NETWORK ON REVERSIBILITY:

CAN THE HARMFUL EFFECTS OF EARLY ENVIRONMENTAL ADVERSITY BE REVERSED IN ADULTS?

Bethesda, Maryland
September 10–11, 2012

SUMMARY

National Institute on Aging
Division of Behavioral and Social Research

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EXECUTIVE SUMMARY

BACKGROUND

On September 10–11, 2012, the National Institute on Aging (NIA) Division of Behavioral and Social Research (BSR) convened a diverse team of experts to launch its Network on Reversibility. The purpose of the Network is to define the scope of future research initiatives and to marshal a trans-disciplinary approach in the development of such programs. The members of the Network will combine their expertise to develop new ideas on how to test the hypothesis that harmful effects of early environmental adversity can be reversed in adulthood. Long-term goals include improvement of unfavorable health trajectories in mid-life and beyond.

The group agreed that there is a sense of urgency for a meeting like the present one. The accumulated body of evidence showing linkages between early adversity and life course morbidities has reached unprecedented levels. Observational studies (e.g., Fragile Families; the Wisconsin Study of Families and Work), "natural" experiments (e.g., the Dutch famine; the London Blitz child deportation; the children of WWII survivors), random assignment experiments (e.g., the Bucharest Early Intervention Project), and animal studies (e.g., cross-rearing studies) have contributed to the current understanding of the connections between childhood events and adult health. In combination with increasing precision in specification of biological mediators, the field is poised to make significant progress.

In keeping with the interdisciplinary culture of BSR, this group of neuroscientists, psychiatrists, epidemiologists, and other specialists, was ideally situated to address the complex scientific, historic, and cultural issues that all work together to pose significant challenges for progress in the field of reversibility of early adverse events.

To maximize the opportunity for an exchange of ideas, the meeting followed an innovative format: moderated panel discussions allowed each participant to assume an active role throughout the meeting and to make significant contributions to the content of each section. Over the months leading up to the meeting, topics of discussion and the subsequent agenda formed organically out of various conversations among members. Sub-groups of two led each of the four sessions around a defined topic. All sessions resulted in extensive engagement and discussion contributions from the entire group. Perspectives shared from these discussions will inform the internal discussion of priorities within BSR.

The group reviewed the available literature and noted that previous intervention studies, designed to test the hypothesis of reversibility in adulthood, have not yielded any effects that could be measured consistently. There is a great need for new ideas regarding the experimental design of such studies. To ensure that these new ideas are feasible, the group identified six complexities and challenges that need to be considered when designing better interventions:

CHALLENGE #1: COMMON CONSTRUCTS AND VARIABLES IN CHILDHOOD AND ADULT DATA SETS

Researchers must take into account the complex relationships between social environments and biological function across the lifespan. Personality traits (i.e., social dominance, agreeableness, conscientiousness, etc.) and intelligence (i.e., fluid intelligence and crystallized intelligence) have been shown to change quite dramatically throughout the life course regardless of adversity. When considering intervention strategies, awareness of these factors is critical.

CHALLENGE #2: THE PROBLEM OF DOSE

Variations in the amount or duration of childhood stress lead to different outcomes and coping mechanisms. Additionally, even too much of a good thing can be bad: Good intentions can actually become harmful if applied without restraint. Human parents who overprotect children from social and physical failure will render them ill-equipped to succeed socially. Similarly, while the positive effects of enrichment are undoubted, overstimulation of newborn mice leads to behavioral differences and deficits in cognitive performance.[1]

CHALLENGE #3: DIFFERENTIAL SENSITIVITY TO SOCIAL CONTEXTS

For a variety of health endpoints (e.g., internalizing behavior problems, respiratory disease, severity of injuries in children, violent injuries in macaques, and memory of stressful events), children can be categorized into high and low reactivity groups based on autonomic and adrenocortical responses. Children exhibiting the highly reactive phenotype will often show different responses depending on the context: A given challenge may produce a better-than-normal outcome in supportive contexts but worse-than-normal outcomes in stressful ones.[2] Similar results have been shown for adults. These individuals have been termed 'the highly sensitive person'.[3] The concept of differential sensitivity, especially when specific to certain periods of the lifespan, is of great importance for the discussion of reversibility. An intervention may not reverse the phenotype per se but may reset the individual into a state in which the differential susceptibility is active. Once reversed to that state, a new stimulus can, once again, create a positive or negative response depending on the social context. A potential research topic for the Network may be identifying and characterizing markers of this social context sensitivity in adult populations.

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[1] D. A. Christakis, J. S. B. Ramirez, and J. M. Ramirez, "Overstimulation of Newborn Mice Leads to Behavioral Differences and Deficits in Cognitive Performance," *Scientific Reports* 2 (July 31, 2012), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409385/.
[2] W. Thomas Boyce. "A Biology of Misfortune." *Focus* 29, no. 1 (Spring/Summer 2012): 1–6.
[3] Elaine N. Aron, Arthur Aron, and Kristin M. Davies, "Adult Shyness: The Interaction of Temperamental Sensitivity and an Adverse Childhood Environment," *Personality and Social Psychology Bulletin* 31, no. 2 (February 1, 2005): 181–197.

CHALLENGE #4: LESSONS FROM LARGE-SCALE SOCIETAL INTERVENTIONS

Interventions occur continuously due to changes in social norms, improved education of the public, access to new resources, Congressional legislation, etc. The prevalence of cigarette smoking, for example, has steadily declined in the United States since 1965. Although it is impossible to pinpoint specific interventions (i.e., policies, perceptions, etc.) that led to the decrease, there are numerous lessons to be learned. For any given impact, there may be countless underlying contributing factors.

CHALLENGE #5: TIME, TIMING, AND CRITICAL PERIODS

An understanding of timing, including when measurements are most accurate and when interventions are most effective, is absolutely crucial when considering potential multidisciplinary projects for the program of the Network. Maternal factors, for example, play a role even prior to conception. The group considered dividing the life course into stages or phases to better characterize 'early' adversity. Currently, most birth cohorts lump ages 0 through 5 together, and the field should gather data to determine if greater power would be achieved by dividing these groups into more specific sub-sets.

CHALLENGE #6: BUILDING BETTER, MORE PARALLEL ANIMAL-HUMAN ANALOGUE STUDIES

Studies in which animal and human behaviors (i.e., social hierarchies) and/or biological characteristics (i.e., epigenetics) are investigated in parallel from the outset are rare. When studying reversibility, skepticism remains regarding the validity of blood-derived cellular models, given that changes in gene regulation have been shown to be cell-type specific. Brain samples can only be obtained post mortem so development of valid analogous animal models is imperative for research progress in the age of molecular phenotypes.

NEXT STEPS

The meeting concluded with the group defining the concrete topics for the next meeting, to be held during February of 2013. It was decided that the team split into groups and prepare discussions for the winter meeting on two topics:

- Critical or sensitive periods (Champagne (convener), Brooks-Gunn, Conti, Power, and Singer)
- Better understanding of the high reactivity phenotype (Boyce (co-convener), Epel (co-convener), Seeman, Singer, and Suomi)

Two further topics of high relevance include:

- Combined analyses across existing cohorts

- Human-animal parallel studies

In addition to planning for the mid-winter meeting, the discussions during this meeting that are summarized in this report will help the Network to consider the possible value of consultants for its work and make specific plans to join forces with companion efforts. Finally, the optimal mechanism for continuing the work of the Network needs to be discussed and submission of an application to the NIA should be considered, which has recently earmarked funds to support networks.

# # #

It seems, in fact, as though the second half of a man's life is made up of nothing but the habits he has accumulated during the first half.
– Fyodor Dostoevsky (1821 - 1881)

INTRODUCTION

Early adversity is linked to a broad range of long-term physical and psychosocial outcomes, many of which are of significant interest to the NIA and BSR. Adult outcomes that have been found to be associated with early adversity include but are not limited to:

General Health
- Premature Mortality
- Obesity

Specific Somatic Disorders
- Bone Disease
- Cardiovascular Disease

Mental Health
- Depression
- Emotional and Behavioral Self-Regulation
- Optimism

Social Health
- Economic Planning
- Productive Social Engagement
- Capacity to Care for an Ill Spouse

Researchers have speculated that most impacts on health are established early and, without intervention, are likely to worsen over the course of life. On the other hand, recent data show that the majority of adults suffering early-life adversity, in fact, do not develop negative outcomes. Additionally, latent effects have been described: At first there may be little or no evidence of negative outcomes following an adverse event(s), but negative outcomes materialize later in life.

The aims for the meeting included collaborative exploration of the evidence related to the field, identification of questions that can be addressed from available data, and conceptual formulation of research projects that promise the highest yield.

