self-control, or lack of self-control, moderated the effects of neighborhood SES, particularly whether or not violent crimes would be committed later in life. For instance, if a child was impulsive, the neighborhood SES or context predicted that he or she would act on negative impulsivity. On the other hand, if a child was in a self-controlled environment with favorable SES, then effects of negative impulsivity was lower and more controlled. Conclusively, the cost and benefits of performing a violent crime was neighborhood-dependent where effects were stronger in poorer neighborhoods.

To a certain degree, self-control is a popular topic within Psychology. There has been promising work explaining how conscientiousness is fostered via academic motivation. In their study entitled, *Establishing Causality Using Longitudinal Hierarchical Linear Modeling (HLM): An Illustration Predicting Achievement from Self-Control (SC)*, Duckworth, Tsukayama, and May (2010) asserted that the predictive validity of personality for important life outcomes was well-established. But, the conventional longitudinal analyses could not rule out the possibility that unmeasured third-variable(s) confounds fully accounted for the observed relationships. Longitudinal HLM with time-varying covariates allowed each subject to serve as his or her own control, and this eliminated any between individual confounds. Furthermore, HLM tested the directionality of a causal relationship by reversing time-lagged predictor and outcome variables. This was exemplified by looking at how within-individual changes in self-control over time predicted educational attainment (GPA), but not the other way around. The team measured SC in 5th, 6th, 7th, and 8th grades to observe changes, specifically subsequent changes in GPA. Results showed that a change in GPA did not predict change in self-control. One could start to eliminate plausible confounds using this approach. Further, with self-esteem (a covariate), this did not happen.

All of this was informative of the bigger picture involving self-control and regulation and its strong relationship with the personality trait, conscientiousness. The methods used to pool data vary across longitudinal studies. However, data pooling offers a promising direction to understanding pathways vis-à-vis mediation and moderation. In the Sloan Study of Youth and Social Development in the U.S. (1992-1997), Schneider and colleagues (1997) aimed to gather an all-inclusive picture of adolescence to understand how young persons form ideas about their personal futures and how they may be influenced by their family, peers, schools, and communities. Results suggested that although youth regarded academic work as most relevant to their futures they were least happy doing it.

Discussion

In understanding conscientiousness, Dr. Richard Suzman pointed out that there is an extension of SC one has to consider called compliance. Compliance is important because it further elucidates how social influences play a role with a person fulfilling a request for someone else, simply because they were asked. This is important in relation to the military training context (where, here, the measures themselves matter).

Reiss commented that model testing benefitted from having both a) meditational pathways that theory under test predicts will link antecedent and consequence but also b) the model tested might contain opportunities to test pathways the theory predicts will _ link antecedent and consequence. This allows testing for the specificity of mediation. Further, a theoretical model may contain a complex set of mediators and moderators; even if the testing this model (in large samples) is statistically tractable; it may not be a candidate for investigation in a single design. What strategies allow for more piecemeal testing of these complex models and for the re-assembly of these specific tests?

Dr. Robert Hauser suggested that one could synthesize large numbers of data observations in forms of correlations from large datasets. This could be done using maximum likelihood strategies to account for missing data where things like GPA and longevity were examined and synthesized (via model work).

Nielsen noted that these large long-term, multi-panel samples begun in childhood and rich in psychological content may be a valuable resource for pathway studies. Of particular interest are studies that include measures of factors later in life that might serve as mediators of longer term outcomes. Some prospective studies with measures of early life personality or self-regulation may present important opportunities to reassess these variables retrospectively, to determine concordance between prospective and retrospective measures, given that most aging studies don't have the benefit of beginning in early childhood. It is not evident how one should perform this task exactly, particularly regarding measures of early self-control.

Question 4: *Temporal Considerations. Some of our major findings concern relative short temporal distances between antecedent and consequent variables whereas as others involve temporal distance of many decades. Particularly for the latter what approaches have been successful in other domains of study and how might they be applied to understand the links between factors apparent in childhood and patterns of successful aging?*

Temporal Considerations: Part 1
David M. Almeida, Ph.D., College of Health and Human Development, The Pennsylvania State University

In his presentation, Almeida discussed macro versus micro time-scales, considered long-term and short-term pathways, presented ways to combine these pathways by using relevant examples (e.g., MIDUS and Daily Stress Processes), and looked at limitations and future directions.

