

Pathways and Mechanisms Linking Early Life Adversities (ELAs) and Adult Health Outcomes

Notes prepared by Sharon Stein Merkin, UCLA

Day 1: January 31, 2017

8:30-9:00: Welcome and introductions

Chris Power, Teresa Seeman

The main objective of the Reversibility Network is to build capacity to advance interdisciplinary research exploring the potential for midlife reversibility of/compensation for risks conferred by exposure to early life adversity (ELA). The Network hopes to address this objective by 1) gaining a better understanding of the life-course mechanisms linking ELA to later life health and well-being, 2) developing and testing later life interventions to reduce or reverse risks to health, and 3) identifying resources needed to advance this agenda and strategies for development. Key elements of the Network include seed funding to support new research and workshops/symposia at professional meetings to attract new researchers to the network, disseminate research, and engage with the broader research community. The Network has three active working groups. The first examines the utility of retrospective and prospective measures of ELA for use in health research. A report from a meeting in October 2016, chaired by David Reiss and Andrea Danese, is available here:

https://www.nia.nih.gov/sites/default/files/d7/2016-nov_reversibility_network_mtg_rev_2016-01-25.pdf. Another workgroup explores how new knowledge about behavioral and neural plasticity can inform the design of “reversibility” interventions. That group met in New York, NY in April 2017, and is co-chaired by Bruce McEwen, Steve Suomi, David Reiss and Lis Nielsen (a meeting report is forthcoming).

This report summarizes discussions at a meeting of the third working group led by Chris Power, Teresa Seeman and Keith Godfrey. The goal of this working group is to build and interpret evidence on the processes, pathways, and mechanisms that lead to poor adult health in those exposed to ELA. To achieve this goal, the working group first aims to establish: (a) the major dimensions of early life adversity, and (b) whether different dimensions or forms of ELA have similar/differing effects on adult health outcomes, and (c) whether the pathways leading to those outcomes differ. It is important to keep in mind the breadth of ELA, which spans a wide range of adversity measures, and that ELAs have the potential to be associated with a variety of outcomes. There has been an emphasis in the literature on emotional and cognitive outcomes, and more recently, a greater interest in cardiovascular and other chronic diseases. The current meeting considers dimensions of ELA and addresses three potential pathways linking ELA to disease: metabolic, inflammatory, and epigenetic. The goal of the meeting is to explore current research in this field, identify the key questions related to this research, and generate discussion of future research needs.

9:00-10:30 Session I: Dimensions of early life adversity

Overview: Katie McLaughlin, Margaret Sheridan

Presentation and Discussion:

Katie McLaughlin and Margaret Sheridan provided an introduction to the dimensional approach of conceptualizing childhood adversity. There are different types of adverse childhood experiences that are highly prevalent among children. Research has shown a strong association between childhood adversity and a variety of health outcomes, primarily worse mental health. Early research in this area addressed adversities one at a time, however, a limitation of this method is that adversities often co-occur. To the extent that such co-occurrence is evident, it can lead to an inability to properly tease out individual types of adversity and their independent effects on outcomes. Another approach in the literature is to utilize a cumulative number of adverse childhood experiences (ACE), where the number of adversities is summed to create a total score. This approach has significant limitations and is possibly impeding research by assuming that different types of adverse experiences in childhood influence health via identical mechanisms (i.e., that distinct adverse experiences will influence development in the same way).

An alternative approach seeks to identify distinct core types of adversity, specifically in the areas of threat and deprivation, although there may be additional dimensions of childhood adversity, such as loss or unpredictability, that have yet to be explored in-depth.

1. Threat reflects experiences involving harm or threat of harm (e.g., exposure to abuse, domestic violence, or other types of violence exposure). Exposure to threat shifts emotional and social information processing to facilitate the rapid identification of potential threats. For example, children who have experienced threat exhibit biases in attention and memory toward threat-related stimuli. Exposure to threat also influences the magnitude of emotional reactions to threat-related stimuli. For example, children who are victims of abuse may have enhanced amygdala responses to threatening, but not to non-threatening, images.
2. Deprivation refers to an absence of *expected* inputs from the environment. Deprivation can occur in both social-emotional and cognitive domains. An absence of consistent interactions with caregivers, reductions in cognitive stimulation and environmental enrichment, and lack of exposure to complex language early in development are examples of deprivation. The mechanisms affected by this type of adversity are somewhat distinct from threat. A lack of environmental stimulation impacts neurocircuitry and processes that rely on early learning. This, in turn, can influence cognitive development, leading to problems with complex cognition like language, executive functioning, and global cognitive ability. These cognitive effects may be mediated by neural processes involving accelerated synaptic pruning in cortical regions that process the types of inputs lacking in the environment, resulting in smaller cortical volume and thickness. There is strong evidence of these effects in children exposed to extreme deprived environments like institutionalization and neglect, including worse memory and other cognitive functions. Other exposures, including poverty, can be associated with deprivation, such as reductions in language exposure and environmental enrichment. For example, children experiencing low socioeconomic status (SES) in childhood are exposed to less complex language earlier in development than higher-SES children, which may contribute to lower levels of cognitive function observed in low-SES children.

This approach aims to determine what types of dimensions may lead to different outcomes, and how these effects might be independent or distinct.

What are the barriers to measuring deprivation and threat? To what extent is there co-occurrence of these types of adversity, to what extent are they correlated? There is some evidence of correlation in the British 1958 Cohort study, but the association is not very high. There is slightly higher correlation in the National Comorbidity Survey Replication – Adolescent Supplement (NCS-A) data, a nationally representative sample of US adolescents aged 13-18 years. These examples are from population-based samples, where co-occurrence of adversities is infrequent. However, in samples that are already at high risk for adversity, co-occurrence will be higher than a population-based sample. For example, in a small laboratory-based study conducted by McLaughlin and Sheridan (n=169) where children were recruited specifically based on exposure to maltreatment, there is high correlation between neglect and abuse, but seemingly controllable association between community violence and parental education.

How can we define these dimensions? One way is to measure components of both dimensions and a variety of emotional and cognitive outcomes. McLaughlin and Sheridan presented examples of how one type of adversity can be adjusted for the other and how it is possible that different types of adversity can affect different parts of the brain. One approach to test these typologies is to use factor analysis while another approach is to use cluster analysis or network analysis that includes various emotional/cognitive outcomes and other aspects of functioning (e.g., fear learning, emotional control, cognitive control) along with measures of adversity. Including all of these outcomes in the same cluster analysis and conducting a network analysis would better establish how these dimensions can hold together. This network analysis approach may be more helpful in specifying the major types of adversity and assessing what factors to consider in each type. Workshop participants expressed interest in seeing if this strategy will work in multiple datasets.

Discussion

Types of Adversity

- Seeman suggested that when considering the co-occurrence of deprivation and threat, perhaps it is important to consider a sub-type of those who experience both types of adversity; this category might imply the need for different interventions. Exploring how these types of adversity cluster might be particularly important.