Additionally, research promoted by the Network may warrant establishment of an initiative that garners the attention of the National Institutes of Health (NIH) more generally. For

example, the NIH Common Fund is supporting programs initiated at BSR, including the Science of Behavior Change (Lead: Jon King) and Health Economics (Lead: John Haaga). Finally, and of significant interest to the group, BSR has proposed a study to the Common Fund examining harmonization of cohort studies for synthetic studies.

SUMMARIES OF THE WORKSHOP SESSIONS

I. FOCUSING OUR LENS ON EARLY ADVERSITY

Jeanne Brooks-Gunn, Ph.D., Columbia University
Terrie Moffitt, Ph.D., Duke University

UNDERSTANDING THE LIFE COURSE

Given the long reach of childhood, it is incumbent on the Network to establish an understanding and consensus of early adversity. When considering potential multidisciplinary projects for the Network, a key understanding is that of timing. The question when measurements should be recorded and interventions be introduced needs to be answered for each specific experiment.

Brooks-Gunn raised the question whether it may be valuable to divide the life course into stages or phases with finer granularity to better characterize 'early' adversity. Current designs of most birth cohorts lump ages 0 through 5 together. The field may gain power by splitting those years into sub-sets (i.e., toddler and pre-school).

The fact that maternal factors play a role even prior to conception would speak for a finer division of age groups. Furthermore, maternal effects on the fetus during gestation have been demonstrated. A substantial number of additional factors have been shown to shape the interaction of the mother with her infant, then toddler, and later child.

TODDLER YEARS

Focusing on the importance of timing of adverse events, Brooks-Gunn presented data on early adversities that may be better examined at smaller age increments. Poverty in the first four years is highly predictive of negative adult outcomes. However, evidence is not available to examine the first year relative to the third year. Abuse and neglect in the first five years is known to be predictive, but smaller increments of measurements are not available. Paternal departure has a significant impact on children, but the effects vary as a function of time. For example, aggression at age 9 is highest in children whose father left before age 3; it is less prevalent when the departure was between ages 3 and 5; and there is almost no effect when the child is left between ages 5 and 9. Alternatively, based on data from older cohorts, Power reviewed effects of parental separation on mental health even after adolescence.

The timing of separation has been examined in animal models. Throughout the duration that rodent pups stay with the mother (approximately 20 days), the mother's parenting usually remains consistent over time. This means that a high licking-grooming mother exhibits that behavior throughout her relationship with the litter. Champagne pointed out, however, that only the early period (the pups' first week of life) is predictive of adult outcomes.

Suomi noted that there is a substantial body of evidence with parallel results in rhesus macaques: Behaviors and relationships of the mothers and babies are completely different during the first 6 months (which correlates to the first 2 years in humans) compared to the rest of the offspring's life course.

Timing of early adversity has been investigated in humans as well. Boyce offered three examples:

- Gregory Miller and Edith Chen investigated the timing of the long-term effects of socioeconomic disadvantage on inflammatory parameters that indicate a persistent vulnerability to respiratory and cardiovascular diseases in adulthood. Their results show that socioeconomic stability at age 2 is highly correlated with high glucocorticoid receptor and low toll-like receptor 4 expression. These two gene products are markers for correct regulation of inflammatory responses. In addition to the critical period at 2 years of age, a second, somewhat less critical time point is present between ages 7 and 9.[4]

- The WSFW includes many measures of parental stress during the first five years of life. Boyce's data indicate that parental stress results in gender-specific differences in DNA methylation for the children as well as the parents. Maternal stress during the first year of life gives rise to differential methylation in both daughters and sons. Paternal stress has the greatest impact on daughters during the pre-school years (ages 4-5). Boyce suggested further research that may provide additional insights regarding gene expression and/or behavioral correlates.

- Using extensive diary-keeping of mother-infant contact and care during the first 6 months of life, Ronald Barr and Boyce examined DNA methylation in those offspring when 2-3 years old. Analysis of samples from the extreme end of the distribution of measures regarding the quality of parenting indicated no difference in methylation in buccal cells.

[4] Gregory Miller and Edith Chen, "Unfavorable Socioeconomic Conditions in Early Life Presage Expression of Proinflammatory Phenotype in Adolescence," *Psychosomatic Medicine* 69, no. 5 (June 2007): 402–409.

PRESCHOOL YEARS

Sheldon White's five-to-seven shift is indicative of a cognitive development that explains improved memory and possibly self-control in this age group.[5] It is during this timeframe that children are enrolled in school worldwide. If this reorganization truly occurs, Brooks-Gunn noted that it is likely to have wide-ranging consequences regarding the mechanisms behind early childhood education and intervention programs. It remains unclear if these programs are improving plasticity (e.g., changing neural pathways) or forcing earlier learning.

Robbie Case's evidence for success in mathematics indicates that students entering school without any concept of numbers exhibit very poor outcomes for math understanding later. An intensive math training intervention during this timeframe has, however, been shown to cause lasting, long-term success.

Robert Siegler showed similar results using board games to influence preschoolers' math understanding. Early childhood programs appear to exhibit greater successes in math than in language in part because there will always be exposure to language in the home.

One major hurdle for the field is the lack of reliable measurement tools. The Flanker Task may yet be the best response inhibition test available.

The group agreed that a significant gap in understanding is the current lack of convincing connections between behavioral and biochemical data. While the behavioral research on birth cohorts is strong and growing, the biochemical understanding in children is in its infancy.

Regarding the life course, the Network agreed on the need for a defined beginning and a defined end. Data should be collected prenatally at the very least and potentially for a substantial period prior to conception. Where to put the end point is less clear and may be exacerbated by cultural factors. After consensus on the start and stop, the Network can make decisions regarding the granularity applied in its methods. In order to make these decisions, the group needs to define evidence requirements.

One example for required evidence is the importance of puberty. Suomi pointed out that importance in rhesus macaques. Two fundamental changes occur at puberty:

- Monkeys undergo hormonal changes that contribute to associated physical changes.
- The way that they are treated by their peers changes dramatically.

Males, for example, are outcast from their social groups, resulting in a very difficult transition.

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[5] Sheldon H. White, "Evidence for a Hierarchical Arrangement of Learning Processes," in *Advances in Child Development and Behavior*, ed. Lewis P. Lipsitt and Charles C. Spiker, vol. Volume 2 (JAI, 1965), 187–220, http://www.sciencedirect.com/science/article/pii/S0065240708604838.

Due to their newfound reproductive potential, females become a major focus of adult male attention where they were previously ignored.

Discussion also turned to work by Charles Nemeroff and his colleagues showing higher prevalence of post-traumatic stress disorder or anxiety later in life if a traumatic event has happened before puberty.[6] Childhood traumatic events can have "profound and long-lasting effects on the development of neurobiological systems, thereby "programming" subsequent stress reactivity and vulnerability" to developing post-traumatic stress disorder.[7]

CASCADES AND ENVIRONMENTS – THEIR IMPACTS ON TRAJECTORIES

The regression discontinuity (RD) design is commonly used to test whether a program or treatment is effective. A critical design element is the presence of a strict threshold above or below which the intervention is applied. This study design is very popular when randomization is not feasible and is based on the assumption that subjects just above and just below the threshold will obtain similar results if the treatment has no effect. If the treatment has an effect, there will be a shift in the regression line above versus below the threshold. This shift, or discontinuity, can be quantified and provide a measure for the effectiveness of the intervention.

Low birth weight, for example, is defined as less than 2500 grams, but sub-populations just above this cut-off are likely to perform as though they were underweight at birth. Another example is the 1966-70 roll-out of the Head Start program; mid-life outcomes show a correlation with Head Start exposure in those counties that could offer the program.

Additionally, the RD study design can be used to identify a condition or shock that triggers changes in the rates of given behaviors. In this case, data obtained at regular intervals (e.g., on a yearly basis) are analyzed to screen for shifts or discontinuities. Knowledge about events or changes in conditions that occurred at the time of the shift can then help to identify triggers of altered health outcomes.

These study designs could aid in understanding downstream cascade events that affect the trajectories of individuals who experienced early adversity, both those with negative adult outcomes and those with positive. By focusing on the off-diagonal cases (those individuals that appear to have overcome early adversity and are thriving in adulthood), RD studies may shed some light on approaches (or their timing) that positively adjust trajectories for the subset of individuals that are unable to move forward.

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[6] Charles B. Nemeroff. "Neurobiological consequences of childhood trauma." *J Clin Psychiatry* (2004), 65:18-28.
[7] Christine Helm and Charles B. Nemeroff. "Neurobiology of Posttraumatic Stress Disorder." *CNS Spectrums* 14, no. 1 Suppl 1 (January 2009): 13–24.