When we examine processes in macro-time, i.e., long-term pathways, the links from predictor to outcome (or predictor to mediator to outcome) are very distant. These pathways are distant because they include observing changes over years or decades. In comparison, micro pathways are snapshots of what is going on during a short interval in the macro timescale. These short-

term pathways involve observing events over weeks, days, hours, and even minutes and seconds. An advantage in considering short-term pathways is that allows us to examine the temporal dynamics of relationships among variables.

An example of a long-term pathway was examined with the Dunedin Multidisciplinary Health and Development Study by Moffitt et al. (2011). In this study, there was consistent evidence for how childhood self-control predicted physical, social, and financial health, controlling for IQ and effects shared by siblings in the same family such as SES. A mediating pathway was investigated: adolescent "snares", including early smoking, dropping out of school, and teen parenthood. Each of these behaviors had effects on adult health (e.g., respiratory disease, substance dependence, sexually transmitted illnesses) as well as with adult wealth (e.g., SES, single-parenting). These early measures of childhood self-control anticipated adult crime in the future.

In the study by Kern et al. (2012), childhood conscientiousness was assessed and predicted health at age 50. For some children who became adolescents, attaining an education was a mediator of this long-term link, while for others, alcohol abuse was a mediator.

These studies provided some valuable suggestions for social and behavioral pathways. Long-term pathways allow researchers to understand the importance of early environments; it essentially shows the lasting effects of childhood experiences. Assessments of childhood predictor variables are so distal that when outcomes are realized in adulthood, they are impressive. However, there are some challenges that come with considering long-term pathways. For example, one is subject attrition. In these long-term analyses, it is impossible to control for all associations, hence, the third variable challenge. Assessing long-term pathways leaves huge gaps between childhood and adult measures. There is a lot that can happen in these gaps but they remain unknown without detailed attention to mediating processes. Almeida suggested that the NIA should think of mechanisms that happen during an individual's midlife as they are amenable to change.

Tracking associations across a short time interval permits a more precise analysis of exactly when in a sequence each observable event occurs. For example the t MIDUS study permits observing predictors and outcomes for individuals over a 10 to 20 year period. This study also permits researchers to observe outcomes of interest on a shorter time-scale, even at the level of second-to-second or day to day. With this approach, one can use personality variables like conscientiousness to show how it is not just a predictor of a consequent variable but a predictor of precisely-timed sequential processes. For example, this method looks at immediate reactivity to a stimulus as well as recovery from a stimulus. Consider again the work by Javaras et al. (2012); they observed a relationship between conscientiousness and a precisely-timed recovery in response to an emotional stimulus. This study capitalized on some of the strengths of studying short-term pathways, including greater specificity; temporal dynamics, or reactivity versus recovery as it applied to chronometry of experiences, and; within-person processes. Another important challenge includes explaining how early experiences predict within-person dynamics and processes. Lastly, studying short-term processes in laboratory poses problems of ecological validity. For example, the laboratory investigator can manipulate variables in ways that may not represent real-life circumstances.

In an attempt to connect long- and short-term pathways in MIDUS, Almeida analyzed retrospective accounts by adults of their childhood disadvantages, including socio-economic status. He hypothesized that childhood disadvantages *may* have a direct (causal) link with daily stressor reactivity as well as with adult chronic health conditions evident later in one's life. This leads to an important question: Are long-term pathways mediated by short-term processes?

Almeida conducted the National Study of Daily Experiences (NSDE) that involved a telephone diary study for eight consecutive evenings. That national sample of participants came from the daily diary project from MIDUS where over 2,000 people participated and there were over 15,000 days of information. The measurement "day" was used as the unit of analysis, and involved several domains of daily experiences including: time use (sleep, work, and social support); physical symptoms (duration and intensity); mood (positive and negative); substance abuse (caffeine, alcohol, and tobacco), as well as productivity (both quantity and quality). Two longitudinal assessments were done approximately ten years apart. Some characteristics of those who participated in the study were: Mean age = 57; 58% female, 42% male; most had some 4-year college education (52%), 20% had more than a 4-year degree, and just over a quarter (28%) had a high school diploma (or less).

