NETWORK ON REVERSIBILITY:

MID-LIFE REVERSIBILITY OF EARLY ESTABLISHED BIOBEHAVIORAL RISK FACTORS

Bethesda, Maryland
February 26-27, 2013

WORKSHOP SUMMARY

Division of Behavioral and Social Research
National Institute on Aging
National Institutes of Health

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ABBREVIATIONS AND ACRONYMS

ACRONYM	DEFINITION
AMPAR	ionotropic glutamate receptor that can be activated by the artificial glutamate analog AMPA (alpha-amino-3-hyroxy-5-methyl-4-isoxazolepropionic acid)
ANS	autonomic nervous system
BDNF	brain derived neurotrophic factor
BSC	biological sensitivity to context
BSR	Division of Behavioral and Social Research
CA3	*Cornu Ammonis* 3 (a region of the hippocampus)
CHD	coronary heart disease
COMT	catechol-o-methyl transferase
CRH	corticotropin-releasing hormone
DNA	deoxyribonucleic acid
DS	differential susceptibility
ESRC	Economic and Social Research Council
fMRI	functional magnetic resonance imaging
FP7	Seventh Framework Programme (of the European Union)
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenal axis
IL	interleukin
IQ	intelligence quotient
MAO	monoamine oxidase
MR	mother reared
NIA	National Institute on Aging
NIH	National Institutes of Health
NMDAR	N-methyl d-aspartate receptor
Oxtr	oxytocin receptor (gene)
PFC	prefrontal cortex
PPAR	peroxisome proliferator-activated receptor
PR	peer reared
PTSD	post traumatic stress disorder
RCT	randomized controlled trial
RXRA	Retinoic X receptor alpha
SES	socioeconomic status
SPR	surrogate peer reared
SSRI	selective serotonin reuptake inhibitor
T_3	triiodothyronine

EXECUTIVE SUMMARY

Background and Mission of This Network

Links between early prenatal and postnatal adverse experiences and physical and mental health in late adulthood have become well established. There is, furthermore, increasing evidence that important adverse experiences may occur more than a generation before the birth of affected individuals. Early childhood experiences in animals and in humans influence the quality of their parenting and thus have an effect across several generations.

Recent research has suggested mechanisms that might account for the persistence of risk of negative health outcomes across many decades. Specifically, personality processes, hypothalamic-pituitary-adrenal axis (HPA axis) and sympathetic/parasympathetic nervous system regulation, telomere structure and function, and epigenetic changes have all been implicated as potential risk persistence mechanisms. Animal and human studies suggest that some of these risk persistence mechanisms are malleable. In fact, preventive interventions well into adult life may blunt or even reverse their negative effect on trajectories of health in aging individuals. In September 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 with the following goals:

1. Develop a program of research that tests feasible preventive interventions that might counter or compensate for risk persistence mechanisms influenced or induced by early adversity. Ideally, design preventive intervention research that can shed further light on the underlying mechanisms. Several current efforts to develop preventive intervention programs draw on recent advances in our understanding of the impact of early adversity. The present effort distinguishes itself by its emphasis on preventive interventions in midlife or after.

2. Marshal a transdisciplinary approach to estimate the likely impact of such a program. For much simpler areas of study, computations of population attributable risk can serve as guides to the expected impact of successful interventions. The present 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, and the risk is moderated by many circumstances across development.

During the first meeting of this Network in September of 2012, participants identified critical or sensitive periods and the concept of differential susceptibility (DS) as two areas that deserved further attention. The “critical period” concept may help explain why early adversity has such a large effect on subsequent development but also explain why earlier rather than later interventions have seemed most effective. Recent research on reopening early critical periods is now highly germane to the mission of this network. “Differential susceptibility” is a recent addition to concepts used to characterize differences among individuals in their response to adversity. Unlike previous concepts, this one posits that the same attributes that make an individual particularly sensitive to adversity may also make him or her more responsive to interventions design to offset the effects of adversity. Thus, the current meeting utilized these two concepts as scaffolds for discussions regarding research designs and data that are currently

missing and that would enable researchers to better understand risk pathways, identify malleable mechanisms, and, ultimately, design effective interventions in midlife.

Critical or Sensitive Periods

The participants reviewed a wide range of available research data from classical studies on filial imprinting to human longitudinal studies and molecular work in model animals. They agreed that the psychobiology of sensitive periods is very well established, and that efforts to re-open these periods are in their beginnings, but show very promising initial results.

The challenge for the Network is now to determine under which circumstances the principles and mechanisms identified in research on critical and sensitive periods can be applied to much broader concepts of early childhood adversity. The participants acknowledged the tremendous challenge that this transition will imply. Stringent definitions and research designs will help to make sure that results from different studies can be used to validate each other.

Differential Susceptibility

The concept of DS is less firmly established than critical or sensitive periods. While participants found the concept to be a very helpful basis for their discussions, they also identified several areas for improvement that future research should address, including the development of a more stringent statistical definition. In particular, the distinction between differential susceptibility and inherited sensitivity (also referred to as “diathesis-stress model”) has to be made more carefully.

The participants started to design experimental paradigms that would be able to test differential susceptibility in a standardized way. For example, they advocated for the use of strictly exogenous environmental variables, such as the impact of the great recession or experimental variation in rearing environments that are possible with non-human primates. They also recommended outcomes that contain measurable variables, such as the metabolic syndrome index, because those can be transferred to animal studies most easily. Identifying susceptibility factors other than genotypes that are stable over time will be a challenge for future research.

A great promise of this research lies in the possibility that stable factors that underlie DS may be used to determine which individuals would receive the greatest benefit from interventions at midlife and beyond.

Discussions

With the concepts of sensitive periods and differential susceptibility as a starting point, the workshop participants identified a number of critical issues that have not yet been addressed by research in a stringent and systematic way. These issues include the following:

Individual differences. Factors that determine individual differences are not necessarily the same as those that determine risk pathways and predict intervention success. Which individual differences are stable over time (e.g., genotypes)? Is it feasible to assume that these differences can predict intervention outcomes?

Critical/sensitive periods and windows of opportunity. When do these periods occur naturally, and can they be induced? Which roles are played by hormonal factors or pharmacotherapy?

Time-shortening measures. How can this Network use existing data/materials and ongoing studies to design research endeavors on pathways and interventions that will produce results in the near future? Can the adoption design be useful to save time? Can this Network expand the Experience Corps Study?

Pilot studies. How can the Network combine existing data and resources from different methods (e.g., observational studies and randomized trials combined with animal model data) to design a number of pilots that can be conducted within a reasonable amount of time?

Toolbox development. Can the participants conceptualize a set of tools that will be useful to the field to standardize efforts when addressing these questions?

Tempo and velocity. The timing (i.e., tempo) of events is as important as the speed (i.e., velocity) with which changes occur. It is important to consider the importance of both of these factors, which sometimes have been conflated in the past.

Statistics. Participants noted the importance of combining data from different approaches, such as observational studies, randomized controlled trials (RCTs), and animal model work. Many of the concepts around differential susceptibility and related models are still too vaguely defined. How can the Network contribute to more strictly defined definitions?

Next Steps

In preparation for the next Network meeting, the participants will identify concrete research questions, pilot studies, and intervention designs that have the potential to answer the questions that are central to this Network. For practical purposes, the group divided into two subgroups that will address the closely related issues of **Pathways** and **Interventions**.

Pathways

Any successful attempt to reverse and not just ameliorate outcomes in adulthood will likely require more knowledge of the underlying, malleable pathways and mechanisms that lead to increased risk for disease. A pessimistic view of these pathways suggests that the underlying biological processes may be so firmly established by adulthood that there is no hope of reversal. A less pessimistic view suggests that, at the molecular level, risk processes may be more malleable than they appear. Furthermore, the natural occurrence of re-opening of critical periods, for example during the start of primiparous motherhood (i.e., having given birth to the first offspring), may provide opportunities for interventions. An understanding of the underlying mechanisms may elucidate concrete strategies to re-open the window of opportunity that once was present during a sensitive period and hence allow for the potential of a successful intervention.

The **Pathways** group will address the following questions:

- Which additional information is necessary to understand the mechanisms linking childhood and major health outcomes? What are the best measurements to describe and define these pathways?
- How many of these pathways can be identified?

- Do the pathways correlate with each other, and how can they be categorized? The fewer or more interdependent they are, the more valuable they will be for intervention design.
- How does knowledge of pathways improve how population attributable risk is calculated?
- Are the pathways constant across cohorts?
- Which pathways are malleable and/or reversible?