During the following discussion of alternative research designs and strategies, Seeman noted that data from the Midlife in the United States (MIDUS) series may be suitable for examination of cascade effects and intervention insight.[8]

Singer recalled an extensive menstrual history taxonomy that showed significant deviation from long-believed assumptions.[9] Brooks-Gunn described a recent study using data from the National Longitudinal Study (NLS), in which life histories of teenage mothers were used to predict cognitive (i.e., reading) and behavioral (i.e., aggression) outcomes among the children.

INVESTIGATE SUCCESSFUL TRAJECTORIES

Boyce described a project measuring childhood health outcomes as a result of stress reactivity in the autonomic and adrenocortical systems. The undertaken measurements identified certain children as highly sensitive to these microenvironments. This highly reactive phenotype occurred both in highly negative epidemiologic profiles for kids from poor, deprived households, and highly positive epidemiologic profiles for kids from supportive, nurturing households.

These results go beyond a simple classification as “vulnerable” or “resilient” and point to the need for an understanding of sensitivity to social context – both adverse and supportive.[10] Similarly, Werner has defined vulnerable and resilient children.[11] Importantly, van IJzendoorn has shown that kids classified with this ‘sensitive’ phenotype are also more responsive to treatment.

Diverging from the stress model to one in which positive outcomes are measured, researchers are focusing increasingly not only on the absence of ill health but the presence of good health. Brooks-Gunn is currently investigating the effects and timing of the introduction of a father figure on youth aggression.

THE APGAR DISCUSSION

Birth is an autonomic stress event and recent evidence has shown the Apgar score to be a reasonably reliable measure of that stress. There is a graded association between the Apgar

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[8] Edith Chen, et al., “Protective Factors for Adults From Low-Childhood Socioeconomic Circumstances: The Benefits of Shift-and-Persist for Allostatic Load,” *Psychosomatic Medicine* 74, no. 2 (February 1, 2012): 178–186.

[9] Tristan Gorrindo, et al., “Lifelong Menstrual Histories Are Typically Erratic and Trending: a Taxonomy,” *Menopause (New York, N.Y.)* 14, no. 1 (February 2007): 74–88.

[10] Bruce J. Ellis and W. Thomas Boyce, “Differential Susceptibility to the Environment: Toward an Understanding of Sensitivity to Developmental Experiences and Context,” *Development and Psychopathology* 23, no. 1 (February 2011): 1–5.

[11] Emmy E. Werner, “Journeys From Childhood to Midlife: Risk, Resilience, and Recovery,” *Pediatrics* 114, no. 2 (August 1, 2004): 492–492.

score and a number of long-term outcomes (i.e., high school graduation and hospitalization through the first 18 years of life).[12]

Investigating markers of positive health in adults rather than continuing to uncover biological evidence for negative health might be a contribution the Network should consider. Carol Ryff has demonstrated that biological markers of psychological well-being are not simply the opposites of poor health. Instead, well-being is characterized by distinctly different biomarker profiles.[13]

Singer cautioned the group that a clear definition of 'health' and consensus on the definition would be paramount to the Network's decision to embark on this area.[14] Suomi suggested that such a definition could be modeled on the one established in response to the animal welfare act. The four tenets include:

- Assessment of Physical Health
- Comparison with Species-Normative Behavioral Repertoires
- Absence of Distress
- Adaptability to Changing Situations.[15]

II. OPENING A WINDOW OF PLASTICITY FOR PERSISTENT RISK MECHANISMS

Elissa Epel, Ph.D., University of California San Francisco
Bruce McEwen, Ph.D., Rockefeller University

TELOMERES

Telomeres and telomerase are critical to the regulatory system for cell division from single cell organisms to complex species. Telomere length is a major integrator of inputs and outputs throughout the lifespan: physiological and psychological stressors shape telomere characteristics and predict the likelihood of occurrence of different diseases of aging.
The system of telomere length and telomerase is tied to survival signals in humans including thought and stress response. The system is shaped throughout the lifespan and contributes to common regulation across tissue types, although some organ-specific differences do exist.

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[12] Douglas Jutte, et al., "Five-minute Apgar Score Predicts Hospitalization Through Age Ten: a Population-based Study" (June 19, 2006). http://citation.allacademic.com/meta/p_mla_apa_research_citation/0/9/4/3/0/p94309_index.html.
[13] Carol D. Ryff, et al., "Psychological Well-Being and Ill-Being: Do They Have Distinct or Mirrored Biological Correlates?," *Psychotherapy and Psychosomatics* 75, no. 2 (2006): 85–95.
[14] A start in this direction appears in Carol D. Ryff and Burton Singer, "The contours of positive human health." *Psychological Inquiry* (1998) 9(1):1-28. There is considerable follow-up to this paper characterizing "health" as decidedly not just the absence of illness.
[15] Melinda A. Novak and Stephen J. Suomi, "Psychological Well-being of Primates in Captivity," *American Psychologist* 43, no. 10 (1988): 765–773.

Overall, shorter telomeres are associated with:

- Elevated basal and reactive hypothalamic-pituitary-adrenal (HPA) axis activity
- Indices of High Limbic Arousal (found in major depression, anxiety, hostility, burnout, and threat reactivity)
- Lower hippocampal volume

TISSUE-SPECIFIC TELOMERASE

Zhou, et al. (2011) examined the relationship between stress and telomerase in the brains of mice.[16] The data show that chronic mild stress dampens telomerase in the hippocampus leading to depression-like behaviors. This stress-induced, low-telomerase depression can be buffered by administration of the antidepressant fluoxetine (Prozac). Depression-like behaviors also are observed upon azidothymidine (AZT) ablation of telomerase. Overall, the authors suggest that hippocampal telomerase is involved in the modulation of depression-related behaviors.

Within the last year, animal studies have begun to examine the effects of telomerase activity in specific cell types that are difficult or impossible to examine in humans (i.e., brain and heart). Decreased levels of telomerase lead to accelerated aging, graying fur, and atrophy of certain brain areas (i.e., olfactory bulb). Upon reactivation of telomerase, these symptoms are reversed or improved, including enhanced neurogenesis, reversal of gray fur, and longer life of the animal.

A limitation of the understanding of brain telomerase is due to a general lack of longitudinal studies. The progression of telomere shortening is known to be very slow during mid- to late-life. Conversely, telomere shortening is significantly faster during the first five years of life, and the trajectory appears to be shaped for life during that period. In the absence of true longitudinality, cross-sectional studies may provide an approximation of the trajectory.

TELOMERASE AND CHILDHOOD

Only limited knowledge is available regarding telomeres during childhood. Epel cited unpublished data indicating that low birth weight and early gestational age are linked to shorter telomeres. Recall of a major life event during pregnancy is related to offspring short telomere length in adults. Pregnancy anxiety is related to shorter telomere length in cord blood. While there is no fetal data, telomerase activity is known to be extremely high and telomere length is long in human babies. During the first few years of life, as the immune system is pruned, there are dramatic changes in telomerase activity and in telomere length, which appear to retain any acquired fetal effects.

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[16] Qi-Gang Zhou, et al., "Hippocampal Telomerase Is Involved in the Modulation of Depressive Behaviors," *The Journal of Neuroscience* 31, no. 34 (August 24, 2011): 12258–12269.

The Peers and Wellness Study (PAWS) has identified life effects that appear to indicate a link between kindergartner temperament and shorter telomeres in buccal cells.

For adolescents, the level of parental education and child's metabolic health (adiposity) is correlated with their telomere length. Furthermore, Shalev, et al. (2012) have shown support for a connection between cumulative childhood stress (violence exposure) and greater rate of telomere attrition.[17] Children exposed to two or more kinds of violence (exposure to maternal domestic violence, frequent bullying victimization, and/or physical maltreatment by an adult) showed significantly greater telomere erosion in buccal cells between measurement at age 5 and measurement at age 10. These results appear to be dose-dependent.

TELOMERASE AND GENETICS

Telomere length and telomerase activity are known to be heritable – approximately 50 percent – and are shaped more by the father than by the mother. Additionally, the age of the father is associated with telomere length – increased age corresponds to longer telomeres.

Multiple genes (around 30) have been linked to shorter telomeres. There are at least three genes which are currently known to regulate telomerase through defined mechanisms. The field appears to be moving toward epigenetic studies as well as investigation of possible gene x environment interactions.

TELOMERASE RELATED TO HEALTH

Significant shortening of telomere length have been shown in caregiver populations. Damjanovic, et al. (2007) showed that dementia family caregivers have shorter telomeres, which can lead to shortened lifespans by as much as eight years.[18] Furthermore, the Keicolt-Glaser laboratory has shown that damaging effects of later-life caregiving are exacerbated in populations that suffered early adversity.[19] The authors speculated that the significantly shortened telomeres could, overall, translate into a seven- to 15-year difference in lifespan. As in other studies on childhood adversity, there is a dose response relationship where the large effects are seen with multiple adversities.