Parallel collection of saliva samples offered a way to investigate several biomarkers related to stress. In NSDE, investigators obtained a daily saliva collection on each of four days: collection was four times per day (when one wakes up, 30 minutes after waking up, before lunch, and before bed) for four consecutive days. Of the over 2,000 participants, investigators collected saliva from 1,740 respondents, or 86% of the participants. Further, there were almost 27,000 saliva samples. This intensive repeated assessment aimed to study the daily stress process, particularly the challenges and frustrations of daily life. These short-term processes are used to elucidate long-term pathways; the short-term processes are naturally occurring and tangible events, where one can assess "life as it is lived"; it involves frequent exposure; it minimizes memory bias; and within-person associations of stressors and daily well-being is a dynamic (reactive) process. The latter was the main unit of analysis associated with the salivary measures.

Individuals with higher, momentary stress reactivity had an increased risk for later depression, chronic health conditions, mortality risk and decreases in financial net worth. This was all independent of the magnitude of stressor exposure. Almeida extended his analyses to show that childhood adversity predicted high stress reactivity and that, statistically speaking, daily stress reactivity mediated part of the relationship between childhood adversity and adult health outcomes.

There are, however, limits to this work so far. First, the data provided on childhood adversity is retrospective. Another limitation is that MIDUS pathways look at biological outcomes and mediators exclusively. Lastly, there is a need for a deeper consideration of temporal dimensions.

Thinking of temporal processes can inform us about the phenomena of interest itself. Researchers can utilize multiple time scales to study associations. Some examples include: hours (family processes), days (social calendar processes), months (mental health processes), and

decades (aging processes). Perhaps understanding the causal processes that shape long-term global trends would benefit from studying those processes that occur over shorter periods; more sampling over time would be needed, but measuring behavior continuously is not practical. Future directions include adding short-term measurement bursts to assess long-term effects.

Temporal Considerations: Part 2
Elissa S. Epel, Ph.D., Department of Psychiatry, University of California, San Francisco

Dr. Elissa S. Epel also addressed temporal considerations by looking at caregivers and stress, echoing a theme from Dr. Kiecolt-Glaser's talk. Years of chronic stress can be filtered down to impact short-term pathways of daily stress response. Epel's interests lie in examining groups with exposure to severe stress, and relating them to the biology of aging. She focuses on immediate, daily stress to understand: How do we conceptualize stress as it unfolds in daily life? What is the right target for intervention? What does this tell us about stress-related processes? The overarching goal is to identify malleable targets associated with the deleterious outcomes associated with chronic stress and determining how we can intervene to alter them.

Epel and colleagues followed caregivers for one and a half years to understand their daily activities as it applied to their caregiving. At the end of the study, they placed individuals into an intervention arm to understand: What does it mean to be a caregiver on a daily basis and how can we measure their dysregulation arising from chronic stress? Stressed caregivers showed changes in emotional responses to waking, to stress, and in emotion regulation. These were very specific enough to become foci for efforts at change through intervention. Given her psychology background, Epel underscored the potential value in psychological interventions and cognitive training programs to alter stress processes and help identify potential neurobiological targets, similar to SOBC.

It is important to understand how stress can affect the immune system. Does it have the same effect as chronological age, in a sense accelerating the known effects of age? A study by Boucher et al. (1998) compared immune cell subsets in young adults with an old cohort. CD8+CD28- cells were greater in the older group, compared to young adults. This type of cell tends to secrete more inflammation with age. Epel found that the high stressed caregivers had CD8CD28- cells that had lower telomerase. Further, the investigators found links between daily stress and lower telomerase in CD8CD28- cells. They observed how individuals appraised stressful events in their life in the course of a week were associated with cell aging. In addition, waking up stressed (with negative anticipatory emotion) was also linked to greater cell aging. So we could understand why caregivers have greater cell aging, in a day they wake up with greater threat appraisals, expecting bad things to happen, and respond to daily stressors with exaggerated perceptions of danger. This work is still in progress, but Epel presented preliminary findings. The question that drives this line of work is: Does chronic stress mimic chronological aging, leading to replicative senescence? So far it looks like it does. The midlife caregivers had greater telomere shortening in the CD8CD28- cells over the 1.5 year. Evidence from work by Kiecolt-Glaser and colleagues suggests that with dementia caregivers it does, with shorter telomeres associated with chronic caregiving stress.