Timing

- An important issue is whether there is a critical time that is crucial in terms of exposure to adversity. Godfrey described the potential of peri-conceptual stress and epigenetic effects that may have an influence on later health. Cognitive deprivation may have distinct effects over various stages across the life course.
 - Sheridan noted that an untested assumption in the data presented is that early life exposure to deprivation occurred at particularly sensitive periods. Jeanne Brooks-Gunn mentioned that there is almost no literature on timing, even though it is crucial to understand role of exposure timing in these associations. One challenge is that many datasets do not link exposures to different time periods, although the UK cohort may be best at this. The Fragile Families study is beginning to explore timing of exposure, but lacks information about exposure during adulthood, as the investigators only collected age 15 data. However, the Fragile Families team was able to anticipate differential effects of new fathers on kids' externalizing behaviors based on time of exposure, but,

surprisingly, found that the effects seem similar across early middle childhood and adolescence. Suomi mentioned similar surprising findings from rhesus macaques where certain environmental hits had the same epigenetic effects in early infancy and late childhood. There is a tendency to look for differential developmental effects, but at the level of gene methylation patterns, they were remarkably similar.

- McLaughlin mentioned that we must keep in mind the system at which we are looking. For example, language learning and other cognitive domains are known to have sensitive periods. In other domains, like emotional systems, we do not know whether there are sensitive periods. Moreover, how we measure timing is also important (for example, orphanage data provide very accurate timing of when environments changed, but observational studies are messier.)
- Danese suggested that we should perhaps consider the idea of timing with regard to genetic effects: are the effects we are seeing environmental or causal? Moreover, is there a potential selection that is stronger for certain types of adversity? Has adjustment been considered for cognitive deficits? This link between deprivation and health may be different if it were inherited rather than environmental. McLaughlin responded that although selection effects are important, some of the strongest evidence of deprivation-health linkages comes from deprivation studies in institutions, where changes in environment led to changes in the outcome.
- Nielsen mentioned National Institute on Aging interest in assessing lifelong trajectories of cognitive function. For example, research on racial differences in late life cognitive function has been enhanced by greater attention to exposures such as education and school quality (e.g., school funding, teacher quality). The association between cognitive function and educational attainment can be unpacked more if we include information on exposures occurring both earlier and later in life.

Interventions

Prevention

- Reiss mentioned work done by Daphne Bugenthal that predicts which mothers might be abusive, specifically those mothers who feel threatened by their child's presence. Bugenthal has an intervention focused on the threat sensitivity of the mother. Important issues in this area might be to explore whether mothers are threat-sensitive, whether targeting threat-sensitivity in mothers prevents abuse, and whether this association is the same for adopted children to gain insight on the genetic link.

Reversing Effects of Deprivation and Threat

- A question arose about whether there is existing evidence that the effects of deprivation and threat are reversible. McLaughlin mentioned that, regarding the threat dimension, there is much evidence about the effectiveness of psychosocial approaches on reversing the effects of deprivation and threat, including desensitizing kids to socioemotional exposure and intensive psychological interventions. In the cognitive domain, there is evidence from institutional studies that some of the harmful effects seem reversible, but less is known about adulthood exposure.

Intervention for Different Pathways

- Seeman was curious about the long-term implications of the different mechanisms that might be involved for deprivation and threat. She inquired whether anyone has looked at adult

implications, and whether deprivation and threat continue to have different pathways that may lead to different outcomes or merge at some level. Additionally, does early life patterning affect adult outcomes differentially? Danese remarked that the pathways may be different, but eventually may lead to the same endpoint.

- Sheridan responded that this is unknown, but if pathways are different, interventions might also look different. For example, if the pathway is via someone becoming a bad problem solver, the intervention should be cognitive. If person is emotionally dysregulated, that intervention may not be effective and even possibly harmful. Despite ending up in the same place (in terms of health outcome), the pathways may be different, and that difference may be crucial to determining appropriate interventions.
- Power stated that there is not an answer to these questions, but exactly as Sheridan predicted, Power and colleagues found differential association for child adversities, with child neglect (but not abuse) associated with later adult cognitive function (memory, etc.), whereas both neglect and abuse were related to later emotional outcomes.
- Terrence Forrester pointed out that because there might be differential responses to the same stimulus, with agnostic biomarkers, perhaps researchers can approach the mechanistic part from the back-end. The suggestion is to compare susceptible and resilient individuals (those who developed outcomes and those who did not) and observe the differences between them. Then, with *a priori* knowledge, we may predict what pathways can affect what exposure, as in a case-control study.
- Godfrey raised the question of whether assessing the different dimensions really matters in terms of interventions. He thinks it does, and added that we should consider the nutritional dimensions as well, because brain dimensions are too narrow. One strategy that has had positive effects so far in the research is bringing together massive datasets and separating out the different dimensions where possible and determining how these mechanisms play out.
- McLaughlin noted that part of why disentangling these dimensions seems complex is because the different health outcomes seem similar (i.e., worse mental health, worse physical health in similar ways). However, where there is separation in the dimensions, the pathways are also different. If the pathways are different, interventions will need to be differently designed. The mechanisms and pathways that lead someone to engage in the identical negative health behavior may differ (e.g., eating poorly as a result of no access to resources to purchase healthy food as opposed to eating poorly as a comforting behavior resulting from stress); knowing these pathways is crucial to identifying appropriate interventions. The problem with survey or population-based datasets is that a lot of these mechanisms are less commonly measured. But that is now changing; cohorts now measure information processing, executive functioning, etc.
- Seeman mentioned that we generally only have retrospective data on adversity, and questioned how good these measures are in adults. She asked if ELA-health associations can be tested well through adulthood? In terms of pathways, by the time you get to adulthood is there some convergence of the different pathways or are these still distinguishable?
- One area where research suggests common pathways is with the hypothalamic-pituitary-adrenal (HPA) axis. There seems to be similar cortisol responses associated with psychological and physical outcomes, indicating that the HPA axis may be a common pathway leading from adversity to mental and physical health outcomes.

Potential Steps Forward

- Godfrey suggested that researchers collaborate on datasets to collect measures of adversity. The main issue is framing the questions in a sharp but simple way. Godfrey stated that the field

needs some specificity regarding measures for type of adversity and health. However, if we can start framing those and put out a call, this can be addressed.