Individuals with shorter telomeres appear to exhibit impaired acquired immune function, indicating serious consequences to shortened telomeres regarding cellular function. In fact,

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[17] I. Shalev, et al., "Exposure to Violence During Childhood Is Associated with Telomere Erosion from 5 to 10 Years of Age: a Longitudinal Study," *Molecular Psychiatry* (00/01/0000), http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201232a.html.

[18] Amanda K. Damjanovic, et al., "Accelerated Telomere Erosion Is Associated with a Declining Immune Function of Caregivers of Alzheimer's Disease Patients," *The Journal of Immunology* 179, no. 6 (September 15, 2007): 4249–4254.

[19] Janice K. Kiecolt-Glaser, et al., "Childhood Adversity Heightens the Impact of Later-life Caregiving Stress on Telomere Length and Inflammation," *Psychosomatic Medicine* 73, no. 1 (January 2011): 16–22.

Cohen, et al. in a paper under review finds that shorter telomeres (particularly in CD8/28- cells) predict vulnerability to the common cold.

Research on human telomeres has been largely limited to fibroblasts, buccal cells, and blood. Little is known regarding relative telomere length in other tissue types. Deceased Alzheimer's patients show short hippocampal telomeres, while deceased heart disease patients show short aortic telomeres. These changes may, however, be more reflective of aged senescent tissue than of disease. Generally, the group considers this an area in which animal studies can bring great value.

NEUROBIOLOGY

In animal models of chronic stress, research has demonstrated changes in dendritic length, branching, and synapse number. The hippocampus shows shrinkage of dendrites and some synapse loss and impaired neurogenesis. The medial prefrontal cortex shows shrinkage of dendrites and loss of synapses, while the orbital prefrontal cortex and the basal lateral amygdala show expansion of dendrites and increased synapse. These changes result in more anxious animals that are also more aggressive, perform poorly on cognitive tasks, and show impaired decision making. In a dangerous environment, these changes are adaptive in the short term. However, long-term stress in humans can potentially result in chronic anxiety disorder.

QUESTION ONE: CAN AGE-RELATED DECLINE BE REVERSED?

Research on brains of animals and humans has shown that an enriched environment increases brain function and has structural effects. Regular, moderate exercise and intense learning increases hippocampal volume, improves prefrontal blood flow, and improves decision making. Learning and practicing of motor skills changes circuitry. Morrison, et al. (2010) showed that chronic stress produces the same degree of shrinkage in the medial prefrontal cortex of young, middle-age, and older rats. However, over a 3-week recovery, the young animals showed a complete recovery, the middle-aged showed partial recovery, and the older animals did not recover.[20]

Neurogenesis declines with age. However, research has shown improved neurogenesis in older rats with the addition of moderate exercise. Similarly, sedentary elderly adults who begin to walk one hour per day, five days a week, over the course of a year will show a larger hippocampus, improved prefrontal cortical blood flow, improved memory, and more efficient decision making capacity.[21]

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[20] Erik B. Bloss, et al., "Interactive Effects of Stress and Aging on Structural Plasticity in the Prefrontal Cortex," *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 30, no. 19 (May 12, 2010): 6726–6731.

[21] Kirk I. Erickson, et al., "Exercise Training Increases Size of Hippocampus and Improves Memory," *Proceedings of the National Academy of Sciences* (January 31, 2011), http://www.pnas.org/content/early/2011/01/25/1015950108.

QUESTION TWO: CAN DEFICITS IMBEDDED BY EARLY ADVERSITY BE REVERSED BY INTERVENTIONS IN ADULTHOOD?

McEwen presented several examples in which adult interventions, both in animals and humans, have indicated the presence of neural plasticity.

In a mindfulness-based stress reduction (MBSR) intervention, Hölzel, et al. (2010) have shown that reductions in perceived stress are correlated with a decrease in amygdala density.[22] Similar MBSR intervention approaches have succeeded to cause improvements in chronic fatigue syndrome, including enlargement of the medial prefrontal cortical gray matter leading to downstream effects on cognitive function, as well as autonomic and hypothalamic pituitary adrenal (HPA) regulations.

Maffei's laboratory has shown reversed binocularity in a monocular depravation animal model after treatment with fluoxetine (Prozac).[23] A caloric restriction intervention has shown similar results as fluoxetine treatment. Furthermore, sufferers of stroke undergoing physical therapy see more rapid recovery when fluoxetine is added to the recovery treatment.[24]

Liston visualized in real-time (24 to 48 hours) the formation and elimination of dendritic spines *in vivo* after treatment with glucocorticoids in adult mice.[25]

The Chao laboratory has demonstrated that glucocorticoids activate TrkB (the brain-derived neurotrophic factor [BDNF] receptor) independently of BDNF itself. This means that in the presence of steady-state levels of BDNF, glucocorticoids activate the receptor, leading to an increased total activation.[26]

Overall, there is a considerable body of evidence for the potential of reactivation of brain plasticity. However, the potential for neuroplasticity in individuals with early adversity is not explicitly known. McEwen emphasized that chronic anxiety and chronic fatigue are adult

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[22] Britta K. Hölzel, et al., "Stress Reduction Correlates with Structural Changes in the Amygdala," *Social Cognitive and Affective Neuroscience* 5, no. 1 (March 2010): 11–17.
[23] José Fernando Maya-Vetencourt, et al., "Experience-dependent Expression of NPAS4 Regulates Plasticity in Adult Visual Cortex," *The Journal of Physiology* (July 30, 2012), http://www.ncbi.nlm.nih.gov/pubmed/22674715.
[24] François Chollet, et al., "Fluoxetine for Motor Recovery After Acute Ischaemic Stroke (FLAME): a Randomised Placebo-controlled Trial," *Lancet Neurology* 10, no. 2 (February 2011): 123–130.
[25] Conor Liston and Wen-Biao Gan, "Glucocorticoids Are Critical Regulators of Dendritic Spine Development and Plasticity in Vivo," *Proceedings of the National Academy of Sciences of the United States of America* 108, no. 38 (September 20, 2011): 16074–16079.
[26] Freddy Jeanneteau, Michael J. Garabedian, and Moses V. Chao, "Activation of Trk Neurotrophin Receptors by Glucocorticoids Provides a Neuroprotective Effect," *Proceedings of the National Academy of Sciences of the United States of America* 105, no. 12 (March 25, 2008): 4862–4867.

outcomes that are exacerbated by early adversity. This may be a potential research pursuit for the Network.

These examples indicate the roles of synapses and dendrite length as critical contributors of neuroplasticity. The group should be mindful that there is far more to brain plasticity and healthy neuronal function than just neurogenesis.

A MODEL OF PLASTICITY

The term neuronal plasticity refers to changes in neural pathways and synapses that are due to changes in behavior, the environment, or neural processes. Importantly, this concept does not imply a simple and sporadic change in behavior but habitual changes. Formation of a habit is reflective of physiological changes in the brain. Neurogenesis, synapses, and dendrite length are all critical contributors to neuroplasticity.

One declared goal for the Network is to establish a model of plasticity and ways to measure its relevance to mid-life phenotypes in humans who experienced early adversity. Ideally, the group will identify extreme, basic interventions that can be tested in animal models, extrapolate that knowledge to humans, and verify changes in outcomes through human trials.

Epel and McEwen suggested a two-step process to guide the team:

- Step one focuses on restoration of the biochemical environment that will promote plasticity while suppressing the effects of stress:
    - Some chemicals of interest for this process may be SSRIs (selective serotonin reuptake inhibitors), BDNF, telomerase, and Omega-3s, among others.
    - Independently, chemicals like these do not cause plasticity – they may, however, facilitate the potential for plasticity.
    - It is feasible that behavioral interventions like vigorous exercise may be enough to prime the biochemical milieu for plasticity.

- Step two identifies potent interventions that will shape plasticity in a strong environmental context to result in targeted learning:
    - Potential fields of study may include the balance between the prefrontal cortex and the limbic system (fMRI studies for connectivity, imaging for examining volume, meditation for thickness of prefrontal cortex, etc.).

The team will need to consider the best timing to successfully embark on the proposed two-step approach. Steps one and two can occur sequentially, staggered, or concurrently.

This innovative approach examines multifaceted interventions and combines biochemical and behavioral manipulations. While multi-factor studies are few, most start with one variable and then increase complexity until the full complement is achieved. An alternative approach is to

start with a full complement of factors and sequentially remove these to unveil effects. The latter approach is ideal for animal studies but impossible for human trials.