This work can extend to studying how this is related to daily stress via waking responses. Epel measured awakening appraisals as part of a daily stress diary. The theoretical framework behind this work is the link between stress responses and appraisals of threat or challenge, which in turn may be linked to the resources individuals have to cope well. She found that caregivers wake up with different emotional and cognitive processes (mood affects) than their non-caregiver counterparts

In thinking about what is the "residue" of chronic stress, it is worthwhile to think of stress reactivity. Stress reactivity measures can offer a profile of "stress vulnerability," and this can provide unique predictions of health trajectories and the risk of early disease. Those with early adversity tend to have an amplified psychological and physiological response to an acute stressor (e.g., with cortisol). For instance, with caregiving, caregivers are experiencing daily occurrences that can lead to other outcomes with regards to threat appraisals. Reasonable intervention targets include exaggerated threat appraisals (upon waking and in response to stressful events) as well as greater emotional avoidance, resulting from appraisals of inability to cope.

Discussion

Epel raised the question: What are the persistent risk mechanisms of chronic stresses and/or adversity in a daily context? One is in stress appraisal. Caregivers were more responsive to an intervention designed to change threat appraisals than non-caregivers; there were more dramatic decreases in perceived stress. Coming from a psychology perspective, Epel resonated with Miller in that biology is not explanatory enough. BSR's reversibility initiative holds promise in identifying both psychological and biological mechanisms that might be amenable to intervention to reverse the deleterious impact of negative stressful exposures on health.

What is it with those who face early adversity? How are they different? This comes down to their relationships with self, their own identity, and their thoughts. When we analyzed those with greater early life adversity and how they responded to daily stress, and to our mindfulness intervention, we learned two things: 1) Early trauma was related to a weak sense of self .that is more affected by stress, and 2) they showed greater benefits from the mindfulness intervention. Epel affirmed that it is critical to have a sense of independence between sense of self and thought. This concept addresses Nielsen's question(s) about how should we be more specific about the mechanisms that might help us reverse persistent risk mechanisms from chronic or persistent life stress.

Telomeres are helpful as a crude biomarker of past stress that may be remedied. So they are helpful to measure but they don't tell us the same information as carefully assessment of daily stress. Telomeres are shorter in adults who experienced more trauma as children. This was also expressed in Kiecolt-Glaser discussion on stress, immune function, and health. But we can't ignore deep psychology in favor of cruder biological mechanisms. Careful attention to the psychological targets of stress reduction interventions will help us reverse the actual drivers of stress arousal, the daily persistent risk mechanisms.

Question 5: *Methods as Tools for Analysis of Pathways. Are there methods and approaches that are now available for enhancing mechanistic understanding of some of our major finding? BSR has supported a broad range of studies in behavioral genetics and more recently the genotyping of large cohort studies including the HRS and WLS, as well as studies that have include measures of gene expression changes associated with psychosocial factors. Are these approaches useful for integrating into mechanistic analyses of principal findings? The same is true of our increasing support of brain imaging studies of processes involved in social, affective and economic behavior. Where might work of this kind be most useful in pushing further our understanding? Closely related are design tactics such as systematic subsampling of population-based survey subjects for more fine-grained laboratory study and/or theory-testing interventions.*

Methods as Tools for Analysis of Pathways: Part 1
Jenae Neiderhiser, Ph.D., Department of Psychology, The Pennsylvania State University

Dr. Jenae Neiderhiser's presentation considers the role of behavior genetics in exploring mechanistic analyses of principle findings from these BSR studies. She explored the question by conveying the importance of thinking about those strategies used to understand gene-environment interplay.

Neiderhiser turned her attention first to gene-environment correlation. She defined three types:

1) **Passive**: Parents' genes influence the way they parent and they impact subsequent outcomes on the children given they share genes and environments.
2) **Evocative**: Children's genes influence the ways parents are parenting and the social environment (parenting, for example) responds to genetically-influenced characteristics of individuals.
3) **Active (or Direct)**: Individuals seek out environments correlated with their genotype.

One strategy used to better understand how individuals' genes and how genes and environments work together is via twin designs. This provides important and relevant insight, particularly when interested in examining the influence of parenting on their children. Neiderhiser singled out the "children of twins" design as especially useful: here the twins are adult parents, but their offspring are included in the sample. One such study focused on the role of parenting in the development of their offspring, offering a powerful approach to tease apart rearing environment(s) from genetic influences on child and adolescent development. The shortcoming of the design is that the children are related genetically in a much more limited way. Children of identical twins share only 25% of genes, similar to half-siblings; this was the upper limit of their genetic relatedness while children of fraternal twins share 12.5% like any other cousin pair. If one was interested in how the child evokes responsiveness from parents, this baseline was quite low.