- Data that are lacking include more extensive life stress interviews, measures of adversity, and emotional control/fear learning data (the cognitive mediators addressed in the proposal for conducting network analysis).
- Epidemiologic studies seem to be considering cognitive outcomes more, but there are additional data that can be easily collected (such as emotional perception data) and is currently not included in those studies.
- Nielsen drew connections with another NIA initiative on the long-term effects of personality, especially conscientiousness and neuroticism, on later life health. Are there links between neuroticism and exposure to threat adversity? What do we know about pathways from childhood neuroticism, early adversity, and adult health? Another pathway to consider is how psychological factors may lead to health behaviors as a response to one's environment. One approach may be to target psychological or behavioral mechanisms instead of targeting biology, as in the National Institutes of Health Science of Behavior Change program. Behavior change may be an under-utilized but effective pathway when considering links between early adversity and physical health outcomes.
- In terms of behaviors, Karen Lillycrop mentioned that unpacking nutritional intake is difficult and that prenatal consumption of alcohol may be important. McLaughlin mentioned that they have used a small 4-item scale for food security as part of measure of material deprivation. Sheridan noted that they are hoping to include more nutritional measures and need more expertise in this. There is a "Baby Connectome" element of the Human Connectome project that is including measures of nutrition and beginning to obtain indicators of social environment.
- Sharon Merkin suggested considering the interaction of poverty and some of the adversity measures; there may be dissonant groups (for example, those with high childhood SES and adversity) who might experience different mechanisms/outcomes. Responses included the idea that child SES is thought of as construct or risk factor, as part of the context in which adversity occurs and not an exposure itself (i.e., poverty as a predictor of the exposure but not the exposure itself; increasing likelihood of experiencing the effects).

Summary Comments

- Reiss: we have brought up key ideas concerning the issue of timing. There are 2 aspects that are especially crucial: when does adversity occur and does it matter?
 - There are some good designs to clarify this: take the child out of the adverse situation (e.g., English-Romanian Adoption Study). Other designs may include examining data after a disaster and measuring how different age groups respond in different ways as was done meticulously for post 9/11 studies. There might be some surprising findings there.
 - Second area of timing relates to the timing of intervention. Existing cohorts have followed subjects after interventions at different developmental periods, in infancy, in early childhood, in adolescence and, --in mother-infant psychotherapy--at the time the adult woman has just born a child. Many of these cohorts can be followed to determine whether intervention timing played a role in their long-term effectiveness (or ineffectiveness).
 - Third timing issue from last workshop: adversity itself affects timing of sensitive periods. Nim Tottenham shows adversity accelerates all the ordinary timing periods. Hard to go

- to a population and ask when it happened and convert that information to create an exposed population.
- Another issue to discuss is the clustering of outcomes and risks. We talked about some of the problems indicating some of the different processes, and how large samples are important for replication purposes. Are we presenting a decent range of potential dimensions in this large-scale clustering effort? Nutrition was first to get into this historically, and nutrition should be included in this list of dimensions. Technical problems are substantial.
 - Godfrey remarked on the comment regarding nutrition and how it is also multi-dimensional. In Southampton, 40% are iodine deficient pre-conception. Does that matter? It seems to matter. IQs of offspring are lower.
 - It will help us to know what interventions might look like. This will help frame the studies we are doing. We shouldn't be doing research unless leading to potential preventive or ameliorative interventions. With that mindset, helps to give sharper focus. Is intervention justified or not?
 - Brooks-Gunn expressed concern at some comments regarding how we operationalize timing and synergistic affects. How do we get to the timing unless charting individual life courses? What type of analyses can we use?
 - Godfrey suggested coming up with action plan about what datasets to pull together and do it.
 - Seeman agreed that is important to keep in mind the target of intervention. Can we lay out what we think the adult consequences might be in terms of cognitive function, emotion processing, behavior? That seems to be the target because if we intervene there it can affect physiology. Can we think of those as we look at the specific pathways that might be driving those adult manifestations? What data do we have and what do we not have? In epidemiologic studies, we typically do not have emotion processing, etc. Should we get the data, or do we start by piecing data together to test these hypotheses?
 - Sheridan suggested looking at cognitive and neuro-processing datasets in adults and seeing what they have. We can also work with Forrester's suggestions, and possibly identify omics (e.g., epigenetic or other non-brain blood/bio markers) that may measure cognitive control vs. emotional control.
 - Godfrey reminded the group to keep in mind the bias from retrospective studies. Other idea is to also collect proxy tissue such as blood to measure genomics and epigenomics.

Session Summary

This session addressed the need for more rigorous and distinct measures of early adversity to improve their specificity and sensitivity in addressing specific mechanisms linking these measures and disease outcomes, as well as to establish a standardized set of measures (currently lacking in the literature). In addition, understanding and exploring types of adversity is crucial to investigating the effects of critical time periods and exposure to adversity, as well as to determining types and timing of potential effective interventions.

Note: this session took place at 10:45 instead of 1:30 PM, as originally planned

10:45-12:15 Session II: Pathways – Metabolic Processes

Overview: Terrence Forrester

Additional contributors: Eric Loucks, Keith Godfrey

Terrence Forrester presented findings from his research on severe childhood malnutrition as an example of metabolic pathways leading from ELA to adverse outcomes in adulthood, and an example of one type of intervention that may be implemented. Forrester discussed the systematic differences between two phenotypes of severe malnutrition, Kwashiorkor (K) and Marasmus (M), with M patients presenting as severely wasted and K less severely wasted. The dietary exposures leading to the two very different syndromes of severe childhood malnutrition, M and K, are not different. M patients, despite severe wasting, maintain protein breakdown (they do not downregulate protein breakdown in response to the undernutrition stimulus) and thus maintain the supply of amino acids to the metabolic pool; in turn maintaining integrated metabolism. K patients, on the other hand, do not maintain an adequate rate of protein breakdown, experience a shortage of amino acids in the metabolic pool and thus fail to sustain integrated metabolism. At recovery from severe acute malnutrition, M and K also behave very differently metabolically, with M having a metabolic architecture of thrift in energy and substrate utilization in contrast to K, which is profligate in use of energy and substrate. M are thus more resilient to long term nutritional deprivation, maintaining functional integrity even while wasting, but K are not as resilient in the face of nutritional deprivation.

Do the systematic differences in clinical presentation and metabolic architecture provide evidence of differences in the developmental origins of such phenotypes? Birthweight data has provided insight as there is evidence of higher birthweight in K patients (effectively normal) compared with M who are approximately 300g lighter at birth. Mortality has been found higher in K patients compared with M; such differences in health outcomes could be the result of fetal programming. Adult survivors of childhood malnutrition may also be important to assess the systematic differences between these phenotypes, and data has shown that adult survivors of M are shorter and have lower relative weight. Forrester suggested that perhaps M patients are also more challenged economically leading to fewer resources resulting in these relative weight differences. The literature on diabetes is not clear regarding the etiology, however it seems that M patients develop higher glucose intolerance, beta cell dysfunction, and higher insulin resistance compared to K and to controls (somewhat surprising findings given their size). Both malnourished groups experience higher blood pressure and peripheral resistance in adulthood. In contrast with measures of glucose impairment, where prenatal and postnatal conditions seem related to the outcomes, for cardiovascular measures, prenatal conditions did not affect outcomes (rather only wasting and diagnosis). This suggests that for some adult outcomes, timing is important.

Cognitive and psychosocial interventions seem to remediate some of these negative consequences but not reverse the effects to the level of controls. There is some interest in determining if the higher susceptibility of M survivors to cardio-metabolic impairment might be related to increased risk for differential cognitive impairment? There is some evidence that M survivors have lower ability to process conflict compared to K survivors, with controls functioning best, then K, and then M survivors.