Interventions

Reviews of current research and intervention strategies by other initiatives revealed a strong focus on very early interventions, when the pace of development is still high and a substantial and lasting change in the trajectory for risk of negative health outcomes can be achieved. However, for the NIA—and for the billions of individuals at risk who may never have an opportunity for early intervention—the critical question is whether successful interventions can still be designed and executed in midlife and beyond. Research on such interventions will be based on knowledge about risk pathways described above. In addition to providing adult human health measures that will be of great relevance for an aging population, this research also has great potential to inform researchers about the nature of the underlying risk pathways.

The **Interventions** group will discuss the following issues:

- What evidence is relevant for estimating the likely effects of various preventive interventions? Which outcomes have the broadest implications for public health?
- Which characteristics of individuals might predict success?
- Are there common risk factors that are influenced by different types of interventions?
- What is the best timing in development for interventions?
- Do the interventions aim at reversal of the pathway, or do they just compensate for the increase in risk? How can preventive intervention research shed light on the mechanisms?

The next meeting in London in October of 2013 will include results from the Pathways and Intervention groups and further discuss which research avenues have the most potential to further the understanding of reversibility of early life risk factors later in life.

# # #

"It's never too late to have a happy childhood."
- Tom Robbins[1]

WORKSHOP SUMMARY

Progress Review and Update

Lisbeth Nielsen and Richard Suzman (BSR, NIA, NIH)

Nielsen and Suzman kicked off this second workshop of the Reversibility Network with a recap of the Network's background and current status. They reviewed a presentation recently given by Nielsen, Reiss, and Suomi at the December 2012 NIA retreat, at which NIA leaders expressed their continuing support of research on reversibility.

Nielsen reminded the group that known long-lasting effects of adverse early environments on trajectories of physical and psychological aging initially motivated this Network. There is a solid body of research in animals and humans documenting the deleterious health effects of early disadvantages, for example:

- Among male physicians with high adulthood socioeconomic status (SES), those with low childhood SES are at increased risk for coronary heart disease (CHD) before age 50 years.[2]
- Poor childhood physical and mental health lead to lower adult income and less social mobility.[3]
- Adverse parent-offspring relationships in rats lead to a heightened physiological stress response.[4]
- Early social deprivation or stress leads to heightened risk of illness in midlife.[5]

Evidence is emerging that the underlying risk mechanisms might be reversible, suggesting the possibility for successful interventions. Interventions in midlife and later are of great relevance for the NIA. The research agenda for this network can, therefore, be summarized broadly as follows:

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[1] In: Still Life With Woodpecker (1980). USA, Bantam (ISBN 0-553-27093-1).

[2] Kittleson, M.M., Meoni, L.A., Wang, N.-Y., Chu, A.Y., Ford, D.E., and Klag, M.J. (2006). Association of childhood socioeconomic status with subsequent coronary heart disease in physicians. Arch. Intern. Med. *166*, 2356–2361.

[3] Goodman, A., Joyce, R., and Smith, J.P. (2011). The long shadow cast by childhood physical and mental problems on adult life. Proc. Natl. Acad. Sci. U.S.A. *108*, 6032–6037.

[4] Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., Sharma, S., Pearson, D., Plotsky, P.M., and Meaney, M.J. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science *277*, 1659–1662.

[5] Danese, A., Moffitt, T.E., Harrington, H., Milne, B.J., Polanczyk, G., Pariante, C.M., Poulton, R., and Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch. Pediatr. Adolesc. Med. *163*, 1135–1143; Conti, G., Hansman, C., Heckman, J.J., Novak, M.F.X., Ruggiero, A., and Suomi, S.J. (2012). Primate evidence on the late health effects of early-life adversity. Proc. Natl. Acad. Sci. U.S.A. *109*, 8866–8871.

- **Identify biobehavioral risk mechanisms.** Find the causes for the persistent effect of childhood environmental adversity on trajectories of aging.
- **Develop novel strategies for reversing risk of negative health outcomes in later life.** Identify behavioral interventions in midlife that might reverse this risk, and determine their impact on the biobehavioral mechanisms that underlie the negative health outcome.

During the first workshop of the Network in September 2012, the participants identified a number of challenges, including the need to better understand individual differences in response to adversity and intervention. They further emphasized the importance of building more parallel animal-human analogue studies. In addition, the participants started to identify fruitful research directions. For example, they advocated for the utilization of existing datasets to identify individuals at risk and to pinpoint adverse and favorable environmental conditions. Finally, they suggested novel experimental approaches to open windows of plasticity in persistent risk mechanisms in midlife and beyond:

- Better clarify early sensitive periods
- Identify mitigating circumstances in both childhood and adulthood
- Relate effects of early adversity to biological profiles
- Improve methods of identifying both positive and negative cascades initiated early in development

One possible strategy to move this research agenda forward involves the use of knowledge about early adversity to identify adults that are at particular risk. This would enable the researchers to identify precisely the circumstances that mitigate or exacerbate the effects of early adversity. Approaches to implement this strategy include combining data from existing cohorts to:

Another recommendation was to combine early-life and later-life data within and across cohorts to clarify the importance of two-hit or multiple-hit models where the impact of early adversity is manifest only when adversity in later life occurs.

A second possible strategy builds on human and animal studies aimed specifically at exploring the malleability of risk persistence mechanisms to test the feasibility of interventions. Possible approaches include:

- Explore the malleability of biobehavioral systems in adult animals
- Use existing animal data to distinguish whether an intervention reverses or compensates for adversity-induced risk
- Conduct experimental studies in humans to explore the plasticity of biobehavioral and psychological systems associated with early adversity

These recommendations informed plans for an NIA request for proposals, approved by the National Advisory Council on Aging at its January 2013 meeting. Nielsen and Suzman further noted that the NIA has earmarked funding for high-priority research networks, with a focus on multidisciplinary approaches. The 2008 BSR review suggested that supporting networks or training had the potential to yield high dividends. It is, however, often difficult for investigators to engage in such efforts, because they are difficult to host in standard grant mechanisms.

Reversibility remains a top priority because of the shifting demographics in the United States toward an older population.[6] Furthermore, the life expectancy in the United States has recently fallen behind other countries for reasons that are not yet understood.[7] Risk factors acquired early in life that influence morbidity and mortality in midlife and beyond are therefore of great relevance to the NIA's mission. Suzman concluded his introduction by noting that the Network is now a bi-national initiative, because it is co-funded by the Economic and Social Research Council (ESRC) of the United Kingdom.

Reiss provided a brief review of the scientific questions that were addressed during the September 2012 workshop. The task for the Network is now to delineate risk persistence mechanisms and to identify the factors that tie exposures to outcomes. Whether or not these mechanisms are malleable is a question that is of utmost importance for the mission of this Network.

Reiss encouraged the participants to work toward the identification of underlying basic principles that funders must take into account when conceptualizing new, effective research programs. The main task for this meeting was to identify the critical questions, rather than look for answers.

Reiss added that at the September Network meeting, there was consensus that two areas are important: "specificity of time" and "individual differences."

The discussions around the specificity of time centered on the concept of critical or sensitive periods. The current workshop therefore dedicated a considerable amount of time to a more detailed review of the critical or sensitive period concept and extended these discussions by asking which of these periods might become re-opened later during life, either naturally or experimentally.

Regarding individual differences, previous discussions of the scientific literature suggested that no matter how severe adverse events are, there are always resilient individuals who do not seem to be affected by negative outcomes. Participants raised the possibility that the individuals who are most adversely affected may be most susceptible to interventions. The concept of "differential susceptibility" might then prove useful to identify and characterize these individuals using stable markers. If proven correct, then this assumption may open the door to very effective interventions in the ideal target population. The current challenge of the Network was to start to elucidate whether and how this assumption could be supported by science.

Session 1: Critical and Sensitive Periods (Frances Champagne, PhD, chair)

Introduction

Champagne explained that the rationale of critical and sensitive periods is based on the understanding that experiences in early development can have profound and lasting effects, while experiences in later development may have less profound effects. If researchers can reinstate the characteristics of the early development, big changes may occur again and change the trajectory. The critical question is which factors and mechanisms enable these profound effects.

[6] Aging and the Macroeconomy: Long-Term Implications of an Older Population, http://www.nap.edu/catalog.php?record_id=13465
[7] U.S. Health in International Perspective: Shorter Lives, Poorer Health, http://www.nap.edu/catalog.php?record_id=13497

The critical or sensitive periods concept has its roots in embryology and has frequently suffered from too broad an application to complex concepts far outside of its original scope.[8] Furthermore, the distinction between a critical versus a sensitive period is likely more quantitative than qualitative. Specifically, sensitive periods are characterized by a more gradual difference in sensitivity than critical periods. Some older or more traditional definitions suggest that the closure of critical periods may in fact be irreversible. Because of the focus of the current workshop on reversibility, participants agreed to consider all periods sensitive, even if they are called "critical" for historic reasons.

Most work on sensitive periods has been focused on early development. During that time, the pace of developmental change is so high that anything that occurs is likely to have a profound effect. Brains form and refine at a staggering pace. The question is then whether we are more sensitive to external stimuli during that time, or whether these simply have more far-reaching consequences because of the high pace of ongoing development.