We have worked to combine our sample of parents who are twins with samples of children who are twins. This was first reported by Narusyte et al. (2008). In order take advantage the genetic relatedness of child twins and of parent twins we combined samples of children who were twins with twins who were also parents. This is called the Extended Children of Twins (ECoT). This examination allows us to distinguish among between evocative and passive gene-environment correlation, and direct environmental influences.

Researchers can also learn a lot by incorporating Parent-Child Adoption Designs. They are difficult to do from scratch, but there are some registry data available for use in Sweden (and possibly elsewhere). These types of designs provide different, unique advantages that are not seen in a typical (or most twin) sample. When a child is placed in an adoptive home at or near birth, and the birth parents are assessed, one can disentangle the rearing environment from prenatal influences and genetic influences; the prenatal influences are particularly interesting, but so are the genetic ones. By separating rearing environment from genetic relatedness, as in a parent-offspring adoption design, one can estimate gene-environment correlation and interaction. In this case, any gene-environment correlations identified with evocative as the adoptive parents and adopted child do not share genes. There is evidence of evocative GE correlation for mothers and fathers hostile parenting behavior.

Taking any one approach to address complex research questions is limiting. Approaching complex questions from multiple directions helps to address criticisms and concerns about design assumption and propagates more confidence in the findings that result. Therefore, adding molecular genetic research – such as GWAS and GCTA– clarifies processes and mechanisms and helps investigators understand what mechanisms may be operating in these complex systems of interest.

This type of work is highly relevant for research on adults. GE correlations are operating on relationships with others, including parent-child, marital, work, peer, etc. and they are pervasive. Unfortunately, there is very little research on GE correlations in adulthood, therefore know very little during this developmental period. MIDUS is making an important contribution because it does measure interpersonal relationships within the context of the twin sample. With this, and other studies, the science should continue to build. With regard to intervention, if researchers are able to disentangle the impact of an individual's genetic influences from environmental influences, they can better, and more successfully, shape positive outcomes. The question of where can scientists target the interventions to get outcomes of interest making an impact for change goes back to Reiss' point(s) stated previously.

Discussion

In elaborating on the discussion of the Swedish Twins Study, panelists suggested utilizing longitudinal studies as a reference. For instance, MIDUS has not looked at twins in their study of parents, but Neiderhiser pointed out that it would be interesting to do so, where only small steps were needed to do this. It was especially possible if one knew the age of the adolescents of interest. It is useful to try to tease these apart as well as it is important. These twin parents varied on the degree of genetic relatedness, i.e., fraternal vs. identical. What was important about the model was that it looked at parents' effects on the child and the child effects on parents.

Methods as Tools for Analysis of Pathways: Part 2

Marc N. Potenza, Ph.D., M.D., Departments of Psychiatry, Neurobiology, and Child Study Center; Yale Center of Excellence in Gambling Research; Women and Addictive Disorders, Women's Health Research at Yale; Yale University School of Medicine

BSR increasingly provides support of brain imaging studies of processes involved in social, affective, and economic behavior. Dr. Marc N. Potenza reviewed several different approaches to integrating an understanding of brain function with other data for elucidating causal pathways. All of these approaches are guided by needs and question generated by major concerns for public health.

Cross-sectional Mediation Modeling

With cross-sectional mediation modeling, Potenza looked at data from the interdisciplinary research consortium on stress, self-control, and addiction that has focused on alcohol, tobacco, and food. This was part of the NIH roadmap initiative, ranging from studies on the rodent to human epidemiology. Potenza studied impulsivity and self-control as related to fMRI assessments in this initiative. He and his team probed these and other data with specific hypotheses in mind. For example, from one sample, they found that self-reported and behavioral measures of impulsivity and related constructs factored separately in a principle components analysis (Meda et al., 2009). In a second sample, they found that behavioral impulsivity was linked to treatment outcome measures in adolescent smokers whereas self-reported impulsivity was not (Krishnan-Sarin et al., 2007). Further, they looked at self-reported and behavioral measures of impulsivity to try to understand the relationship between stress and hazardous drinking. They found that self-reported impulsivity, and not behavioral impulsivity, mediated the relationship between stress and hazardous drinking (Hamilton et al., 2013).