Epigenetic evidence is more limited; the question relates to the hypothesis that there should be systematic differences in the epigenome of these two phenotypes that might help identify the pathways involved. Most of the difference in genes have been found in the immune system (using muscle cells), showing differential methylation identifying insulin signaling, regulating body size and composition and leading to glucose signaling differences and insulin resistance differentials.

The focus of intervention research has been on stroke, the most important outcome of the cardio-metabolic profiles discussed. Research addressed the question of whether we can mitigate this risk of recurrent or incident vascular disease by focusing on cardio-metabolic risk profile through behavior modification. Forrester described one such intervention of raising physical fitness with evidence of increases in brain plasticity, increases in walking speed, and improved glucose tolerance in stroke survivors, risk factors that could reverse the risk about 60% for second stroke. Measuring improvement in the glucose-insulin relationship may serve as a proxy for risk of re-stroke. It appears that interventions that can improve physical fitness and mobility may lead to better glucose control; these may not reverse damage but can mitigate the negative outcomes.

Forrester described what he sees as the 3 main questions: 1) can we intervene to prevent the interactive cardio-metabolic and neurocognitive deficits that emerge out of early life malnutrition? 2) Where in the life cycle do we have the best opportunities for intervention? 3) What tools do we have at our disposal?

Discussion

- Reiss asked if it is possible that exercising in midlife might correct metabolic dysfunction? The response was yes, and there is much literature on this. Forrester noted that exercise can help brain dysfunction for those who have been stunted and severely malnourished (particularly for those with cardiometabolically-driven cognitive impairment).
- Could brain changes represent one of the confluent pathways, in other words, two distinct early adversities (e.g., psychosocial or malnutrition deprivation) ending up producing similar impairment in brain function?
- McLaughlin noted that pattern of brain findings seems similar to what they find (cortical thinning, pruning too quickly). Could be a reflection of accelerated development due to environmental stress.
- Reiss suggested that one of the issues this presentation raises is that the environment begins at conception, supporting the idea of developmental programming, where the fetus is already exposed to this environment. He also pointed out that the brain dysfunction mentioned in this presentation may represent one of the potentially confluent pathways we discussed before, where different types of early adversity lead to similar impairment. It would be interesting to think through research designs to test how disparate environmental insults might produce the same target for intervention (for example, exercise might be an intervention for both metabolic and brain dysfunction pathways?). Perhaps exercise or “exercise plus,” that is, exercise coupled with an additional intervention that may be more effective after exercise (with exercise increasing neuroplasticity).
- Sheridan noted that what is most useful about brain measurements is that they are objective and can be measured same way. These measurements are thus ideal in terms of comparing across different cohorts and different exposures.

Keith Godfrey presented data on development and life course strategies

- Some of the consequences of a threatening developmental environment include prematurity, sarcopenia, early puberty, while secure developmental environments represent investments in longevity and size, including neuronal, nephron, cardiomyocyte numbers, and larger adult bone mass and muscle growth.
- Trajectories of risk are set early on. There is the possibility of intervention in later life, but the process is more difficult and often requires more ongoing intervention.

- There is increasing interest in exploring genome to phenotype, and epigenomic consequences. Godfrey presented data on altered epigenetic regulation in offspring.
 - The data show an interaction between pre/post-natal periods and the association between childhood diet and adiposity at 9 years of age (outcome). Poor childhood diet was associated with 9-year fat mass but only in those with prenatal abdominal growth faltering (of fetus). The factors related to prenatal abdominal growth include mother's birthweight and uterine capability to maintain fetal growth.
 - Certain aspects of fetal growth are driven by placental size and others are driven by placental transport capabilities and are not size-dependent.
 - Some of the adaptations to maintaining fetal growth have downstream health implications and consequences.

Eric Loucks presented data on cardio-metabolic mechanisms of ELA

- Data from the New England family study on parental emotional care score and coronary heart disease risk (Framingham) showed significant relationships in females between parental emotional care and later risk of heart disease. When the Framingham risk components were explored separately, smoking was shown to be strongly associated with coping and a behavior that can be initiated in early life (before age 18). However, the association remained significant even after removing smoking from the Framingham score, indicating other pathways may play a role as well.
- Data from the CARDIA study utilized the Risky Family score and showed that smoking (but not cholesterol) in both genders is associated with ELA (as outcome).
- Data from the Georgia Stress and Heart Study including children and followed them up over time show an increase in blood pressure in adulthood associated with reported ACE in childhood.
- A systematic review (by Midei and Matthews) indicated an association between exposure to childhood violence (any interpersonal) and subsequent obesity. A review by Danese included different types of violence, but mainly childhood maltreatment (victimization by adult).
- Interventions: In the Abecedarian project, compared to the control group, the treatment group (males only) had lower Framingham risk scores, metabolic syndrome, and systolic blood pressure. (Campbell et al.).
- The Big Picture: We are often seeing associations between ELA and obesity, some association with lipids and cumulative risk scores.

Discussion:

- It is important to keep in mind that most of these measures are based on retrospective reports. At the last meeting of the Network, Danese and colleague identified large number of cohorts in which it would be possible to compare retrospective and prospective reporting and examine whether the findings are consistent when looking at both forms of reports of ELA
- Godfrey asked whether anyone would challenge the concept that metabolic pathways connect ELA and health?
- Godfrey: Important to also look at infection dimensions and not just stress and brain association. Also mentioned IL6 levels in mother during pregnancy predict offspring adiposity, independent of mother's obesity levels. Cytokines have effects on mother and placenta and potentially indirectly on fetus. But exact pathway is uncertain.

Interventions

- Seeman initiated a discussion about how to apply this emerging knowledge to the design of “reversibility” interventions by asking, if we think about how early experience sets in motion some patterns of managing metabolism, what does this mean for considering what interventions can be more or less effective later in life?

Physical (Aerobic Interventions)

- Forrester responded that, in general, it seems that energy expenditure and specific interventions can affect cognitive outcomes. Emerging data indicates that if you have high cardiometabolic risk load driving low cognition, this damage can be partially reversible.
- Reiss asked whether it is leg exercise specifically. There is evidence for benefits of both aerobic and resistance exercise. Aerobic exercise may be advantageous because it integrates multiple systems; brain, neural control, hepatic function, muscular function and cardiovascular function.
- Lillycrop noted that there are some ongoing exercise and diet interventions with obese pregnant mothers. This intervention seems to have long term effects on child and mother (and this was only mild exercise).
- Godfrey reported on an intervention being conducted in the UPBEAT study. It was hard to get obese mothers to exercise, and it was found that kids are not less overweight at birth, but are thinner at 6 months of age. These were the first data where intervention targeted at mothers has reduced adiposity of offspring.
- Lillycrop suggested looking at the structure of DNA to also see what genes can be regulated.