Champagne further noted that the perception that there is less sensitivity later in life might not be true, once researchers look closer at molecular mechanisms. At the gene expression levels, mechanisms can remain dynamic through later stages of life.

Imprinting

Sensitive periods have been demonstrated in classical studies of filial imprinting.[9] After hatching, birds will imprint and usually follow the mother. If no mother is present, a duckling can imprint on a model that looks like a male duck. Locomotion appears to have a critical effect on imprinting efficiency. Detailed experiments have, furthermore, mapped out a critical period curve. Depending on the timing of the imprinting event, the degree to which the duckling will imprint to the male duck will vary. It also has been shown that social rearing influences the degree of imprinting.[10] Socialization extends the length of the critical period. Champagne commented that this work has served as the basis for a substantial body of scientific work on attachment.

She then discussed the role of fear in imprinting. Fear generally competes with imprinting. The end of the sensitive period therefore coincides with maturation of the fear response.[11] McEwen quoted work in rats on mechanisms known to be important in this development, including maturation of the amygdala during low glucocorticoid levels. To enhance attachment to the mother, glucocorticoids are low and fear is suppressed.[12]

Because malleability of mechanisms regulating sensitive periods is of critical importance for the network, Champagne concluded the review of imprinting studies by showing results from a study that

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[8] Caldwell, B.M. (1962). The usefulness of the critical period hypothesis in the study of filiative behavior. Merrill Palmer Q. Behav. Dev. *8(4),* 229–242. http://www.jstor.org/stable/23082541

[9] Hess, E.H. (1958). Imprinting in animals. Sci. Am.*, 198*, 81–90.

[10] Canon, P. (1959). Socialisation and imprinting in brown leghorn chicks. Anim. Behav. *7*, 26–34.

[11] Hess, E.H. (1959.) Two conditions limiting critical age for imprinting. J. Comp. Physiol. Psychol. *52*, 515–518.

[12] Landers, M.S., and Sullivan, R.M. (2012). The development and neurobiology of infant attachment and fear. Dev. Neurosci. *34*, 101–114.

exposed chicks to N-methyl d-aspartate receptor (NMDAR) antagonists.[13] Chicks who received the treatment could imprint much longer than the control animals. This means that NMDAR antagonists can extend the critical period. The question still remains whether this process could be repeated later in life.

A more recent study[14] showed that levels of the thyroid hormone triiodothyronine (T_3) are higher in imprinted than in dark-reared animals. In dark-reared animals, exogenous T_3 was able to re-open the sensitive period and enable imprinting. T_3 has a number of brain maturation effects. Champagne's ongoing research includes studies on bisphenol-A, which interferes with this system and has widespread developmental effects.

Visual System Development

Champagne used the refinement of the visual system by experience as a second example of well-established sensitive periods in biology. Monocular occlusion experiments in cats[15] have revealed plasticity in ocular dominance columns. About half of the cells in Layer IV of this region responds to binocular input, while the other half is specialized to process monocular input. After blocking vision from one eye, the corresponding Layer IV area shrinks at first, after which the neurons processing input from the other side take over.

The development of these ocular dominance columns has a sensitive period. Consequences differ depending on when individuals become deprived of their vision.[16] In general terms, early deprivation has larger effects than later deprivation.

Relevance for the Network

Champagne briefly reviewed data from her own studies on pain sensitivity, emphasizing the fact that the same stimulus will not elicit the same response at different time points. Pain responsiveness changes during the life course. In order to achieve similar results, the researchers therefore have to use a different pain stimulus at each time point. The same applies in research on maternal care, which also declines with age of offspring. This may have implications for critical periods for language. Infants hear and perceive language differently compared to adults. In general, the nature of the stimulus has to be adjusted to take account of the development of the system under study.

Champagne also reminded the group that there can be multiple windows of sensitivity. Extensively studied examples include adult female brain changes during pregnancy and the early post-partum period. During late gestation, hypothalamic neurons in the mother's brain gain the ability to very rapidly release oxytocin by forming gap junctions. The intracellular environment of all involved neurons thereby becomes the same. An action potential in one neuron then automatically elicits action potentials in all neurons. The gap junctions disappear after parturition, but the system will develop more efficiently

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[13] Parsons, C.H., and Rogers, L.J. (2000). NMDA receptor antagonists extend the sensitive period for imprinting. Physiol. Behav. *68*,749–753.

[14] Yamaguchi, S. et al. (2012) Thyroid hormone determines the start of the sensitive period of imprinting and primes later learning. Nat. Commun. *3*,1081.

[15] Hubel, D.H., and Wiesel, T.N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J. Physiol. (Lond.) *160*, 106–154; Wiesel, T.N., and Hubel, D.H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. J. Neurophysiol. *26*, 1003–1017.

[16] LeVay, S., Wiesel, T.N., and Hubel, D.H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. J. Comp. Neurol. *191*, 1–51.

during subsequent pregnancies. Therefore, although there are multiple windows of plasticity, the changes that occur during the first window are somewhat different from those necessary for the following periods. At the behavioral level, many model animals struggle with their new role as a first-time parent, but become much better at it with subsequent pups.

Champagne concluded her presentation by noting that different brain regions develop at different rates, and that different periods appear critical for different outcomes. For example, sensitive periods for development of the senses generally precede those for language and higher cognition. It still remains to be understood if these periods are reversible, and whether developments that occur during sensitive periods are easier or harder to reverse than those occurring during other time points. Spontaneous, passive reversal of these developments, however, appears to be rare.

Evidence from Human Longitudinal Studies on Early Adversity and Long-term Outcomes

Power noted that there is a very large body of knowledge on links between early adversity and negative health outcomes. Rather than provide a comprehensive review,[17] she focused on the additional knowledge needed to address these health issues in midlife.

The birth cohort field has developed a good understanding of normative development, which can refer to a generation or an individual. This is critical because it is impossible to study influences unless the trajectory is known. Birth cohort studies that have continued for several decades have helped to document normative development across functional domains.

It also is important to consider the timing of influences on adult outcomes. Within their limitations as observational studies (which cannot infer causation), many studies have shown that prenatal factors and socioeconomic circumstances and adversities influence a large number of adult health outcomes. Power further noted that cohort studies have suggested that commonly employed statistics may be inflating the importance of adult life factors: If adult social circumstances reflect an individual's origin and the journey leading to these circumstances, then the importance of events occurring under these circumstances will be over-emphasized.[18] Disentangling the individual contribution of early versus later influences is a great challenge. As an example, a paper noting the importance of childhood adversities in the development of posttraumatic stress disorder (PTSD) was part of the materials provided to the participants ahead of the workshop.[19] Power noted that many researchers fail to acknowledge the co-evolution of health influences and social position. Observational studies can identify the major pathways yet not determine causation. To understand causation better, the major effects first need to be identified.

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[17] The April 2013 issue of the *Annual Review of Public Health* will contain a review by Power, Kuh, and Morton titled "From developmental origins of adult disease to life course research on adult disease and aging: Insights from birth cohort studies."

[18] Hobcraft commented on this later during the workshop, quoting data from large studies that apparently suggest that childhood and adult adverse events show no significant interactions, but rather act in a purely additive manner.

[19] Berntsen, D., Johannessen, K.B., Thomsen, Y.D., Bertelsen, M., Hoyle, R.H., and Rubin, D.C. (2012). Peace and war: trajectories of posttraumatic stress disorder symptoms before, during, and after military deployment in Afghanistan. Psychol. Sci. *23*, 1557–1565.

Moffitt noted that longitudinal studies offer a unique opportunity to discover possible over-estimation of adult effects. In particular, once an effect of an adverse event during adulthood has been identified, one can look back at childhood data to reveal early determinants. She added that the agreement between childhood events and later recollection of these events is not always strong, but that both measures correlate with outcomes. Perceived adversities may thus be as important as those that can be measured objectively.

Power posited that one of the most critical questions to be answered is whether the aim should be to completely wipe out effects of early adversity, or rather to try to minimize the effects. In either case, it is important to better understand the timing of events, namely when do sensitive periods occur, and how should data be partitioned to detect them reliably. Another critical question is the role of mediators and moderators of health outcomes.[20] Given the enormous diversity of outcomes, are there a finite number of mediators?

If every outcome has its own mediator, then the challenge is going to be considerably harder. Power noted that cognitive function, emotional health, physical health, and social identity/ health behavior are critical dimensions in which these mediators operate. Outcomes that are influenced by several of these dimensions will likely be harder to reverse than those with major influences by single domains.
Power emphasized the importance of observational studies, because it is often unethical to expose people to adversity. She then expressed concern that some researchers have been overly optimistic regarding the potential of mid-life interventions, noting that if we ignore the trajectory that leads to the outcome, we may achieve nothing but the substitution of one risk behavior with another.