Epel introduced the concept of the "triple threat" of early adversity, which includes overactivation of the limbic system (threat sensitivity), dampening down of the executive system (self control), and the social attachment system, which may each require a different intervention strategy.

Epel argued that training in mindfulness, including a benevolent component (promoting social connection, positive affect, and compassion), targets most threats of early adversity. Alternatively, the group debated the potential research utility of environments in which physical and emotional stressors are used to moderate behavior and bond teams.

In addition to those mentioned in detail above, several other intervention strategies were briefly discussed:

- Caloric restriction has shown increased plasticity, but the effects on the neurochemical environment are unknown.[27] Epel highlighted the controversial nature and status of this approach. In unpublished data of long term restrictors, caloric restriction is not associated with longer telomeres.
- Group effects of meditation (i.e., MBSR) are often weak. However, once a decreased perception of stress is achieved, there is likely a correlation to a change in telomerase. The group noted the need to differentiate between attentional and social attachment meditation.
- The team discussed Michael Merzenich's work on cochlear implants. It is remarkable that, over time, the brain reorganizes to make sense of the sounds.[28]
- An alternative to the love and compassion model for intervention is the boot camp approach.
- Some insight may be learned from Jens Pruessner's work using the Trier Social Stress Test (TSST). Results show that individuals with low self-esteem have a smaller hippocampus, hypersecrete cortisol, and do not habituate to repeated stressors.[29]

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[27] Maria Spolidoro, et al., "Food Restriction Enhances Visual Cortex Plasticity in Adulthood," *Nature Communications* 2 (2011): 320.
[28] Xiaoming Zhou, et al., "Natural Restoration of Critical Period Plasticity in the Juvenile and Adult Primary Auditory Cortex," *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 31, no. 15 (April 13, 2011): 5625–5634.
[29] C. Kirschbaum, et al., "Persistent High Cortisol Responses to Repeated Psychological Stress in a Subpopulation of Healthy Men," *Psychosomatic Medicine* 57, no. 5 (October 1995): 468–474.

III. FOCUSING ON THE MOST SALIENT OUTCOMES OF EARLY ADVERSITY IN MID-LIFE AND BEYOND

Christine Power, Ph.D., University College London
Teresa Seeman, Ph.D., University of California Los Angeles

No single study can gather all imaginable data, and each study has its strengths and weaknesses when it comes to data collection. Comparisons can be drawn between cohorts to enhance the knowledge gained. For example, the MIDUS study enrolled 7,108 Americans (ages 25 to 74), while the 1958 National Child Development Study (58 Cohort) follows 17,000 Britons from their birth in 1958. Both studies collect information on various behavioral, social, and psychological factors over the participants' life course.

Similarities among cohorts are easily recognized as being very valuable, because they allow researchers to effectively increase their sample size. Meanwhile, differences between the studies can easily be overlooked as very valuable sources of information. For example, the 58 Cohort and the similar 46 Cohort (the National Survey of Health and Development) show markedly different trajectories on obesity. Research shows the 58 Cohort has gained weight earlier and faster than the 46 Cohort.

OBESITY

Power reflected on the fact that the 58 Cohort and the 46 Cohort follow very different trajectories on obesity. Regarding diabetes risk, the duration of an individual's status of being overweight is directly correlated with one's glucose metabolism. Monitoring the onset of obesity is critical, but data on duration are lacking in most studies and would provide additional insight. For other mid-life risk factors, such as blood lipids, an adiposity trajectory of lower adiposity at earlier life stages followed by greater adiposity in mid-life has been associated with particularly unfavorable lipid profiles in adulthood. These distinctions highlight the need for the Network to clarify desired outcomes.

Caloric restriction has been shown to increase plasticity in the brain. Epel noted that obesity induced by visceral fat is distinctly different from lifestyle-induced obesity. The phenotype of visceral adiposity is actually a whole-body syndrome that likely starts early in life. The visceral fat phenotype is related to lower serotonin levels, depressed mood, reward dependencies, and a whole set of impulsivity-related traits. Functional brain systems of interest include executive function, cognitive function, and self-regulation.

Due to the relationship between visceral fat and these psychological traits, this sub-group of obese individuals is easier to identify and possibly easier to influence toward a change in behavior. In adults, behavioral indicators of this phenotype are similar to those characterized by reward dependency (i.e., food addiction). This sub-group of obese people scores poorly on self-reported measures of impulsive personality traits, such as the Barratt Impulsiveness Scale.

The waist-hip ratio is a more informative measure than body mass index (BMI) for this sub-group. The Network agreed that the addition of waist-hip ratio to ongoing youth studies would be useful.

Epel noted that, unsurprisingly, longer durations of obesity result in shorter telomeres.

There is a strong correlation between the phenotype of visceral fat and heightened psychosocial stress in adults. While researchers have, traditionally, not made the distinction regarding visceral fat (or waist-hip ratio) in youth studies, it is known that violence experienced by 5-9 year olds is highly correlated with obesity – and these children are known to suffer high psychosocial stress.

As body image norms have changed in parallel with the obesity epidemic, so too have the levels of anorexia in the United States. Very small numbers of adolescents lean toward extremely thin body types.

James Jackson's research has shown that overeating can have temporary protective features with regard to mental disease in adult black males but results in detrimental downstream effects later in life. These latent effects may be indicators of masked psychosocial stress during mid-life, when food was used to blunt depression.[30]

VULNERABILITIES

Early adversity leads to adult health vulnerabilities. Westerlund, et al. (2012) showed that adversity (both socioeconomic and psychosocial) in adolescence was associated with increased allostatic load among those reporting job strain in mid-life, indicating increased vulnerability to environmental stressors in adulthood.[31] Without intervention, early adversity is compounded by later life adversity, which worsens the trajectory for this sub-group.

A goal for the Network is to devise feasible intervention recommendations to be applied during adulthood.

Potential targets varied from those at the individual level (i.e., behavior, social engagement, psychological outlook, and physiology/pharmacology) to environmental targets (i.e., neighborhood design or workplace interventions). In addition to examining targets, the group considered the timing of potential interventions across the life course (i.e., youth, adults, mid-

[30] James S. Jackson, Katherine M. Knight, and Jane A. Rafferty, "Race and Unhealthy Behaviors: Chronic Stress, the HPA Axis, and Physical and Mental Health Disparities Over the Life Course," *American Journal of Public Health* 100, no. 5 (May 2010): 933–939.
[31] Hugo Westerlund, et al., "Social Adversity in Adolescence Increases the Physiological Vulnerability to Job Strain in Adulthood: A Prospective Population-Based Study," *PLoS ONE* 7, no. 4 (April 25, 2012): e35967.

life, and/or seniors). The most powerful interventions are those in which the change and timing are optimal.

In recent years, the body of evidence for considerable neuroplasticity in later life has grown. Power and Seeman presented examples of plasticity across the life course:

- Sommers, et al. (2012) showed that expansion of Medicaid led to increased longevity for seniors (≥ 65 years old).[32] It was noted that this study did not indicate improved quality of life for these individuals. Survival five years after diagnosis is a common metric, but study participants contended that quality was of greater significance than quantity of life. Conti cited a recent article in *Health Affairs* comparing cancer survival rates in Europe and the United States relative to their underlying financial investments.[33] The significantly higher investment in the United States appears to result in better cancer survival chances for Americans.
- In recent years, researchers have been touting the benefits of physical activity throughout the life course. There is moderately good evidence to support these claims. Nicklas, et al. (2005) showed improved physical function in older adults with knee osteoarthritis after an exercise intervention.[34,35]
- Psychosocial interventions have, generally, shown less success. Analysis on the ENRICHD (Enhancing Recovery in Coronary Heart Disease) study shows that lack of social support and depression are important predictors of morbidity and mortality in patients with coronary heart disease. Furthermore, patients who have suffered myocardial infarctions do not respond well to psychosocial interventions. This is another example where timing of the intervention contributes to their outcomes.

The group discussed the need for considering alternative models for psychosocial interventions – focusing not on patients but perhaps on prevention efforts as a more malleable point in the life course (before disease is manifest).[36]

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[32] Benjamin D. Sommers, Katherine Baicker, and Arnold M. Epstein, "Mortality and Access to Care Among Adults After State Medicaid Expansions", *The New England Journal of Medicine* 367 (13 September 2012):1025-1034. http://www.nejm.org/doi/pdf/10.1056/NEJMsa1202099.

[33] Tomas Philipson, et al., "An Analysis of Whether Higher Health Care Spending in the United States Versus Europe Is 'Worth It' in the Case of Cancer," *Health Affairs (Project Hope)* 31, no. 4 (April 2012): 667–675.