Cognitive Interventions

- Nielsen noted that NIA is also exploring a range of potential cognitive interventions, including combinations of cognitive training, mindfulness, along with mild exercise. The question remains whether anything is better than nothing or whether tailoring the particular exercise or intervention based on the specific deficit (associated with ELA) might be important.
- Godfrey asked whether NIA is currently supporting interventions with brain/cognitive activity and a nutritional component. Nielsen responded that some nutritional interventions are in the cognitive domain, and will follow up with a list. Godfrey noted that there are mechanistic reasons as to why this combination is likely to have synergistic benefits.
- Seeman asked if exploring the different elements of diet be helpful? Godfrey responded that it depends on how good the tool is to detect different dietary elements (e.g., fatty acids).

Behavioral Interventions

- Seeman pointed out that we already know what behavioral interventions make a difference, but the question is, how do we maintain those?
- Nielsen noted that the NIH Science of Behavior Change Common Fund Program is focusing on this question, looking at whether focusing on specific mechanistic targets - self regulation, stress reactivity – that are presumed to play a role in initiating and maintain behavior change, can improve our interventions. The big question, from a reversibility perspective, is whether individuals with ELA present with behavioral phenotypes or are more or less deficient in these target domains (self-regulation, etc.). If so, what are the implications for how we design interventions to manipulate self-regulation targets in these different phenotypes? This question has been raised in the SOBC Network, but no projects are currently addressing this issue.

Timing of Interventions

- McLaughlin asked how can we re-open plasticity in later life. There seem to be some later plasticity enhancers. Exercise can be a good candidate. A brief intervention, paired with exercise can be an interesting option. It might also be effective to deliver cognitive interventions that are briefer, more sustainable, and paired with exercise.
- Nielsen underscored that NIA is most interested in exactly this question, regarding whether interventions can occur at least in midlife. While there is also clear value in interventions earlier in life, NIA is particularly interested in what can be done for people later in life.
- Godfrey urged a partnership between NICHD and NIA to identify optimal timings and time points. Early life investigations can unlock what might be important for later interventions.
- Reiss noted that one place where child and adult come into play together is in interventions on mothers, which also affect children later on.
- Seeman raised the potential of a program of research to look at relative benefits of targeting at different time points. If you find there is more “bang for your buck” at younger age, that is important information, but it would also be important to know that it’s not too late for an intervention later on, and what the limits are.

Session Summary

This session explored one particular pathway through which ELA might affect health, namely, via metabolic processes. There was much discussion about the potential for reversibility in this pathway. In particular, most of the promising methods of intervention involve physical exercise, although other components were mentioned as potential contributors, including behavioral, cognitive, and dietary interventions. It is unclear, although of great interest, how effective interventions are at various stages across the life course, especially after the relatively elastic periods of childhood and adolescence.

Note: this session took place at 1:30 PM instead of 10:45 AM, as originally planned

1:30-3:00 Session III: Pathways to Adult Outcomes – Issues Of Causality

Overview: Erick Loucks

Additional contributor: Chris Power

Eric Loucks described the challenges in causal inference as applied to early life adversity research. Specifically, is the ELA-health association causal and what would convince us of that? There are three major issues to focus on with regard to this issue of causality: residual confounding, evaluation of specific types of ELA, and testing interventions that might mitigate the health effects of ELA.

Potential residual confounding should be addressed in ELA studies, including measures such as SES and parental mental health. One way to address this issue is to utilize Directed Acyclic Graphs (DAGs) to identify common prior causes to ELA that might influence both ELA and health. One example of this is the association between ELA and Intima-media thickness (IMT) observed in CARDIA. This association was reduced after adjusting for childhood SES, but this adjustment did not reduce the association between ELA and the Framingham CHD risk score. An analysis of data from the New England Family Study also highlights the potential for confounding. Utilizing propensity score matching, when prior causes were added, the effect size decreased and was no longer statistically significant.

Evaluating specific ELA factors is also crucial in investigating the potential causal effect of ELA and health outcomes. Different types of ELA can affect health differently. For example, when analyzing the different ELA questions in CARDIA separately, rather than as one Risky Family Score, some of the questions were associated with CHD risk and some were not (physical abuse in females but not males; parents know what you were up to versus did you feel loved, etc.). Is there a continuum of ELA, an issue of degrees, or are these different types of ELA focusing on different aspects of adversity? Dong et al 2004 showed how different components of ACE affected ischemic heart disease differently. Danese pointed out that those ELA measures were all retrospective.

Finally, examples of effective interventions can inform our understanding of the causality of the ELA-health association. Data from the Nurse-Family Partnership study, and Perry Preschool study showed improvements in health over time. A systematic review of mindfulness interventions studies has shown improvements with regard to depression, even out-performing antidepressant effects. Moreover, studies have shown that mindfulness-based cognitive therapy may be more effective in conjunction with or instead of antidepressants for those having experienced childhood abuse. Mindfulness seems to also be most effective in improving physical outcomes (for example, blood pressure) when other interventions are not effective. Loucks presented some data in progress showing that mindfulness seems to be most beneficial in those with increasing ACE scores.

Chris Power presented data on specific growth trajectories for those who experienced abuse that indicate a pattern of low weight gain or “lighter” childhood and then sharp increase in the rate of weight gain at older ages (young adult-adulthood). This lighter growth earlier on and increased growth has also been seen among those reporting physical abuse in the 1958 cohort. This pattern should remind us to consider alternative explanations about causality, and question to what extent this weight gain can be attributed to ELA. For example, body size might influence an individual’s risk of being abused. Alternatively, exposure to ELA may actually be reflecting earlier exposure to adversity (pre-natal?). Another explanation may be related to personality; thus, this type of growth trajectory may actually be reflecting increased experiences of pain or increased sensitivity of particular people with regard to their childhood experiences. It is important to consider different patterns and alternative explanations when approaching these issues of ELA-health associations.

Discussion

- Godfrey noted that postnatal weight gain might be instilled prenatally, and thus postnatal growth can reflect a prenatal effect.
- Reiss suggested another explanation- that weight gain may be associated with belief in being abused. [In comparing the retrospective/prospective data, it was found that] those who recall abuse but may not have documented abuse are more neurotic, and also more likely to experience pain. Groups that are defined based on recall may thus be defined by a distinct sensitivity to the environment and a higher likelihood to gain weight. It is possible that this trajectory we are mapping of weight gain is mapping this feeling of vulnerability, fewer boundaries, etc. This is a plausible explanation for those effects.
- Godfrey discussed two patterns: gestational obesity, subsequent obesity, and rapid weight gain (Godfrey termed “high route”); and a second pattern of rapid growth only later in life associated with early traumatic experiences (Godfrey termed “low route”). Power confirmed that these are the two patterns they see in their data.