Early Deprivation Experiments in Monkeys

Conti reviewed results from her studies in monkeys on early deprivation. She compared mother-reared (MR) to peer-reared (PR) and surrogate peer-reared (SPR) animals. SPR monkeys had much greater risks for adverse health outcomes.[21]

Early Childhood Interventions

Conti also reported results on adult health outcomes from the Perry Preschool Project and the Carolina Abecedarian Intervention. For the Abecedarian study, data from a biomedical sweep at age 35 were available. This sweep includes a physical examination at a doctor's office and a venous (non-fasting) blood sample that was analyzed for biomarkers of cardiovascular and metabolic disease. This is the first time that data of this kind have been collected during adulthood for an early childhood intervention.

Perry Preschool Project

This program was based on a small (n=123), randomized experiment originally conducted in Ypsilanti, Michigan, between 1963 and 1967. All included children were of African American origin and were characterized as having low IQ and low SES. The average age of the mothers at birth was 25.5 years. The intervention comprised 12.5 hours per week of structured activities during the school year, teaching a curriculum based on Piaget and Vigotsky ("plan, do, review"). Children aged 3 and 4 years were

[20] Discussed in: Boyce, W.T., Sokolowski, M.B., and Robinson, G.E. (2012). Toward a new biology of social adversity. Proc. Natl. Acad. Sci. U.S.A. *109 Suppl 2*, 17143–17148.
[21] Conti, G., Hansman, C., Heckman, J.J., Novak, M.F.X., Ruggiero, A., and Suomi, S.J. (2012). Primate evidence on the late health effects of early-life adversity. Proc. Natl. Acad. Sci. U.S.A. *109*, 8866–8871.

included, and the intervention lasted 2 years in total. Furthermore, the children had biweekly teacher visits and monthly group visits accompanied by their parents. In 2010, this intervention would have cost $9,604.30 per year per child.

Carolina Abecedarian Intervention

The Carolina Abecedarian Intervention was carried out in Chapel Hill, North Carolina, and included 111 children born between 1972 and 1977. This intervention was more intensive than the Perry Preschool Project and comprised 8 hours of structured activities per day for 50 weeks per year. Ninety-eight percent of the children were African American. The average age of the mothers at birth was 20.3 years. Compared to the Perry study, this intervention focused more on learning games and on developing language skills. The intervention was a small doubly randomized experiment, comprising a day-care component (0-5 years) and a school-age component (5-8 years). This study also included nutritional and healthcare components (free primary pediatric care); in 2010, it would have cost $15,388 per year per child.

Health Outcomes

Because of the small sample size, compromised randomization, non-random attrition, and multiplicity of hypotheses to be tested, Conti used bloc permutation tests, stepdown methods, and inverse probability weighting. The most important difference between the two studies is that health outcomes in the Abecedarian Intervention were based on a thorough biomedical test and examination, while the Perry outcomes were assessed by self-report only.

Conti presented results on the effects of the day-care intervention. Male participants of the Abecedarian study showed several improved outcomes compared to the control group. These included lower blood lipid levels and lower risk scores for metabolic syndrome and hypertension. They also had been hospitalized fewer times by the age of 35. Males in the Perry Preschool Program did not show improvements in obesity, but smoked significantly less than the control group. Results from mediation analysis suggested that reduction in externalizing behavior was the main mechanism. The ability to sit still and execute tasks to the end, developed by the intervention, likely helped participants to self-regulate and reduced externalizing behavior.[22] The Abecedarian Intervention, however, had small if any effects on smoking behaviors.

The Abecedarian Intervention also has data on parental behaviors, which allows for testing of responses to the intervention. These data show a significant increase in maternal attachment to male study participants.

Conti concluded that environmental enrichment during critical or sensitive periods might ameliorate adverse effects of early experiences.

Future challenges include an analysis of possible predictors of positive outcomes in the control groups. Furthermore, the study population, which has now reached adulthood, can be exposed to additional interventions. It would be very interesting for this Network to learn how such interventions would change the well-documented trajectories.

[22] Heckman, J.J., Pinto, R., and Savelyev, P. (2013). Understanding the mechanisms through which an influential early childhood program boosted adult outcomes. Am. Econ. Rev., forthcoming.

Molecular and Cellular Mechanisms

McEwen reviewed studies that demonstrate the remarkable and lasting effects of stress on brain structure and molecular gene expression in normal experimental animals.

Remodeling

The adult brain has a remarkable capacity of structural modeling. Dendrites grow or shrink. Synapses appear and disappear, and neurogenesis occurs all through the lifespan, especially in the hippocampus. Remodeling of dendrites is not restricted to brain damage situations: under normal conditions, neurons in the prefrontal cortex (PFC) shrink with stress,[23] while neurons in the amygdala increase in size. Anxious animals have been shown to have larger amygdalas but may show impairments in PFC connectivity. Application of NMDAR blocking drugs attenuates the shrinkage of PFC.[24] Other sites that undergo frequent changes include the nucleus accumbens and periaquaeductal gray. Recent research suggests that remodeling is the rule rather than the exception in the adult brain.

Circadian disruption is also a very important factor for brain plasticity.[25] Animals in a 20-hour clock disruption experiment became heavier and had higher insulin and leptin levels. Neurons in the PFC became less complex, leading to cognitive inflexibility. McEwen pointed to data on humans in shift work that are consistent with these findings. Furthermore, in a study conducted by his group, medical students studying for their board examination underwent functional magnetic resonance imaging (fMRI) and a task of mental flexibility. The results showed that those students with higher scores on a perceived stress scale displayed reduced mental flexibility and that the responsible circuit included the PFC.[26]

The hippocampus is a brain area that has frequently been investigated in plasticity studies. The *Cornu Ammonis* 3 (CA3) area has been shown to shrink under stress. This area also is very vulnerable to seizures. One hypothesis is, therefore, that the remodeling mechanisms might constitute a protection from excitotoxic effects. The volume of the same area is increased by voluntary exercise and an enriched environment. These findings are mainly based on rodent data, but supporting human data on the effect of exercise are now emerging.

An ongoing gene expression study investigates the effect of an acute glucocorticoid challenge in naïve or chronically stressed animals. Preliminary results show that prior exposure to stress leads to a remarkable change in the profile of genes that are activated in response to the challenge. In fact, out of

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[23] Liston, C., Miller, M.M., Goldwater, D.S., Radley, J.J., Rocher, A.B., Hof, P.R., Morrison, J.H., and McEwen, B.S. (2006). Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J. Neurosci. *26*, 7870–7874.

[24] Martin, K.P., and Wellman, C.L. (2011). NMDA receptor blockade alters stress-induced dendritic remodeling in medial prefrontal cortex. Cereb. Cortex *21*, 2366–2373.

[25] Karatsoreos, I.N., Bhagat, S., Bloss, E.B., Morrison, J.H., and McEwen, B.S. (2011). Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. Proc. Natl. Acad. Sci. U.S.A. *108*, 1657–1662.

[26] Karatsoreos, I.N., Bhagat, S., Bloss, E.B., Morrison, J.H., and McEwen, B.S. (2011). Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. Proc. Natl. Acad. Sci. U.S.A. *108*, 1657–1662.

about 500 genes activated in the naïve and the stressed group, only 228 genes were the same. McEwen and colleagues are now exploring the underlying mechanisms.

Epigenetic Regulation

McEwen then reviewed the role of epigenetic mechanisms in plasticity. Only unfolded DNA can be read and expressed, and histones control the folding and unfolding of DNA. Post-translational modification of histones, therefore, plays an important role in gene expression regulation and has been implicated in numerous disease processes. Work from McEwen's group has shown that acute stress activates repressive histone marks, especially in the dentate gyrus and the CA3 area of the hippocampus.[27] Follow-up research now suggests that this response selectively silences certain retrotransposon DNA elements.[28] This response to an acute stressor habituates if chronic stress of the same kind is experienced.

Effects of Stress, Experience, and Aging

Chronic restraint stress alters the gene expression profile of the hippocampus to a novel, heterotypic stressor.[29] The genome thus becomes re-programmed to respond to stressors in a different way after multiple exposures.

McEwen's group has shown that aging reduces resilience to chronic stress in the PFC.[30] Whether or not these changes in gene expression profiles might be reversible remains to be addressed. The structural plasticity, however, has been shown to be largely reversible, with the possible exception of the amygdala. It is possible but has not yet been proven that this may explain why highly emotional events cause long-lasting memories.

McEwen then noted the importance of excitatory amino acid receptors in these paradigms. Ionotropic and metabotropic receptors are differentially regulated by chronic versus acute stress, and they likely play an important role in stress response and homeostasis.