[34] Barbara J. Nicklas, et al., "Physical Function and Its Response to Exercise: Associations with Cytokine Gene Variation in Older Adults with Knee Osteoarthritis," *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 60, no. 10 (October 2005): 1292–1298.

[35] The NIA has a major on-going trial – Lifestyle Interventions and Independence for Elders (LIFE) Study – focused on this topic.

[36] The discussion of prevention efforts with a focus on resilience training in the last four chapters of Steven Southwick, Brett T. Litz, Dennis Charney, and Matthew J. Friedman, *Resilience and Mental Health: Challenges Across the Lifespan*. (2011) Cambridge, UK: Cambridge University Press, is particularly illuminating.

GAP ANALYSIS

Identification of gaps is a crucial step in the Network's roadmap. The group considered two broad approaches:

QUESTION ONE: IS THERE ANALYSIS TO BE DONE ON AVAILABLE DATA?

The Network has extensive experience designing, executing, and analyzing various studies and should capitalize on that expertise. Existing studies can be mined to provide greater value. Done well, comparative analysis between parallel studies can provide greater insight than data within a single study. Similarities may exist between studies that are not always explicitly clear. For example, Power and Seeman called attention to extensive parallels regarding the data fields in the MIDUS Study and the 1958 Birth Cohort Study:

Mid-life in the United States (MIDUS)	Mid-life in the 58 Cohort
-- Childhood	-- Childhood
-- SES	-- SES
-- Life events	-- Life events
-- Abuse	-- Abuse
-- Affection from parents	-- Affection from parents
-- Adulthood (longitudinal data)	-- Adulthood (longitudinal data)
-- Rich psychosocial	-- Rich psychosocial
-- Rich SES	-- Rich SES
-- Health	-- Health
-- Self-reports (longitudinal data available)	-- Self-reports (longitudinal data available)
-- Biomarkers	-- Biomarkers
-- Mortality	-- Mortality
-- CMS linkage – exploring for older adults	

The Network should consider possibilities for additional comparative studies such as those presented by Power and Seeman. Preliminary suggestions included examination of two cohorts from two different countries or across different age groups. Analysis of these cohorts in parallel may provide insights beyond what an individual study can offer. For example, the 58 Cohort may enhance understanding of the childhoods of MIDUS participants while the MIDUS study may forecast beyond mid-life for the 58 Cohort.

QUESTION TWO: WHAT IS MISSING THAT COULD BE ADDED TO EXISTING STUDIES, OR ARE NEW STUDIES REQUIRED?

Existing studies can be enhanced by the addition of a few measures (i.e., waist-hip ratio in youth studies). Within large cohort studies, smaller populations could be identified in which additional measures would add value. For example, in Power's work, sub-populations have been selected to examine methylation signatures. Within a small sub-group of 40 males, data have shown relationships between methylation and socioeconomic position.

In addition to the MIDUS Study, other large cohort studies exist that have followed participants into adulthood. These can be valuable sources for additional data for this group that can be included in comparative studies. Power and Seeman highlighted the Health and Retirement Study (HRS), the Multi-Ethnic Study of Atherosclerosis (MESA), the Coronary Artery Risk Development in Young Adults (CARDIA) study, the English Longitudinal Study of Ageing (ELSA), and the National Longitudinal Study of Adolescent Health (Add Health).

Smith and others have been promoting the addition of a retrospective collection of childhood data for the HRS.[37] In certain cases, research has shown that retrospective data can be highly accurate. For example, within the MIDUS study, there are twins and siblings whose memories of childhood socioeconomic status are highly concordant (0.98-0.99). For more socioemotional memory (i.e., childhood perception of the relationship with a parent), the alignment of recollection between twins or siblings is lower but still fairly high (0.6-0.7). There is evidence that ill individuals tend to 'remember' more adversity than well individuals.

When considering potential targets for adult intervention, Seeman recommended the Network consider possible requirements for new and/or different analytic tools and techniques (i.e., recursive partitioning over classic regression models or attribution theory). For example, based on current birth cohorts like Fragile Families, there may be value in examining childhood participants' perceptions in adulthood. Comparison between data collected during the event (in childhood) to perceptions/memories of those events in adulthood may provide insight on coping mechanisms for early adversity. Furthermore, adult attachment literature may shed light on methods by which adults persevere through adversity. Adult care of a child is known to be crucial to the success of the child through the life course. What is unknown is how that care is important. Therefore, another potential research avenue may be to understand the biological changes, if any, in adults who have overcome early adversity. This work could be performed in non-human primates.

Too few studies gather data on both children and parents. The Network agreed that long-term goals include further exploitation of the current birth cohorts. The study should take advantage of access to mothers, fathers, or other caregivers. Furthermore, extensive studies on parent-child relationships are perfectly suited for animal studies both in rodents and non-human primates.

[37] J.P. Smith, "Reconstructing Childhood Health Histories." *Demography* 46, no. 2 (May 2009): 387–403.

IV. PERSISTENT RISK MECHANISMS

Frances Champagne, Ph.D., Columbia University
Gabriella Conti, Ph.D., University of Chicago

The Network examined the dynamics of gene expression and epigenetics. These biological markers may play a role in "memorializing" early adversity as well as provide clues to delineating mechanisms tied to very specific outcomes.

MAIN POINTS

The Suomi lab observed macaques raised in various mother-child situations. The mother-reared control infants remained with their biological mothers, as usual. The test animals were individually raised in a nursery for 37 days after which they were transitioned to adverse environments. The peer-reared animals lived in groups of four monkeys close in age. The surrogate peer-reared animals lived alone with a "surrogate" most of the day and were grouped with three peers for 2 hours per day.

Early adversity has persistent effects on gene expression. Conti presented microarrays analyzed at 4 months that indicated up-regulation of 85 genes and down-regulation of 164 genes in the surrogate peer-reared populations. The results were similar for both groups not raised by their biological mothers. Additionally, these results overlap with those discovered in the Chicago Health, Aging, and Social Relations Study (CHASRS), in which perceived social isolation in humans led to changes in gene expression similar to those of the nursery-reared monkeys.

Early adversity has persistent effects on neurobehavioral, cognitive, and health outcomes. After age 1, macaques raised in these alternative environments were returned to typical living arrangements including a regular social structure. Conti showed that males of the surrogate peer-reared population exhibit a significantly higher probability of developing illness, both physical and mental.[38]

Several behavioral mechanisms of persistent risk have been identified. These range from diminished educational attainment to personality functions such as reduced delayed discounting, impulsivity, vigilance, suspicion, biases in social perception, and high levels of aggressiveness. These were addressed in Champagne and Conti's presentation. In short, personality traits (i.e., social dominance, agreeableness, conscientiousness, etc.) and intelligence (i.e., fluid intelligence and crystallized intelligence) change throughout the life course regardless of adversity. When considering intervention strategies, awareness of these factors is critical.

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[38] Gabriella Conti, et al., "Primate Evidence on the Late Health Effects of Early-life Adversity," *Proceedings of the National Academy of Sciences* (May 21, 2012), http://www.pnas.org/content/early/2012/05/18/1205340109.

Conti described a lifecycle developmental model linking early- to late-life, with a focus on mechanisms (i.e., biological, behavioral, etc.). In short, outcomes are affected by specific inputs (i.e., early adversity) and changes in investment (i.e., contribution of the parent). Throughout the life course, many events occur that will impact outcomes. Levels of that accumulated impact are moderated by the investment made to change that trajectory.

Conti highlighted the importance of the interface between social environments and biological function. In reaction to changes in the environment, organisms will undergo physiological changes (i.e., gene expression) that will have downstream impacts on overall health. Greater understanding of this relationship is critical.

Furthermore, the interface between animal systems and those of humans is one in which significant parallels can be drawn. Conti noted that knowledge gained through understanding biological mechanisms in animals is transferrable to those mechanisms in humans. For example, data from peer-reared macaques are mirrored in human children raised in orphanages.

GENE EXPRESSION

Given that early adversity leads to adult outcomes, it is valuable to understand the role of gene expression in that relationship. As shown by Conti, early adversity is known to alter gene expression. Less understood is whether there is a causal relationship between that expression and changes in outcomes. Many questions regarding that relationship remain unanswered:

- Which outcomes are affected by gene expression?
- In which tissue types is gene expression being analyzed?
- Should specific target genes be examined or is global gene expression analysis more informative?

Champagne theorized that mediation and path analyses in animal studies are not fully maximized yet by the field. In addition, targeted reversal of gene expression can be approached using pharmacological targeting.