In contrast with the model presented by Duckworth, Potenza did not think of impulsivity as the opposite of SC, but instead, thought of them as separable/dissociable but likely related constructs that fit within a larger set of psychological theory. An example includes the Theory of Approach and Avoidance, which can be assessed using the BIS/BAS scale. Potenza and colleagues have explored the relationship between stress and SC and how it was mediated by measures of impulsivity and behavioral inhibition and activation dimensions (Hamilton et al., 2014).

Exploring Incident Disorders and Moderators

Recreational gambling is associated with better cross-sectional health. In tying with the theme of harmonization, one should consider integrating gambling-related measures into ongoing studies, given it is a popular activity among functioning adults. However, cross-sectionally, at-risk (i.e., problematic) gambling is associated with multiple negative health measures. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is a large, nationally representative survey with data designed to determine the use of alcohol use disorders and their associated disabilities in the general population. Specifically, in the NESARC data, over 30,000 individuals were assessed in 2 waves.   Potenza and his group examined the extent to which at-

risk problematic gambling at wave 1 was associated with incident psychiatric conditions as well as incident medical conditions. They found that there was amongst older adults an association between at-risk problem gambling and incident anxiety and substance use disorders as well as cardiac conditions (Pilver et al., 2013; Pilver and Potenza, 2013). Within the general adult population, the researchers examined whether gender moderated the relationship between incident substance use disorders relative to at-risk problem gambling. They found that there was an increase incidence of nicotine dependence and an increase incidence of alcohol use disorders in women and men, respectively (Pilver et al., 2013). This study provided an example of how we might use existing longitudinal data to extract additional information.

Integrating Psychiatry, Psychology, Endocrinology, and Neuroimaging to Understand Obesity: a focus on Motivation and Control

An example of this level of integration is to understand obesity and the still-controversial hypothesis that it arises from a food addiction [see Ziauddeen, Sadaf, and Fletcher (2012a) and (2012b), and Avena et al. (2012) as an example of the controversy].

As part of an interdisciplinary research consortium, Potenza and colleagues compared a group of obese persons to individuals with a lean body mass. Using GLM-based contrasts between the two groups, he examined psychological and neurobiological processes related to the exposure to food cues. Participants were exposed to favorite-food cues as well as stress cues, as the latter are linked in some people to increase patterns of eating. Compared to the lean group, there was evidence of greater regional brain activation in the obese group to both food cues and stress cues, particularly in areas associated with reward-motivation (Jastreboff et al., 2013). The researchers also collected measures of subjective food craving. There were links in the obese but not in lean individuals to specific brain regions related to motivation and reward, including the thalamus and hippocampus. Similar patterns of activation were associated with insulin resistance, and results indicated that regional brain activation in reward-related areas mediated the relationship between insulin resistance and subjective ratings of food craving. The team has further applied these approaches to explore neurobiological mediators leading to drug addiction.

Psychotherapy Development Center: Integrating fMRI and RCT Approaches to Understand Brain Mechanisms Underlying Behavioral Change

Potenza presented another tool by which to analyze pathways as it applied to understanding brain imaging studies. Given that he and his collaborators have interests that lie in trying to understand the neural correlates that are related to the active ingredients of behavioral therapies for individuals with addictions, they used cognitive tasks designed to test cognitive control. Particularly, they obtained pre-treatment measures and looked at regional brain activations in individuals with cocaine dependence, and then observed prospectively the treatment outcome. Results showed that certain brain regions, like the striatum, were linked to post-treatment drug abstinence (Brewer et al., 2008). A different pattern, implicating the prefrontal cortex, was observed in subjects remaining in the trial versus dropping out.

Moving forward, researchers should consider integrating different approaches to neuroimaging data to understand neural circuitry function, which can shed light on psychological processes as

well (Xu, Potenza, Calhoun, 2013; Xu et al., in press). In a multidisciplinary fashion, various approaches (i.e., psychophysiological interaction, dynamic causal modeling, intrinsic connectivity distribution, independent component analysis, etc.) may be applied to other behavioral and biological measures in "traditional" and mediation/moderation models. These integrative approaches present the greatest potential for addressing major Public Health concerns.

Potenza asserted that it is important, in planning treatment studies to identify and target separable domains, such as impulsivity, emotional regulation, stress responsiveness, etc. Translating biological investigation into improved prevention, treatment, and policy interventions is an effort best achieved through integrative, multi-modal, interdisciplinary research. Building on existing datasets is a cost-efficient and scientifically efficient way of moving the process forward.