Molecular and Structural Evidence for the Effectiveness of Interventions

McEwen's group has successfully used S18986, an AMPA receptor (AMPAR, an ionotropic glutamate receptor) modulator, to attenuate age-related behavioral and biological changes.[31] Other interventions that have shown success include:

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[27] Hunter, R.G., McCarthy, K.J., Milne, T.A., Pfaff, D.W., and McEwen, B.S. (2009). Regulation of hippocampal H3 histone methylation by acute and chronic stress. Proc. Natl. Acad. Sci. U.S.A. *106*, 20912–20917.

[28] Hunter, R.G., Murakami, G., Dewell, S., Seligsohn, M., Baker, M.E.R., Datson, N.A., McEwen, B.S., and Pfaff, D.W. (2012). Acute stress and hippocampal histone H3 lysine 9 trimethylation, a retrotransposon silencing response. Proc. Natl. Acad. Sci. U.S.A. *109*, 17657–17662.

[29] Gray, J.D., Rubin, T.R., Hunter, R.G., and McEwen, B.S. (2012). Chronic restraint stress alters the gene expression profile of the hippocampus to a novel, heterotypic stressor. Program No. 899.06. 2012 Neuroscience Meeting Planner. New Orleans, LA: Society for Neuroscience. Online.

[30] Bloss, E.B., Janssen, W.G., McEwen, B.S., and Morrison, J.H. (2010). Interactive effects of stress and aging on structural plasticity in the prefrontal cortex. J. Neurosci. *30*, 6726–6731.

[31] Bloss, E.B., Hunter, R.G., Waters, E.M., Munoz, C., Bernard, K., and McEwen, B.S. (2008). Behavioral and biological effects of chronic S18986, a positive AMPA receptor modulator, during aging. Exp. Neurol. *210*, 109–117.

- Regular physical activity,[32] which leads to increased hippocampal volume and PFC blood flow, as well as improved executive function and memory
- Cognitive-behavioral therapy,[33] which reduces anxiety and decreases the volume of the amygdala
- Social support and integration, such as the Experience Corps,[34] which leads to improved executive function, blood flow, and overall health

Whether or not the effects of these interventions would be additive if tried simultaneously has not been tested yet.

Facilitators of Brain Plasticity

McEwen pointed to a growing body of evidence indicating that application of the antidepressant fluoxetine (a selective serotonin reuptake inhibitor, SSRI) may re-induce plasticity.[35] In humans this should, however, only be attempted in combination with concurrent targeted behavioral interventions because agitation that occurs as a side effect increases suicide and homicide risks. Because this Network is interested in systematic use of existing data in effective ways, the large datasets that exist on fluoxetine use for the treatment of mood and anxiety disorders are a potentially remarkable untapped asset. These datasets could be harnessed for studies on mechanisms of plasticity. Suomi noted that he is currently studying effects of fluoxetine in monkeys and that results are expected to be available shortly.

Additional inductors of plasticity reported in the literature include food restriction[36] and exogenous glucocorticoids.[37] Whether or not endogenous glucocorticoids participate in plasticity has, however, not

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[32] Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D.X., Hu, L., and Kramer, A.F. (2006). Aerobic exercise training increases brain volume in aging humans. J. Gerontol. A Biol. Sci. Med. Sci. *61*, 1166–1170; Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Hu, L., Morris, K.S., White, S.M., Wójcicki, T.R., McAuley, E., and Kramer, A.F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus *19*, 1030–1039; Konopack, J.F., Marquez, D.X., Hu, L., Elavsky, S., McAuley, E., and Kramer, A.F. (2008). Correlates of functional fitness in older adults. Int. J. Behav. Med. *15*, 311–318.

[33] Davidson, R.J., and McEwen, B.S. (2012). Social influences on neuroplasticity: stress and interventions to promote well-being. Nat. Neurosci. *15*, 689–695.

[34] Carlson, M.C., Erickson, K.I., Kramer, A.F., Voss, M.W., Bolea, N., Mielke, M., McGill, S., Rebok, G.W., Seeman, T., and Fried, L.P. (2009). Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. J. Gerontol. A Biol. Sci. Med. Sci. *64*, 1275–1282.

[35] Maya Vetencourt, J.F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O.F., Castrén, E., and Maffei, L. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science *320*, 385–388; Chollet, F., Tardy, J., Albucher, J.-F., Thalamas, C., Berard, E., Lamy, C., Bejot, Y., Deltour, S., Jaillard, A., Niclot, P., et al. (2011). Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. *10*, 123–130; Castrén, E., and Rantamäki, T. (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev. Neurobiol. *70*, 289–297.

[36] Spolidoro, M., Baroncelli, L., Putignano, E., Maya-Vetencourt, J.F., Viegi, A., and Maffei, L. (2011). Food restriction enhances visual cortex plasticity in adulthood. Nat. Commun. *2*, 320.

[37] Liston, C., and Gan, W.-B. (2011). Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. Proc. Natl. Acad. Sci. U.S.A. *108*, 16074–16079.

yet been addressed. If endogenous glucocorticoids do participate in plasticity, then this mechanism may be harnessed for successful interventions.

Critical and Sensitive Periods—Conclusions

Champagne concluded the first session by noting that induction of plasticity, according to current knowledge, must employ at least a two-fold approach. Specifically, plasticity-promoting factors should increase, while plasticity-inhibiting factors, such as adhesion between cells, should decrease. Whether or not a molecular system is malleable may depend on the ability to develop and stabilize neurons and their synapses in the right places while suppressing adhesions that would interfere with this process.

Based on this notion of a dual approach, substantial progress has been made in understanding the reversibility of critical periods in the development of the visual system. Combined application, for example, of chondroitinase ABC, fluoxetine, and environmental enrichment, can recover acuity in animals that developed amblyopia due to the lack of visual input during a critical period.[38]

Champagne reviewed additional evidence supporting the important influence of enrichment on visual cortical plasticity[39] and successful recovery of visual acuity by epigenetic treatments.[40] For example, valproic acid, which is used in humans for the treatment of epilepsy and bipolar disorder, promotes histone acetylation and may help to restore visual acuity.

The NOGO receptor is a known axonal growth-inhibiting molecule that prevents plasticity. Mice usually prefer music, although not strongly, when they are exposed to it during a certain critical period. NOGO receptor mutant mice, however, develop a very strong preference for music or silence, depending on which they have been exposed to, and regardless of the timeframe of the critical period.[41] This shows how removal of one molecular inhibitory mechanism leads to long-term behavior changes outside the critical period.

Participants discussed the importance of naturally occurring sensitive periods and opportunities to use these for targeted interventions. Puberty and other periods of rapid hormonal changes may constitute opportunities for effective interventions during windows of plasticity.

Overall, the participants agreed that the psychobiology of sensitive periods is very well established and that efforts to re-open these periods are in the beginning stages, but show very promising initial results. However, applying these concepts much more broadly to link early child adversity to later outcomes is a very large step. Making this transition successfully will require significant effort to carefully develop the necessary stringent research designs.

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[38] Morishita, H., and Hensch, T.K. (2008). Critical period revisited: impact on vision. Curr. Opin. Neurobiol. *18*, 101–107.

[39] Scali, M., Baroncelli, L., Cenni, M.C., Sale, A., and Maffei, L. (2012). A rich environmental experience reactivates visual cortex plasticity in aged rats. Exp. Gerontol. *47*, 337–341.

[40] Silingardi, D., Scali, M., Belluomini, G., and Pizzorusso, T. (2010). Epigenetic treatments of adult rats promote recovery from visual acuity deficits induced by long-term monocular deprivation. Eur. J. Neurosci. *31*, 2185–2192.

[41] Yang, E.-J., Lin, E.W., and Hensch, T.K. (2012). Critical period for acoustic preference in mice. Proc. Natl. Acad. Sci. U.S.A. *109 Suppl 2*, 17213–17220.

Session 2: Differential Susceptibility (Elissa Epel, PhD, chair)

Introduction

Epel explained that the focus of this session would be on depth rather than breadth. Specifically, understanding the principles and critically reviewing the evidence in a few examples is more helpful for the network than a comprehensive summary of the field. Similar to the challenge encountered in the sensitive period paradigm, the role of the Network is to prioritize questions for the future.

Study of Biological Sensitivity to Context (BSC) in Kindergarteners

Obradović was invited by the Network to present results from her work on individual variability. The main objective of her work is to explore the variability of adaptation in contexts of adversity and to identify processes that enable some children to achieve remarkable resilience. Differential susceptibility is not a vulnerability factor, but rather a plasticity factor. Highly reactive children are more affected by their environment. If exposed to a poor environment, they are more likely to experience bad outcomes, but they will do better than average in a good and supportive environment.