As an example of this reversibility, increasing or decreasing DNA methylation changes levels of the glucocorticoid receptor in the rat hippocampus resulting in changes in stress response. In this experiment, animals with early adversity were indistinguishable from controls.

Expression levels of targeted genes can be increased or decreased using viral vector delivery and control mechanisms. For example, maternal effects on estrogen receptor levels lead to specific social and reproductive outcomes. In animals that received low maternal care, levels of estrogen receptor are increased using injection of viral vector into the mouse brain, which results in correction of their social and reproductive trajectories.

Recent research has focused on identifying factors that moderate the impact of early adversity. Elliot used a social defeat model in which adult mice are abused by larger, dominant animals to

examine methylation of *Crf* (a marker of stress) in the brain. Results led to the categorization into resilient and susceptible mice. Interestingly, Nestler's lab has demonstrated that socially defeated males can pass this susceptibility to offspring.[39]

Researchers would like to understand how stable the gene expression result is over time. However, usually numerous variables contribute to these expression phenotypes and their stable expression. Champagne showed that offspring of high licking-grooming mothers show significantly higher expression of estrogen receptor than offspring of low licking-grooming mothers. This difference is maintained beyond the weaning stage and into adulthood.[40]

Tissue-specific epigenetic effects, including DNA methylation, are particularly challenging to study given the current model limitations. While a great effort is ongoing examining methylation, the relationship between methylation and gene expression remains unclear. The Network noted three papers of particular interest:

- Angela M. Devlin, et al., "Prenatal Exposure to Maternal Depressed Mood and the MTHFR C677T Variant Affect SLC6A4 Methylation in Infants at Birth," *PLoS ONE* 5, no. 8 (August 16, 2010): e12201.
- Marinus H. van IJzendoorn, et al., "Methylation Matters: Interaction Between Methylation Density and 5HTT Genotype Predicts Unresolved Loss or Trauma," *Biological Psychiatry* 68, no. 5 (September 1, 2010): 405–407.
- Erin L. Kinnally, et al., "Epigenetic regulation of serotonin transporter expression and behavior in infant rhesus macaques," *Genes Brain Behav.* 2010 Aug; 9(6):575-82.

REVERSIBILITY IN RODENTS

Adding enrichment items to the cages stimulates rodents. As reviewed by Fred Gage, equipment for the cages is categorized to three types:

- Exercise
- Social and Sensory Stimulation
- Exposure to novelty

Champagne added that rats are highly social while mice tend to be more territorial and aggressive. Another caveat is that most studies are performed in males.

[39] David M. Dietz, et al., "Paternal Transmission of Stress-induced Pathologies," *Biological Psychiatry* 70, no. 5 (September 1, 2011): 408–414.
[40] Ian C. G. Weaver, et al., "Epigenetic Programming by Maternal Behavior," *Nature Neuroscience* 7, no. 8 (2004): 847–854.

Overall, environmental enrichment reverses the effects of maternal separation on stress reactivity.[41] There are examples where interventions have compensated for damage and where interventions reverse defects acquired during early adversity. She explained that low licking-grooming mothers produce pups that become low licking-grooming mothers only when the environments remain stable. Pups of low licking-grooming mothers can be converted to high licking-grooming mothers by changing the environment. The newly acquired high licking-grooming phenotype will be inherited by their offspring.[42]

Several additional papers were mentioned in this context:

- D.D. Francis, J. Diorio, P.M. Plotsky, M.J. Meaney, "Environmental enrichment reverses the effects of maternal separation on stress reactivity." *J Neurosci*. (2002) 22(18):7840-3.
- A. Fischer, F. Sananbenesi, X. Wang, M. Dobbin, L.H. Tsai, "Recovery of learning and memory is associated with chromatin remodelling." *Nature*. (2007) 447(7141):178-82.
- I.C. Weaver, F.A. Champagne, S.E. Brown, S. Dymov, S. Sharma, M.J. Meaney, M. Szyf, "Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life." *J Neurosci.* (2005) 25(47):11045-54.

CONCLUDING REMARKS

Members of the group noted that many additional questions that could not be discussed in detail remain to be answered:

- Can blood/peripheral gene expression patterns be used to predict those in the central nervous system (CNS)?
- Does early-life adversity alter gene expression similarly in peripheral and CNS tissues?
- Can peripheral gene expression patterns be used as a biomarker of CNS effects?

Several questions that were discussed during the meeting either did not generate consensus to be taken further or were considered too complex and out of scope for the Network in the immediate future. The group may revisit these issues at a later time point.

[41] Darlene D. Francis, et al., "Environmental Enrichment Reverses the Effects of Maternal Separation on Stress Reactivity," *The Journal of Neuroscience* 22, no. 18 (September 15, 2002): 7840–7843.
[42] Frances A. Champagne and Michael J. Meaney, "Transgenerational Effects of Social Environment on Variations in Maternal Care and Behavioral Response to Novelty," *Behavioral Neuroscience* 121, no. 6 (December 2007): 1353–1363.

ADDITIONAL CONSIDERATIONS FOR THE NETWORK

1. A possible tool for better understanding of the pathways between early adversity and adult outcomes may be the examination of life histories and development of taxonomies in currently available data sets. It is well understood that successful interventions will work for specific participants in an experimental group. Of greater value for the field may be insight on why given interventions have succeeded or failed in given populations. Taxonomies of life histories may represent a doorway to that insight. For example, given that the highly reactive phenotype described by Boyce is likely susceptible to a broad range of environmental inputs (both adverse and favorable), there is value in constructing a taxonomy of these individuals. And because these individuals are likely similarly susceptible to interventions, these taxonomies will inform potential intervention strategies en large. This methodology provides the framework to simultaneously test both the taxonomy approach and the intervention strategy.

2. Similar to life history taxonomies, Apgar scores are another area of untapped clinical data. Recent studies examining correlations of biology and behaviors to the Apgar score appear to support its value in a broad sense. Furthermore, the scores represent data that can be added to existing cohorts or subsets of cohorts. The Network would be well served by researching the logistics and resources required to launch a pilot study.

3. As discussed earlier, establishing definitions for health and well-being is critical to pursuing projects that aim to understand profiles of healthy individuals over ill individuals. Champagne and Suomi highlighted requirements of presence and/or maintenance of human health, and not simply the absence of poor health. Singer cautioned the group about the complexities of required cultural considerations. The group did not reach consensus regarding whether or not it is worthwhile to engage in such efforts.

4. A factor that was left out of the meeting discussions is the role of gut bacteria in the life course and the interplay to all the other systems the Network has discussed. Researchers are learning that the current host-parasite paradigm is inadequate without incorporation and understanding of the significant role of gut bacteria. Spotts noted two recent studies reporting links of the microbiome to obesity. Huh, et al. (2012) reported that infants delivered by caesarean section had an increased risk for childhood obesity due to exposure to maternal bacteria.[43] And Trasande, et al. (2012) showed that exposure to antibiotics during the first 6 months of life is associated with consistent

[43] Susanna Y. Huh, et al., "Delivery by Caesarean Section and Risk of Obesity in Preschool Age Children: a Prospective Cohort Study," *Archives of Disease in Childhood* 97, no. 7 (July 1, 2012): 610–616.

increases in body mass from 10 to 38 months.[44] The Network remained, however, divided regarding the feasibility of pursuit of microbiome data as a potential project.

Overall, challenges are driven by accumulation of behavioral and biological (including epigenetic) data and by identifying meaningful correlations of data elements. Study design challenges to address the vast amounts of data need to be met. Due to its multidisciplinary nature, the Network is an ideal forum to start pursuing these goals.

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[44] L. Trasande, et al., "Infant Antibiotic Exposures and Early-life Body Mass," *International Journal of Obesity* (August 21, 2012), http://www.nature.com/ijo/journal/vaop/ncurrent/abs/ijo2012132a.html.

APPENDIX 1: PRE-READ MATERIALS

Cole, Steve, Louise Hawkley, Jesusa Arevalo, Caroline Sung, Robert Rose, and John Cacioppo. "Social Regulation of Gene Expression in Human Leukocytes." *Genome Biology* 8, no. 9 (September 13, 2007): R189.

Conti, Gabriella, Christopher Hansman, James J. Heckman, Matthew F. X. Novak, Angela Ruggiero, and Stephen J. Suomi. "Primate Evidence on the Late Health Effects of Early-life Adversity." *Proceedings of the National Academy of Sciences* (May 21, 2012). http://www.pnas.org/content/early/2012/05/18/1205340109.