Interventions

- Seeman asked if the interventions implemented when they are already overweight be differentially effective in these two groups.
- Danese pointed out that there are about 5 studies in patients who underwent bariatric surgery, and the outcomes are poor in people who report ELA.
 - Reiss added that this was the only area of research on medical (in contrast to psychiatric) syndromes that showed that recalled ELA is associated with treatment resistance.
 - Forrester asked if this was related to adherence? Answer is not sure.
 - Godfrey- one suggestion is that bariatric surgery alters the gut of microbiome, in turn altering short chain fatty acids and other mediators, which themselves have epigenetic effects with consequences for metabolic and brain function

Causality/Genetics

- Seeman asked if the group thinks there is value in thinking about some of these causal criteria. What is recommended to nail down that causality?
- Danese noted that one thing we have not mentioned is selection effects, where some predispositions may be genetically transmitted. For example, a lack of impulse control may be associated with adversity and more vulnerability to gain weight (i.e., may be related to both the exposure and outcome). There was an attempt to test this in twin samples, to see if the effect of bullying on being overweight is independent of genetic factors. There are now improved genetic measures available, so that we can start considering reasonable proxies for these genetic factors. As this measure improves, that could be one way of narrowing the causality.
- Reiss noted some warning signals in the literature, including the idea of pleiotropy: the same genes have effects on both measures of the environment and on the behavioral or disease outcome (e.g., Godfrey study). The problem is we don’t know most of the genes involved, so how do we do the residual confounding analysis? Can have remaining residual confounding.
 - There are 3 possible designs to keep in mind: 1) conventional twin study (MZ difference design where one twin exposed and one is not); 2) adoption studies, of which there are two ongoing adoption studies, one started years ago in Colorado and one by Reiss’s team with large number of subjects; 3) studies of foster families, especially for children

placed there early in life. Variation in these studies can't be due to gene-environment correlations.

- Another source of residual confounding relates to what extent the child evokes or selects an adverse environment. Studies have suggested that the apparent association between abusive parenting and child outcomes could be due to genes with impact on both the environment and the outcome. Most of these pleiotropic genes have not been identified.
- Another reminder of potential residual confounding: in many of the MZ twin studies, the association between education and health disappeared when you take into account genetic measures.
- McLaughlin made the point that perhaps we should pursue behavioral factors regardless as to whether or not they are genetically based.
- Reiss responded that the question of genetics is relevant when we explore mechanisms. Is the outcome a result of genetics or exposure?
- Danese stated that identifying pathways is important for prevention purposes.
- Sheridan cautioned that we should be careful and think about importance of genes. We should keep in mind behavioral studies with irresponsibly high estimates of genetic effects; we should hold these studies accountable for testing what they are showing, and they should reliably show actual differences of exposure. Also, seems like a cross design of twin studies with longitudinal cohort studies, is vulnerable to error and bad study design. This is an historical concern and we should be careful in study design.
- Danese noted that some exposures are more reliable than others (e.g. bullying can be very reliable), and for other things you can use another study design. Genes have influences that should not be dismissed.
- Miller worried that we spend so much time and money on gene studies, but we cannot really get the effect size we can get from the exposures. You can look to animal models, since we often lean on animal studies for causal leverage when it comes to the study of disease. Danese noted, however, that animal models are useful with clean exposures. These adversity exposures are hard to implement in animal studies and difficult to translate to humans.

How Genetics Potentially Relate to Interventions

- Godfrey noted that this is one reason we need to get into interventions. The world has been misinformed about twin studies, and then in population based studies you get different conclusions. But one does need to take into account genetic background of the individual and when you do, you see remarkable gene-environment interactions.
- Reiss emphasized that it's not heritability that we are after in the twin studies, rather, it is what these genetically informed studies tell us about the environment. They point to a class of influences that siblings share. These classes are very useful for looking for environmental causes and designing interventions. Modern studies show non-shared environments are unstable but stabilize in early adulthood (for example, a leading candidate is marriage - siblings differ in marriage experiences). The lifespan perspective (and shared vs non-shared environments) is not clarifying the heritability, but points to the category of environmental influence that can play a big role and serve as an important tool.

Purpose of Causality- Mechanism vs Intervention

- McLaughlin commented that the strongest evidence of causality of environment is interventions that change the environment and result in strong effects. With genetic studies, an important question is, what are we actually going to do with that information?
- Seeman noted that one aspect of causality is understanding mechanisms; the other part of it is where at these points you can effectively intervene. If intervening has positive consequences, is not that really important? It does not really matter what happened earlier, does it? What would be an effective target, regardless of the past, and what can we do now to intervene?
- Danese noted that early adversity has environmental effects, but interventions are not telling us that there are no genetic effects. Even entirely genetic conditions can be remediated by environmental conditions. But understanding the mechanism, both genetic and epigenetic, may give us clues as to where to intervene.
- Loucks noted that for abuse/neglect, Mendelian study can be a causal tool for inference.
- Danese emphasized that the question is not whether an association is causal, but is the effect of intervention able to reverse the association?
- Steven Gillman noted that genetics is one type of residual confounding. But there is also residual confounding by early SES. The implications of that is there are other pathways or types of pathways implicated by socioeconomic condition. This can also potentially illuminate other opportunities for intervention.
- McLaughlin pointed out that the idea of measuring adversity dimensionally is also to minimize bias. Even though we do not call it residual confounding, that is part of the reason to consider all constructs of adversity and not just pick and choose. Seeman suggested that the dimensional approach would let you get more of a handle on causality because differential predictions of relationships.
- Miller stressed that control is only as good as measurement, so we need to be careful of mis-measured predictions. Also, the exposures are not highly correlated, but enough that they can pull out common variance. This is a blunt approach. The question of what is a confounder and what is on the causal pathway is not always clear (e.g., adult SES as confounder or pathway?).
- Power suggested ways we can build up sophistication in causal criteria. One way is taking the dimensional approach and broadening this approach from psychological to physical outcomes. Also, can we devise measures to look at dose-response, so we can assess burden of adversity? Adding up adversities may not be informative, but if we build up a better measure of deprivation, that might be helpful in looking at criteria. This does not prove causality, but improving on measurements of deprivation would be another step.
- Suomi noted that what may be confounding in one stage of development may be causal in another stage.
- Loucks asked what is the causal piece in the reversibility network? The value of interventions is, once we clarify the hypotheses, we can intervene and test some of the mechanisms and see if we can get movement on those mechanisms.
- Danese, playing devil's advocate-, asked whether, if we find an effect of an intervention, are we confident we are able to describe a causal effect of adversity? What we might be doing with intervention is opening an alternative pathway. If we ask people to exercise, the pathway might be increasing calories or reducing inflammatory effects. The concern is that the intervention test is not truly test of causation regarding ELA.
- Nielsen noted that we are trying to test specific hypotheses about the role of a particular mechanism on a pathway; the question is, can we measure change in that mechanism and

demonstrate that this change had an effect on a subsequent change in behavior or another outcome? Danese responded that there could be many pathways leading to the same outcome.