To study these processes, Obradović measured kindergarteners' responses to laboratory challenges testing parasympathetic nervous system and HPA reactivity. She then subjected them to a stress reactivity protocol that included mild social, cognitive, sensory, and emotional challenges. Additionally, she gathered information from the children, their parents, and their teachers about their level of adaptation.[42]

Low-reactive children showed higher engagement under low adversity and lower engagement under high adversity as compared to the high-reactive children. The same applied to externalizing behavior. These results may suggest that physiological reactivity can serve as a marker of sensitivity. The role of physiological reactivity might, however, depend on:[43]

- The type of challenge (e.g., cognitive versus interpersonal)
- The timing (results in fall can be different from spring)
- Stress response systems (e.g., the sympathetic nervous system versus the HPA axis)
- Social contexts (e.g., family versus peer)
- Behaviors (e.g., clinical versus community samples)
- Development (e.g., puberty)

Physiological reactivity can, therefore, not simply be assigned to each individual just once. A problem with reactivity by environment interaction studies in the past might lie in the fact that reactivity has mistakenly been assumed to be static across the life span, similar to a genotype. There is some evidence that the visceral nervous system and HPA axis work in an additive manner with regard to physiological

[42] Obradović, J., Bush, N.R., Stamperdahl, J., Adler, N.E., and Boyce, W.T. (2010). Biological sensitivity to context: the interactive effects of stress reactivity and family adversity on socioemotional behavior and school readiness. Child Dev. *81*, 270–289.
[43] Obradović, J., Bush, N.R., and Boyce, W.T. (2011). The interactive effect of marital conflict and stress reactivity on externalizing and internalizing symptoms: the role of laboratory stressors. Dev. Psychopathol. *23*, 101–114.

reactivity.[44] Furthermore, the Adaptive Calibration Model[45] predicts substantial gender differences, most markedly under very severe and traumatic stress.

Obradović cautioned that it still remains to be understood if physiological markers of sensitivity simply represent the same phenomena expressed at different levels of assessment, or if they represent unique types of sensitivity to context.[46] She is also currently working on more complex models of reactivity that can be broken down into several latent components[47] and on models of developmental cascades.[48]

In summary, future research on physiological reactivity as a dynamic process will have to consider the interplay between multiple systems, trajectories of responses, influences of self-regulation and appraisal, as well as longitudinal continuity and change. Context matters, and there may be periods during which it exerts weaker or stronger influence on biological sensitivity. Sophisticated models will be required to disentangle causes and effects.

Resilience and Recovery

Several workshop participants commented on the fact that "resilience" is being used to describe many different behaviors and outcomes. High IQ and agreeable temperament, for example, are said to lead to resilient children. In the differential susceptibility context, the low-reactive children have sometimes been described as being resilient. The term is, however, poorly defined, and the workshop participants therefore spent some time to agree on a common definition and measures that can be used to quantify resilience.

Epel presented results from her work on caregivers to provide measures of resilience. Exposure to sporadic versus chronic stress is very different, and caregivers often are faced with very long periods of constant stress. Therefore, they carry a much larger stress burden than the average person. When comparing caregivers who are vulnerable for an adverse outcome (e.g., depression) to those without that vulnerability, it turns out that the actual stress burden is, on average, the same. The non-vulnerable caregiver, however, has a much lower perceived burden caused by the chronic stress. The difference in the amount of perceived stress between the vulnerable and the non-vulnerable caregiver can be used as a measure of resilience. Based on these data, it is not possible to say if the perception of the vulnerable or of the non-vulnerable caregivers is "correct." Epel's data further showed that resilient caregivers were very strong suppressors in a post-dexamethasone cortisol challenge, and that the vulnerable caregivers had a significantly elevated risk for metabolic syndrome.

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[44] Bauer, A.M., Quas, J.A., and Boyce, W.T. (2002). Associations between physiological reactivity and children's behavior: advantages of a multisystem approach. J. Dev. Behav. Pediatr. *23*, 102–113.
[45] Del Giudice, M., Ellis, B.J., and Shirtcliff, E.A. (2011). The Adaptive Calibration Model of stress responsivity. Neurosci. Biobehav. Rev. *35*, 1562–1592.
[46] Obradović, J., and Boyce, W.T. (2009). Individual differences in behavioral, physiological, and genetic sensitivities to contexts: implications for development and adaptation. Dev. Neurosci. *31*, 300–308.
[47] Burt, K. B., and Obradović, J. (2013). The construct of psychophysiological reactivity: statistical and psychometric issues. Devel. Rev. *33*, 29–57.
[48] Obradović, J., and Hipwell, A. (2010). Psychopathology and social competence during the transition to adolescence: the role of family adversity and pubertal development. Dev. Psychopathol. *22*, 621–634.

is defined during early (pre-and postnatal) development. Furthermore, cross-sectional aging data suggest that cognitive decline starts as early as the early 20s and proceeds at a constant pace over the lifespan.[52]

Godfrey reviewed examples of prenatal risk factors for adult phenotypes and discussed a recent theory according to which a "mismatch" between the developmentally induced phenotype and the subsequent environment increases susceptibility to adult cardiovascular disease and type 2 diabetes.[53]
He commented that past research on prenatal exposures has introduced a somewhat artificial distinction between effects of nutrition and of stress. The Dutch famine, for example, was certainly accompanied by high stress levels in the population.

Godfrey presented a flow chart from the Early Nutrition Project,[54] a current European study under the Seventh Framework Programme (FP7), which has received a total of 11.5 million Euros in funding. This study investigates the roles of genetic diversity and obesogenic environments, fetal overnutrition, accelerated postnatal growth, and mismatched fetal undernutrition and postnatal overnutrition in the etiology of obesity.

He concluded his presentation with a review of work from his laboratory on epigenetic modification of gene expression by a protein-restricted diet and folic acid.[55] A protein-restricted diet during pregnancy in model animals had significant effects on peroxisome proliferator-activated receptor (PPAR)-gamma and glucocorticoid receptor expression that led to measurable downstream effects on gene expression, beta-oxidation, and gluconeogenesis in the offspring. In humans, he found in two independent groups of children that epigenetic gene promoter methylation of the retinoid X receptor alpha (RXRA) gene at birth is associated with a child's later adiposity.[56] In the experimental studies in animals, maternal undernutrition, unbalanced nutrition, and overnutrition are established drivers of epigenetic change in the offspring, and preliminary evidence suggests this is also the case in human pregnancy.[57]

Differential Susceptibility – Conclusions

Participants discussed the concept of differential susceptibility and noted that the concept could be valuable for the Network if

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[52] Park, D.C., and Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. Annu. Rev. Psychol. *60*, 173–196.
[53] Gluckman, P., and Hanson, M. (2006). Mismatch. Why Our World No Longer Fits Our Bodies. Oxford University Press.
[54] http://www.project-earlynutrition.eu
[55] Lillycrop, K.A., Slater-Jefferies, J.L., Hanson, M.A., Godfrey, K.M., Jackson, A.A., and Burdge, G.C. (2007). Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br. J. Nutr. *97*, 1064–1073; Burdge, G.C., Hanson, M.A., Slater-Jefferies, J.L., and Lillycrop, K.A. (2007). Epigenetic regulation of transcription: a mechanism for inducing variations in phenotype (fetal programming) by differences in nutrition during early life? Br. J. Nutr. *97*, 1036–1046.
[56] Godfrey, K.M., Sheppard, A., Gluckman, P.D., Lillycrop, K.A., Burdge, G.C., McLean, C., Rodford, J., Slater-Jefferies, J.L., Garratt, E., Crozier, S.R., et al. (2011). Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes *60*, 1528–1534.
[57] http://www.project-earlynutrition.eu

- it can be defined more rigorously statistically
- it can be tested in standardized experimental paradigms
- the underlying factors are stable over time
- it can help identify which individuals would benefit most from interventions at midlife and beyond

Statistical Definition

Many studies in the past have not made a careful enough distinction between differential susceptibility and other models (e.g., inherited sensitivity, goodness of fit, social enhancement).

The participants emphasized the need to work with strict definitions to avoid confusion regarding what constitutes "evidence for" or "replication of" a differential susceptibility finding. Furthermore, past studies have made the mistake of labeling high reactive children as "difficult" and low reactive children as "resilient." More precise language will help to disentangle the concepts of DS and resilience. Researchers should also be more careful to distinguish between the effects of pace and of timing (also referred to as "tempo") in their studies.

Standardized Experimental Paradigms

Participants expressed the need to standardize experimental paradigms for research on differential susceptibility factors. Education, for example, is not a good choice for an environmental variable, because it might show interactive effects with the DS factor. The participants thought that simple paradigms would be most successful. For example, researchers only should use entirely external events, such as the recent recession, as childhood adversities. The participants then recommended the use of measurable outcomes, such as the metabolic syndrome index, because such outcomes can be transferred easily to animal models. Simple interventions, such as exercise, can then be added. The participants started to assemble a list of candidate factors and contexts that could be tested using such paradigms. This preliminary list is included as Appendix 1 of this report. The participants also will review the existing literature for extant data from which the above variables could be derived.