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APPENDIX 2: WORKSHOP AGENDA

AN ARMATURE FOR OUR DISCUSSION OF THE REVERSIBILITY OF RISK MECHANISMS THAT PERSIST LONG AFTER EARLY ADVERSE EXPERIENCE

September 10-11, 2012

Background and focus:

The links between early pre-natal and post-natal adverse experience and physical and mental health in late adulthood are becoming well established. There is increasing evidence that important adverse experience may begin at least a generation before the birth of affected individuals: experience in the early childhood—in animals and in humans—influences the quality of their parenting and thus has an effect more than a generation after it occurs. Recent research suggests mechanisms that account for the persistence of these risk across many decades in the life the individual: personality processes, impacts or organ systems from the HPA axis to the limbic system to the forebrain, telomere structure and function as well gene expression profiles. Animal and human studies suggest that some of these risk persistence mechanisms are malleable; preventive interventions well into adult life may blunt their negative effect on trajectories of health in aging individuals.

The purpose of our Network is to address two main questions:

1) **How can we best develop a program of research that tests feasible preventive interventions that might correct or compensate for risk persistence mechanisms influenced or induced by early adversity?** Can this preventive intervention research be designed to shed further light on the mechanisms themselves? There are several current efforts to develop preventive intervention programs drawing on what is known about the impact of early adversity. *Our effort is distinguished by its emphasis on preventive interventions in mid-life or after.* While there is no consensus on the temporal boundaries or characteristics of "mid-life" we hope a by-product of our work together might improve our psychobiological understanding of this middle game in adult development. As a consequence, we might delineate more rational temporal boundaries for its beginning and ending as well as clarify the malleability of persistence risk mechanisms within those boundaries.

2) **How can we marshal a trans-disciplinary approach to estimate the impact of such a program of risk reduction?** For much simpler areas of study, computations of attributable risk can serve as serviceable guides to the expected impact of successful interventions. Our effort is complicated by the fact that many adverse circumstances, some correlated with each other, are under consideration; moreover they exert their effect through many intermediate mechanisms. Further, both the immediate impact of adversity and the persistence of risk mechanisms are moderated by a number of naturally occurring variations in the person and in the immediately surrounding social context. Nonetheless, *it would be difficult to attract financial support for a major effort at mid-life prevention (or intervention at any life stage) without a rational estimate not only of its feasibility but also of the likely magnitude of its impact.*

Proposed format of the meeting:

During the course of our phone calls there was universal agreement that prepared presentations would deaden discussion. All participants want to get down to brass tacks quickly: to explore collaboratively the evidence related to our work, to identify questions that can be addressed from available data and to formulate conceptions of research programs that will have the highest yield. Thus, for our first meeting, we are proposing a highly collaborative model. The structure of our agenda flows naturally from our phone conversations with all of you. It makes fundamental sense that as authors of this agenda all of us have a chance to lead a portion of the discussion on the full day of our meeting on September 10th and on the subsequent half-day on the 11th.

Monday, September 10

8:45-9:00. **Brief introductions to the meeting**: Richard Suzman, Steve Suomi, David Reiss, and Erica Spotts

9-10:45 focusing **our lens on early adversity**.

Discussion leaders: Brooke and Temi, *convener*

Given our increasing knowledge of long-term effects, what early adversities should be the focus of our collaborative work? What modifiers of their initial impact are central to our work? Can these adversities be grouped by common mechanisms by which they become "embedded" in long term psychological and biological risk mechanisms? How early in developmental time should we travel (e.g. to the childhoods of parents)? How late? Does it make sense to include widespread adversities of early adulthood such as unemployment and military combat or are these to be regarded either a moderators or as amplifiers of early adversity? How can we make use of existing human or animal data sets that permit more exact delineation of sensitive periods in individual development for the maximum impact of specific adversities (e.g. studies of the long term effects of famines with clear beginning and end, 9/11, monocular occlusion, cochlear implants, adoption studies, rodent licking and grooming, macaque peer and surrogate rearing)?

10:45-11 Break

11-12 Opening **a window of plasticity for persistent risk mechanisms**.

Discussion leaders: Bruce and Elissa, *convener* (through electronic connection).

In our phone conversation and brief literature review we have considered monocular occlusion as a model system for early adversity and its reversible brain changes but where do we need to go to understand the reversibility of other brain consequences of severe early adversity? Given increasing evidence for plasticity in key brain areas what program of research might translate these findings into human trials and how might these trials be designed to further understand adult brain plasticity? Along these lines, does current evidence suggest intervention strategies that first, restore key brain areas to a level of plasticity that characterizes younger individuals, and then—as a second step-- provide critical training or other behavioral intervention that capitalizes on that renewed plasticity? Telomere length and function are also sensitive to prolonged stress and early indications are that telomere function can be restored by diet, exercise and stress reduction (as in meditation). Where are we now in understanding the links among the HPA axis, the limbic system and telomere function? How can we

focus such integration on mid-life trials for restoration of function? (Because of the relative brevity of this session we may consider other risk persistence mechanisms--such as reduced immunocompetence, chronic inflammation and personality patterns--in other sessions.)

12-1:15 Lunch break

1:15-2:45 Focusing on the most salient outcomes of early adversity in mid-life and beyond.

Discussion leaders: Teresa, *convener* and Chris

The improvement in unfavorable health trajectories in mid-life and beyond is the motive of our network and the reason it has already attracted the strong interest of NIA and possibly other funding agencies. The range of long-term outcomes of early adversity is broad. Of most interest to BSR/NIA may be general medical health and well being, emotional and behavioral self-regulation, optimism, economic planning and security, cognitive reserve, satisfying and productive social engagement and the capacity to care for an ill or demented spouse. Impairments in most of these domains have already been linked to severe early adversity. In terms of research planning is their any strategic advantage to extending this set of outcomes, to selecting some over others or in grouping them? Are there variations at mid-life or beyond among individuals, families or social settings that mitigate the long-term effects of early adversity on these outcomes? In what way do these "naturally-occurring" differences provide clues for preventive intervention or even for therapeutic intervention after negative outcomes are fully apparent? In what ways can we use a clearer definition of outcomes to specify early "markers" and the timing of when they should be added to existing longitudinal studies of children and adolescents (e.g. markers of chronic inflammation, assessments of cardiovascular function etc)?

2:45-3:00 Break

3:15-4:45 Persistent risk mechanisms.

Discussion leaders: Frances and Gabriella, *convener*

In the session on "windows of plasticity" we will have already considered three domains of persistent risk factors: selected brain functions and their plasticity, the HPA axis and telomere function; it is possible we might want to return to these in this session. However, this session might give us an opportunity to examine other domains, notably the dynamics of genes expression and the role it may play "memorializing" early adversity and providing clues to delineating mechanisms that are tied to very specific outcomes from cognitive function to maternal competence. With respect to gene expression dynamics there are several potential questions to consider. We know that early adversity is associated with expression of many genes but how clear are we that these changes mediate the impact of early adversity on outcomes? In the cases where a mediating role has been demonstrated what individual differences might, from the outset, mitigate the impact of adversity of these profiles of gene expression? Once established, are gene expression profiles enduring and can they be reversed through pharmacologic or behavioral interventions? What do we know about the links between gene expression profiles obtained from peripheral tissue and those in the central nervous system?

This session may also give us a chance to consider behavioral mechanisms of persistent risk. These range from diminished educational attainment to personality functions such as reduced delayed discounting, impulsivity, vigilance, suspicion, biases in social perception and high levels of aggressiveness. What do we know about these mechanisms, their persistence, and connections with other risk persistent mechanisms and their malleability? Might interventions aimed at these behavioral consequences for early adversity also affect other risk persistent mechanisms?

6-8 pm Continuing discussion at dinner

Tuesday, September 11

9-10:15. Synthesizing main themes. Discussion leaders: Tom, *convener* and Burt.

In reviewing Monday's work three angles of regard seem plausible. First, might be a focus on the most promising lines of research on mechanisms of risk persistence and their malleability. Second, would be a brief review of what we have learned about other comparable efforts to synthesize data on early risk and how best to coordinate our effort with these other initiatives. For example Gabriella and Burt are co-chairing another initial effort on this general topic based in the Health Inequalities Network at the University of Chicago. Third, and most time urgent, what funding strategies might be elaborated now to capitalize on promising findings and assure maximum integration of efforts in this field. We might consider a "strategy" of funding that would consider a full range of scientific activities from conferences, special research training, and funded scientific network as well as pilot and more large-scale research.

10:15-10:30 Break

10:30 – 1 Next steps, Steve and David

Integrating all that has come before this discussion will focus more concretely on the next steps for our Network. This will include planning for our mid-winter meeting, considering the value of consultants to our work, specific plans for linking with companion efforts and a discussion of mechanism for continuing the work of the network including an application to NIA for one of the special grants now being awarded for supporting networks.

This discussion period includes a **working lunch from 12-1.**

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