- Reiss suggested applying the DAG model to interventions. It is true that if intervention affects mechanism that provides preliminary evidence that it is in causal chain, but you may have affected other mechanisms you did not measure. There are now confounders because not causally linked. Can we use intervention studies as causal proof, by adding null mediators (that we don't think will work) or other mediators as confounders to account for residual confounding?
- McLaughlin noted that if the goal is to intervene through a compensation strategy, even if not a causal pathway, we can still accomplish this.
- Danese suggested a need to balance between observational and intervention studies.
- Nielsen suggested that this line of thought could tie back to the dimensional approach. If one type of adversity may be related different hypothesized causal mechanism, interventions might target different processes to test these hypotheses.
- Loucks pointed out that different interventions can affect people differently. For example, if people have higher levels of loneliness, mindfulness may be useful because of the socialization involved and not because of the mindfulness training itself.

Session Summary

This session addressed the issues related to causal inference of the pathways between ELA and health. Are there guidelines researchers should follow to establish such causal inference? There was much discussion about the theoretical importance of establishing causality in order to implement effective interventions.

3:15-4:30 Day 1 Summary Discussion

Suggested Next Steps:

Measuring ELA

Obtaining ELA Data

- (Loucks): Providing information as to available datasets including retrospective and prospective ELA measures.
- (Sheridan): Utilize large population of datasets that include measurement of adversities as well as measurements of development to get a broader sampling of adversities in existing studies.
- (Sheridan): For those datasets with good follow-up information, develop more specific measures for the specific nodes (or mediators) that hold the outcomes together. For example, many datasets will have good measurement of one or another exposure (e.g., poverty, maltreatment, etc.). But few will have good measurement of these exposures **and** good measurement of neurobiology. The idea is that these neurobiological measures (a) mediate the link between outcomes and health and (b) that these mediators will 'link' otherwise desperate measures of adversity to each other.
- (Loucks): The field might benefit from vetted measures. Measurement standardization and improvement is important and needed.
- (Sheridan): Many studies already have good measure of deprivation (from studies conducted in the home) and adequate cognitive measures, so we can at least start there. Seeman asked if those different measures can be shared with the group and posted. Brooks-Gunn was asked if she can share these measures.
- (Nielsen): May be useful to outline the cluster of measures of the behavioral phenotypes to include and distinguish some particular pathways. One example of framework that describes psychological constructs at multiple levels of analysis is the RDOC matrices put together by NIMH: <https://www.nimh.nih.gov/research-priorities/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml>

Methods to Measure ELA

- (McLaughlin): Examine network structures in large population based samples; there is a need to identify relevant cohorts with these data.
- (McLaughlin): Develop a systematic way to assess additional dimensions, and not only the two discussed today (threat and deprivation).

Summarizing Literature

- (Loucks): Conduct a systematic review and meta-analysis of existing studies to synthesize the literature. This would inform future research, and would allow for practical and cost-effective assessment of most needed interventions given constraints of our health care system.

Addressing Major Issues/Challenges Related to Data Collection

- (Godfrey): A major impediment to this research is the ethical component. For example, the need to report sexual abuse. We should explore the best ways to ascertain information in an ethical way, without negating duty of care.

- (Sheridan): Despite the difficulty, we should encourage researchers to try and do this – it is possible to put the right measures in place. One option is to develop abuse potential inventories. For example, ask parents questions highly correlated with abuse behaviors but are more about attitudes rather than directly asking about those behaviors (e.g., parenting practices, family conflict).
- (Danese): In the context of a large study, the time investment is small compared to all the other data. So, it is really not as hard as it seems to collect these data. Social services can be informed, but that shouldn't be a barrier. In addition, communicating risk would be part of the standards in place.
- (Seeman): Suggested a pilot study to see how these measures can best be implemented.
- (Godfrey): Asked if there is an existing position paper with recommended guidelines addressing these issues. This would be a good service to the research community.
- (McLaughlin): Developing measures is important because some of the measures currently used are inadequate. For example, CTQ score is good for measuring abuse but not for neglect. Other measures are used even though they are not good. Often indicators used are measuring perceptions rather than behaviors.
- (Miller): Expressed concern about ascertaining adversity via questionnaires/self-reports.
- (Danese): It might be useful to rely on official records, to ask parents about the children in a way that may not be leading.
- (Sheridan): Interviewing children can be a good option. It is possible to obtain reasonable information even from young children.
- (Loucks): Suggested implicit association tests to get past some of the self-reporting issues. Miller responded that these tests have limited test-retest reliability and don't capture traits well.
- (Reiss): Suggested using computer assisted interviews. Anonymous data collection will help people become willing to provide information. This will also address the reporting dilemma, since investigators cannot identify the research subject this way. Sheridan responded that it is more complicated ethically if the reporting is anonymous since the abuse is ongoing.
- (Sheridan): Home questions are useful (and do not have to be administered by psychologist). Observing parent-child interactions may even be better than obtaining self-reports.
- (McLaughlin): Multi-dimensional neglectful behavior scale for kids including a number of questions might be used. Power responded that large scale cohort studies ask many questions that might be used in this way.
- (Miller): Need to be careful about conclusions: some of these scales are based on certain race/ethnic groups and social class (so would be confounded by those factors). McLaughlin responded that we should remember we are often asking about the stimulation in general and not the particular factors (e.g. does your mother read with you?).

Epigenetic/Metabolic Consequences

- Godfrey suggested that we look across a range of studies covering metabolomics and epigenomics, alongside these other measures of ELA. In this way we can perhaps develop more of a metabolic toolkit (spanning a larger range of effects). We should work together to do this as a consortium. A more crystallized cohesive set of questions would also be more interesting to potential funders.
- Reiss asked Miller whether there is comparable indication for inflammatory markers. Miller responded that there have been many immune-based studies that have explored this, but it is difficult to synthesize the work because of the variety of cell types and cohorts that have been considered. There are clearly some pathways that may be relevant, including perhaps

glucocorticoid signals and probably catecholamine. There is less of an epigenetic story in immune cells, but enough there that it is worth exploring.

- Godfrey suggested it may be worth looking at measures in blood and urine, now that so many more metabolites are defined.
- Seeman suggested that we think about measures that have been utilized in small studies and what we might be able to identify as available and useful in larger studies (and if unavailable, would it be possible to obtain?). For example, urine measures are currently available in MIDUS. Furthermore, the Network has limited pilot funding that might target such high value activities. Reiss further suggested that the pilot funds might be used to test the feasibility of a standard panel of abuse measures, likely psychological consequences and key biological mediators. The limited pilot funding might be enough to establish feasibility of pursuing certain objectives, and to establish a collaborative proposal.
- Nielsen suggested that another option might be using measures used in the larger population-based studies and including those measures in the smaller studies where we have the ability to intervene or look at more intermediate pathways (going in the other direction than we were talking about) to see if there are potential cross-walks between the more time-consuming measures and the shorter measures used in surveys.
- Miller mentioned that many studies utilize dried blood spots, but not as much urine.
- There was a general suggestion that we circulate a list of what datasets are available, and what measures they include. Reiss stated that the first step would be identifying studies that have measures we need. Systematic inventory that provides clear picture of what studies are out there and what measures they are using and what is available.
- There was general consensus that we collaborate to identify the available data as well as the main biological pathways that should be measured and included.