Stability Over Time

A true DS factor should be latent and stable. Genotypes are stable over time, and therefore obvious factors to include as candidates. The biological and physiological mechanisms behind DS, however, are still too poorly understood to judge which factors may turn out to be stable over time. Adoption studies may be helpful to assess the influences of biological and genetic contributions to DS across generations.

Prediction of Most Responsive Individuals

Reiss noted that several studies have been published that found that the differential susceptibility alleles that moderate response to the environment in childhood also predict better response to short-term interventions in adolescents if not adults. The workshop participants, however, noted that there are examples of genes that increased the likelihood of pathological behavior and *reduce* the chance of therapeutic success. Turning to the ANS and HPA indicators of differential susceptibility, they wondered about the longevity of these indices of individual differences. Also, after many years, the initial effects of a genotype will have created a plethora of downstream effects, which may, in adulthood, be the main determinants of behavioral responses. Whether it will be possible to reverse these mechanisms and break up entrenched pathways remains to be studied. As a result, the role of differential susceptibility factors in identifying individuals with the best chances for treatment success cannot yet be answered.

Integrative Discussion I: Next Steps

The Experience Corps Study

Seeman presented results from the Baltimore Experience Corps Study[58] as an example of a longitudinal study that can be extended by additional research questions of relevance to this Network. The main goal is to help older adults remain engaged in society. In addition, young children also benefit by receiving help from older mentors with their schoolwork.

The intervention of this study is a program that recruits volunteers (60 years old and older) to serve in elementary schools. At baseline, this group is characterized by mainly African American ancestry, low SES, and high prevalence of diabetes and hypertension.

The schools must assign meaningful work to the participants and may not ask them to help with office work. The study protocol requires a substantial commitment from each participant; a minimum of 15 hours per week of volunteer work is mandatory. Seeman reported that many participants actually exceed this requirement. For the study to be successful, it also is critical to assign a minimum number of volunteers to each school, so that the volunteers can form support groups. Initially, the main motivation for the volunteers is to help the children and make a noticeable difference in the school. At the same time, they are exposed to an adult health intervention.[59] They appreciate the new social contacts they are establishing through the program. They also show measurable physical and psychosocial benefits. For example, they report a greater feeling of being needed after becoming a participant in the program. In fact, the dropout rate so far has been only about 10 percent. There is, however, considerable variability in the number of hours that the volunteers spend at the school.

The requirements for participation include a mini-mental test and background check. Assigned classrooms are right now in the K-3 grade range, but the program has plans to include additional grade levels on both ends. Each volunteer must have at least a high school diploma and attend a refresher course once per year. In addition, he or she also receives periodic training during the weekly team meetings. The gender distribution is currently shifted toward higher female participation. It would be desirable to have more male participants, but some men do not want to work with the smallest children. Results from the children indicate beneficial effects on reading and vocabulary. Furthermore, the children report increased social contacts, and many see their mentors in their neighborhood outside of school hours.

If the Network wanted to study subgroup differences in this group, then it would be possible to add a retrospective assessment to the study protocol.

Pathways and Interventions

The participants identified “Pathways” and “Interventions” as two closely related topics that will become the focus of the next meeting, to be held in London on October 14-15, 2013.

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[58] http://www.jhsph.edu/research/centers-and-institutes/johns-hopkins-center-on-aging-and-health/research/projects/Experience_Corps_pages/index.html

[59] Glass, T.A., Freedman, M., Carlson, M.C., Hill, J., Frick, K.D., Ialongo, N., McGill, S., Rebok, G.W., Seeman, T., Tielsch, J.M., et al. (2004). Experience Corps: design of an intergenerational program to boost social capital and promote the health of an aging society. J. Urban Health *81*, 94–105.

The **Pathways** group will address which additional information is necessary to understand the mechanisms linking childhood and major health outcomes. What are the best and most reliable measurements to describe and define the pathways? How many of these pathways can be identified? Which functional domains do they belong to? Do they correlate with each other, and how can they be categorized? The participants noted that few pathways or functional clusters render greater value for intervention designs. This group also will review current risk models and identify possible strategies to get an estimate of population attributable risk. Finally, of great importance for this Network is to determine whether the pathways are constant over time, malleable, and/or, in the best-case scenario, reversible.

The **Interventions** group will start to work on identifying the most promising interventions (preferably in mid-life and after). This work will be guided by the mandate to identify the outcomes with the broadest implications for public health. In addition to finding risk factors and factors that determine individual differences, future research also should identify factors that predict success of interventions. These factors may but do not necessarily overlap. Ideally, the complexity of the system might be reduced by research aiming at the identification of common factors that are influenced by different types of interventions. Additional research will address the issue of the best timing of interventions, especially in relation to naturally occurring critical or sensitive periods and windows of opportunities.
Finally, this group will address what research will be necessary to determine whether an intervention aims at reversal of the pathway or just compensates for the increase in risk. This type of research can thus contribute to the pathway characterization by shining additional light on the underlying mechanisms.

Both groups will consider a number of overarching issues:

1. The factors that determine individual differences in response to early adversity are not necessarily the same as those that moderate the pathways later in development, nor do these same factors necessarily predict intervention success. Of interest are stable individual differences that influence response to adversity, shape subsequent paths, and moderate intervention efforts.

2. Critical or sensitive periods and windows of opportunity occur naturally. A better understanding of the role of hormonal changes and life events (e.g., marriage, first-time parenting) is required. Furthermore, the induction of these periods by pharmacological or behavioral means may re-open opportunities for plasticity and reversal of risk.

3. Longitudinal studies and interventions take time. Both groups are therefore strongly encouraged to look for time-shortening measures wherever possible. This implies the use of existing data and materials of ongoing studies to design research endeavors that will produce results in the near future. Participants will consider the use of combinations of experimental paradigms and known time-shortening designs such as adoption study, which provide an opportunity to assess risk across generations. The Network will further develop concrete ideas to expand the Experience Corps Study.

4. Participants are tasked to design a number of prototype pilot studies that can be conducted within a reasonable timeframe. This likely will require the combination of results from different methods (e.g., observational studies and randomized trials combined with animal model data).

5. On several occasions during the discussions, participants noted a critical need for a more standardized set of methods and paradigms that can be applied to this research. A "toolbox" of such methods would be of great value to the field, and the participants will start to conceptualize a set of tools in preparation for the next meeting.

6. Research in this field has, furthermore, conflated the concepts of timing (also referred to as "tempo") and velocity**.** Both of these are important factors, and a better distinction between effects caused by timing and velocity will help the field to standardize its efforts.

7. Finally, participants will aim to work out the statistics of differential susceptibility in a more stringent way. The current vague definitions have led to confusion, and a contribution by this Network to more stringent definitions may greatly enhance comparability between different approaches and results.

Integrative Discussion II: Planning for the October 14-15, 2013, Meeting in London

Additional Research Questions

Several Network members expressed great interest to learn more about fetal programming. The option to invite experts in this field to the London meeting was discussed. Participants also raised the idea of inviting experts on additional cohort studies and/or behavioral change to participate in future discussions.

Challenges for the Next Meeting

The activities of the Network are maturing and have progressed from the review of basic research data to the identification of two focus areas that will be critical for the understanding of mechanisms and design of interventions.

At the London meeting, the participants will present results from the Pathways and Intervention groups. Discussions are expected to focus on possible research avenues with high potential, which are high risk yet high gain, but also research questions that should not yet be pursued, because they may be too speculative to embark on in the current state of the field. Finally, another goal of the London meeting will be to produce concrete and practical advice for funding agencies in the United States and Britain within the near future.

APPENDIX 1: CANDIDATE DIFFERENTIAL SUSCEPTIBILITY FACTORS AND CONTEXTS

**** * * PRELIMINARY DRAFT * * ****

List of Candidate Differential Vulnerability Factors

This list should not include factors for inherited sensitivity to stress, such as polymorphisms that are only sensitive to adversity but not supportive environments.

Behavioral

- Highly sensitive ("environmentally permeable")
- Child measures: behavioral inhibition, negative emotionality
- Adult measures: perceptual sensitivity, exaggerated stress responses, threat, rumination, openness to new experiences

Physiological

- Sympathetic and parasympathetic nervous systems
- Neuroendocrine reactivity (HPA, inflammatory processes)
- Co-elevation of HPA and autonomic nervous system (ANS) activity
- Neural circuitry, responsivity (perhaps: startle)
- Appetite regulation
- Metabolic pathways, e.g., gluconeogenesis, fatty acid metabolism

Genetic Polymorphisms in the Following Systems

- Serotonin
- Dopamine
- Monoamine oxidase (MAO)-A
- Oxytocin receptor (Oxtr)
- Brain derived neurotrophic factor (BDNF)
- Interleukin-6 (IL-6) receptor
- Catechol-O-methyltransferase (COMT)
- Corticotropin-releasing hormone (CRH) receptor, glucocorticoid receptor (GR)
- OTHERS

Epigenetic

- Methylation
- Histone modification
- Chromatin modification of stress reactive genes
- Small and large non-coding RNAs

Gene expression patterns (outcome vs. early DS factor?)