Discussion

With the obesity addiction model, Nielsen stated that there was a transformation of circuitry for reward process with normal development aging. In BSR's experience, studies have typically invested in answering questions like, "What is the impact of aging on decision-making or, SES, etc.?" Given that some of these biological processes are changing at different rates for some people, is there a way of integrating measures into our surveys that can tap this change? How should we think about embedding these kinds of tasks into longitudinal studies that we currently support, knowing that we have this full range of variation?

Potenza acknowledged that there were multiple answers. In situations where funding is limited it may be possible to use measures of highly specific psychological processes as proxies for the very expensive neuroimaging techniques.

Reiss summarized the relationships between the short-term analyses of processes, as presented by Epel and Almeida, and the work of Potenza. In both cases, researchers were approaching the characterization of dynamic processes varying across a limited time frame. This is a time scale that is familiar grounds for interventions that help individuals manage, cope and reframe the momentary challenges—such as food cues and stressful circumstances. Again, however, explorations of these short-term processes are expensive and we need guidance about the minimally adequate tools that are available. Moreover, how do we move from the intensive investigations such as those described by Potenza to more affordable assessment of individuals and a veridical monitoring of their treatment progress?

Reiss recognized that Potenza made great distinctions between impulsivity and its close neighbors using data from brain imaging and making inferences to make distinctions. He stated that there is an interest in BSR in more specifically probing the processes presented. As a Division, BSR could move some biologically informed proxies into the work we do, related to the psychological and behavioral constructs we use. Potenza affirmed that his lab is currently trying to devise clear definitions to better apply methods used to understand pathways via brain imaging and interdisciplinary methods to apply to BSR.

Summary and Next Steps

John T. Cacioppo, Ph.D., Departments of Psychology and Psychiatry & Behavioral Neuroscience and Lisbeth Nielsen, Ph.D., BSR, NIA

Nielsen asked the panel to consider how BSR should move forward with pathways studies, given the rich arrays of approaches considered at the meeting. Particularly, she asked for guidance in setting priorities for exploring specific mechanisms linking antecedent and consequents and about relevant disciplines that might be useful to engage in supporting BSR efforts in this domain.

Seeman suggested that BSR leverage data already available in order to better identify what some of the targets of intervention might be. She stated that there is a lot to learn about observational data, including what is consistent with causality. In this context, one should think about ways to leverage those existing studies by piggybacking on them. Where could one subsample to do some imaging, to address challenges, or more in-depth biology? Rather than starting a whole new study, are there more ways to build efficiently on the data you currently have? Researchers could use the data currently available in targeted ways.

Almeida suggested that some of the interest expressed in this meeting comes from longitudinal studies that started in childhood where these individuals are now getting older. Many of the researchers involved in these earlier studies were really child developmentalists. Working together with these childhood developmentalists on the issues related to adulthood and aging is worthy of future study and investigation.

Neiderhiser emphasized, as Miller had, the importance of good measurement as a start to transforming research. These should include measurements of social relationships among individuals. Higher quality measurements within family as well as outside family would be a great place to start. For example, twin studies have and should continue to examine marital quality and parent-child relationship.

Goldstone suggested that it would be worthwhile to have work supplemented by computational, process-oriented models. These could possibly be explained in some terms of scale dependencies or flow models showing where some people are far from being at risk while others are close to being at risk. Supplementing research with more process-oriented models is important.

Jablonski stated that, in general, researchers have seen rich presentations of phenotypic data. It would be worthwhile to establish more studies of longitudinal cohorts of youth or on older caregivers including the effects of stressors on gene expression. Irreversible changes in IL-6 levels following high stress speak to some major genetic change occurring that cannot be reversed (i.e., such as a methylation issue) and is worth investigation. When delving into the exploration of mechanisms, one must think about this. Geneticists are willing to pair up to investigate these topics, and this would be a great potential for extending these.

Epel commended BSR on their work linking population-based health with more of the mechanistic sub-studies. She affirmed that BSR already leads in this area and is on the right

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track with the portfolio of proposed mechanisms. However, with limited resources, extended longitudinal studies from childhood are prohibitive. But capturing processes across a greater span of life (than encompassed in the study) might be possible if valid retrospective measures are available.   As discussed, examining current (adult) stress reactivity in is an important area of study, and figuring out what the best measures of stress reactivity are is essential. In general, researchers should invest in incorporating mechanistic measures that assess reactivity to real-life stressors. She also stated that standardized measures for surveys would yield a lot of fruit as well.

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