- Common ontology

TELOMERE SHORTENING /EARLY CELL SENESCENCE

MATERNAL ILLNESS

DEVELOPMENTAL TEMPO

List of Candidate Contexts

STRESSORS AND ADVERSITIES

- Neglect
- Traumatic events

FAMILY ENVIRONMENT

- Maternal warmth
- Harsh parenting
- Marital conflict
- Father depression
- Family distress
- Mental illness/addiction
- Undernutrition, unbalanced nutrition, and overnutrition
- Chemical exposures
- Social context influences/“Exposome” additive inputs

PROTECTIVE

- Parental warmth
- Beneficial experiences and exposures
- Supportive interventions

APPENDIX 2: WORKSHOP AGENDA

Network on the Reversibility of Health Risks in Adults with Early Adverse Environments

Tuesday, February 26, 2013

9:00 a.m. **INTRODUCTIONS AND UPDATE**

Introduction of Members, Guests, and NIH Staff

Brief Review of the Meeting

- ***Stephen Suomi, PhD***, The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and ***David Reiss, MD***, Yale University

NIH Updates

- ***Lis Nielsen, PhD***, National Institute on Aging (NIA)

9:30 a.m. **CRITICAL AND SENSITIVE PERIODS: PHENOMENA, MECHANISMS, AND INTERVENTIONS**

- ***Frances Champagne, PhD***, Columbia University and Critical Period Workgroup Chair

Defining Concepts

- What is a critical period and what is a sensitive period
- Classic studies of critical/sensitive periods within the visual system
- Temporal changes in "plasticity" in the developing brain

Evidence: Human Studies of Critical/Sensitive Periods and Plasticity

- Vulnerability to early life adversity
- Adoption studies
- Longitudinal studies

10:45 a.m. **BREAK**

11:00 a.m. **Evidence: Animal Models for the Study of Critical/Sensitive Periods**

- Vulnerability to early life adversity
- Early life deprivation and later life enrichment studies
- Cross-fostering

Mechanisms of Lifelong Plasticity

- Epigenetic pathways—reversible control of gene activity
- Growth factors/neurotrophins, synaptic plasticity

Intervention Strategies: Revisiting and Reawakening Plasticity

- Recovery in the damaged CNS
- Plasticity induced through pharmacologic/behavioral therapies

12:30 p.m. **LUNCH**

1:30 p.m. **INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY TO FAVORABLE AND UNFAVORABLE ENVIRONMENTS**
Elissa Epel, PhD, UCSF, ***W. Thomas Boyce, MD***, University of British Columbia, and the Differential Susceptibility Workgroup

Indices of Differential Susceptibility: Measurement Issues and Theorized Relations between Constructs

- Childhood measures
- Adult measures
- Cross-sectional association among behavioral, psychophysiological, and genetic indices
- Longitudinal homotypic and heterotypic continuity and change across development

Defining the Construct of Differential Susceptibility

- Reactivity and recovery as DS factors, and process-oriented outcomes of resilience
    - ***Jelena Obradović, PhD***, Stanford University
- Group discussion of promising measures (validated or new ideas) of major stressor exposure, 'resiliency' to stress, recovery from stressors
    - ***Elissa Epel, PhD***, UCSF and Differential Susceptibility Workgroup Chair
- Empirical and speculative ideas on DS (10 minute informal talks), where to look and not to look
    - ***Keith Godfrey, PhD***, University of Southampton, ***John Hobcraft, PhD***, University of York, and ***Essi Viding, PhD***, University College London
- Group discussion on conceptual framework for DS, directions for measurement of markers of DS (as well as of adversity, resiliency and recovery, and key outcomes). Prioritize the questions, which will help guide the next section (discussion of study opportunities)

3:15 p.m. **BREAK**

3:30 p.m. **Sample Data Sets for Investigation of Differential Susceptibility**

- Variation among children in response to adversity
- Variation among adults in the long-term consequences of childhood adversity
- Variation in response to discrete, naturally occurring changes in adversity
- Variation in response to planned, standardized interventions

4:30 p.m. **INTEGRATIVE DISCUSSION:**
Differential Susceptibility, Critical Periods: Implications for Preventive Intervention in Adults with a History of Severe Environmental Adversity in Childhood

Wednesday, February 27, 2013

9:00 a.m. **INTEGRATIVE DISCUSSION I**
Critical Next Steps in Promoting a Program of Research on Reversing the Effects on Adult Health of Early Prenatal and Postnatal Adversity
Stephen Suomi, PhD, NICHD and ***David Reiss, MD***, Yale University

10:30 a.m. **BREAK**

10:45 a.m. **INTEGRATIVE DISCUSSION II**
Planning for the London Meeting
John Hobcraft, PhD, University of York and ***Essi Viding, PhD***, University College London

12:00 p.m. **ADJOURN**

APPENDIX 3: PARTICIPANT ROSTER

Farheen Akbar, MPH
Research Program Analyst
Division of Behavioral and Social Research
National Institute on Aging
Email: Farheen.Akbar@mail.nih.gov

Thomas Boyce, MD (by phone)
BC Leadership Chair
Development Neuroscience & Child Health
University of British Columbia
Email: Tom.Boyce@ubc.ca

Jeanne Brooks-Gunn, PhD
Professor
Co-Director
National Center for Children & Family Policy
Columbia University
Email: Brooks-Gunn@columbia.edu

Frances Champagne, PhD
Associate Professor
Department of Psychology
Columbia University
Email: Fac2105@columbia.edu

Gabriella Conti, PhD
Assistant Professor
Harris School of Public Policy
University of Chicago
Email: Gconti@uchicago.edu

Elissa Epel, PhD
Associate Professor
Psychiatry
University of California
Email: Eepel@lppi.ucsf.edu

Melissa Gerald, PhD
Program Officer
Division of Behavioral & Social Research
National Institute on Aging
Email: Melissa.gerald@nih.gov

Keith Godfrey, BM, FRCP, PhD
Professor
University of Southampton
Director, Center for Developmental Origins of Health and Disease
Email: kmg@mrc.soton.ac.uk

Jennifer Harris, PhD
Contractor
Division of Behavioral and Social Research
National Institute on Aging
Email: harrisje@mail.nih.gov

John Hobcraft, PhD
Professor
University of York
ESRC Strategic Advisor for Data Resources
Email: John.Hobcraft@york.ac.uk

Jonathan King, PhD
Program Officer
Division of Behavioral & Social Research
National Institute on Aging
Email: KingJo@mail.nih.gov

Bruce McEwen, PhD (by phone)
Professor
Laboratory of Neuroendocrinology
Rockefeller University
Email: Bruce.Mcewen@rockefeller.edu

Terrie Moffitt, PhD
Professor
Duke University
Director, Environmental-Risk Longitudinal Twin Study
Email: Terrie.Moffitt@duke.edu

Lisbeth Nielsen, PhD
Chief, Individual Behavioral Processes Branch
Division of Behavioral and Social Research
National Institute on Aging
Email: Nielsenli@nia.nih.gov

Jelena Obradović, PhD
Assistant Professor
Developmental and Psychological Sciences
Stanford University
Email: Jelena.Obradovic@stanford.edu

Christine Power, PhD
Professor
Epidemiology & Public Health
University College London
Email: Christine.Power@ucl.ac.uk

David Reiss, MD
Clinical Professor
Child Psychiatry
Yale University
Email: David.Reiss@yale.edu

Teresa Seeman, PhD
Professor
Director, Epidemiology Core Instruction
University of California Los Angeles
Email: Tseeman@mednet.ucla.edu

Stephen Suomi, PhD
Chief
Laboratory of Comparative Ethology
National Institute of Child Health & Human Development
Email: Suomis@mail.nih.gov

Richard Suzman, PhD
Director
Division of Behavioral & Social Research
National Institute on Aging
Email: SuzmanR@nia.nih.gov

Barbara Torrey, MS
Volunteer
Division of Behavioral and Social Research
National Institute on Aging
Email: Torreybb@mail.nih.gov

Essi Viding, PhD
Professor
Director, Developmental Risk and Resilience Unit
University College London
Email: E.Viding@ucl.ac.uk

Rose Li and Associates, Inc. Contractor Staff:

Rose Maria Li, MBA, PhD
Senior Project Manager
Email: rose.li@roseliassociates.com

Silvia Paddock, PhD
Science Writer
Email: silvia.paddock@roseliassociates.com