Addressing ELA and Outcome Measurement in Future Studies

- Nielsen asked, what are the most practical ELA measures for intervention?
- Sheridan suggested that maybe the approach should be more data-driven, in that perhaps we focus on measuring factors that many other researchers are already collecting that can be tied to cognitive function or emotional activity, etc.
- Godfrey noted the need to be careful with some of the panels that are prone to poor measurement. First layer is agnostic, and data driven, and then we can take a candidate approach.
- Reiss identified two data problems: 1) downstream measures, including metabolic mediators, etc., and 2) how to best measure the independent variable (range of adversity). How do we get valid measures of actual adversity?

Sheridan agreed that this is a particular problem because of retrospective data. Reiss mentioned that in children there may be problems with prospective data as well (for example, undisclosed adversity).

- Godfrey mentioned videos of parent-child interactions as an example of a data/tool that can be used to measure adversity in a different way. Reiss asked if you can obtain information about extreme cases of adversity on these videos? The response is that these are more of a general measure of parental competence, but perhaps more objective measure of at least one component of parent-child interaction.
- Reiss stated that the careful measurement of some of these intervening variables might inform adult ascertainment. If we identify specific intervening mechanisms, and can measure them precisely, they can then be subjected to the usual criteria for a diagnostic test (in cohorts where

we have good prospective measurement of adversity obtained in childhood). Are these measures in adulthood (of the intervening variables) sensitive and specific enough to enhance currently used retrospective measures.

- Miller noted that this is a recurring issue, and that no one has come up with compelling evidence that you can reliably differentiate discrete emotions at the physiological level.
- Seeman suggested that different types and timing of adverse exposures may ultimately lead to different consequences for brain development in emotional networks (threat response, etc.), and other systems. The question is, can these biological downstream consequences be objectively measured in adults? Can we come up with better measurement of those biological systems, even if different pathways lead us there (i.e., different types of adversity)?
- McLaughlin noted that some of the emotional processes we are concerned with are not so hard to measure. Using neural phenotypes to nail down specificity can lead to more widely usable measures.
- Reiss suggested that the network analysis proposed by Sheridan and McLaughlin might help with this.
- Godfrey urged the development of new technological tools can give us much more data (for example, phone apps, etc.).
- Nielsen noted growing interest at NIH to explore the potential for technological tools to be deployed for research and intervention on a wide scale. There is also an activity spearheaded out of NYU called Kavli Human Project intended to leverage technology and multiple data sources to map behavior across New York. That group has been soliciting recommendations from the field for what should be included in their assessment battery. They are interested in hearing from investigators about which measures are essential to understanding patterns of behavior.
- Godfrey mentioned the UK Biobank, which includes 50,000 people who have had brain scans and provide additional data, as another potential resource.

Day 2: February 1, 2017

Notes prepared by Sharon Stein Merkin, UCLA

8:30-10:00 Pathways – Epigenetics

Overview: Karen Lillycrop

Additional contributors: Eric Loucks, Greg Miller, Steve Suomi

Karen Lillycrop presented data on epigenetics, processes that induce long term changes without changes to gene sequence. The focus was on DNA methylation that is largely established in early life. The epigenome seems most susceptible to early life factors, when the environment can most likely affect this process due to increased plasticity and differentiation in early life. Lillycrop presented data from various animal (and some human) studies, and reviewed some of the evidence that epigenetics can hold the memory of early adversity, including the influence of maternal and paternal diet on methylation. The presentation included the following main conclusions:

- Several experimental studies indicate that ELA can alter the epigenome
- Timing of exposure can induce distinct responses and persistence of effects. Although epigenetic effects seem more likely and persistent if exposure is in early life, the effects seem to persist across the life course.
- The timing of exposure seems critical to identifying harmful exposure. In early life there is also potential for long-term change, while adult exposure is more likely to lead to transient epigenetic change.
- A major limitation of the research is that there are likely major differences in tissue-specific methylation, and it is important to look for methylation differences associated with specific phenotypes (Lillycrop presented a specific example related to adiposity).
- Important questions related to this research:
 - How much methylation is required to change phenotype?
 - Can these epigenetic markers induced by ELA be used as biomarkers?
 - Is intervention feasible using knowledge of specific epigenetic processes?

Discussion

Association between Methylation and Expression

- Miller asked how strong the association is between methylation and expression? That is, does methylation imply difference in expression? Lillycrop responded that in approximately 60% of the studies, the direction is as expected; in other cases, the association is in the same direction (high methylation, high expression), or indication of methylation and no expression. While there are higher associations found in animal studies, the data on humans are more limited. In human studies, for example, there are minimal associations found between methylation and expression in immune cells.
- Lillycrop also stated that these results depend on how you look at methylation; a more in-depth analysis of methylation in animals (i.e., targeting promotor regions) will more likely show more methylation.

- Godfrey mentioned that some of the data are beyond just measuring associations, with functional consequences being supported by in vitro experiments. Lillycrop agreed that we can test how methylation affects gene expression directly, but this is harder to do in non-laboratory conditions.
- There is evidence that changes in the environment are associated with methylation and possibly with change in gene expression (phenotype).
- Research cannot determine yet if these changes are due to methylation or if methylation is a consequence of the phenotypic change we see.
- Since the change in methylation that we see is generally small within any one CpG ($\leq 15\%$), it is also unclear if this is enough of a change to explain a change in phenotype.
- Godfrey added that intergenic regions of some of the CpGs are more developmentally plastic; and areas vary in terms of how much they are genetically determined. When there is a genomic influence, it is usually within 100 base pairs of a methylation site (although not exclusively).

Behavior and Epigenetic Change

- Power asked if there is evidence that behavior can affect change via epigenetics. Lillycrop responded there is a fair amount of work looking at epigenetics and behavior with regard to nutrition. There have been associations between methylation receptors and fat mass in children. There is the potential to uncover epigenetic marks that might be associated with particular phenotypes.
- Can such epigenetic markers be used for interventions? Animal studies have shown that cross-fostering with a more attentive mother can induce phenotypic change. This suggests the possibility of behavioral interventions.

Transgenerational Transmission

- Rachel Yehuda's work on PTSD and offspring of Holocaust survivors was mentioned, but Danese noted that these findings were controversial.
- Suomi mentioned animal studies that have shown that changing environmental situations in rats between litters changes maternal styles.
- Danese mentioned Isabelle Mansuy's work on mice; 3 generation mice studies have shown patterns of transmission that are not just behavioral but also show DNA changes.

Human Studies

- Similar exposures to what we see affecting animals have been associated with methylation phenotype changes in humans. Maternal diet, prenatal stress, and childhood maltreatment have all been shown associated with change in methylation and phenotype in humans.
- Teh et al, with PCA analysis, showed how genotypes differentiate a group of people by ethnicity but not by methylome, indicating other factors related to methylation not explained by genetics. That study estimated 25% of the variation in methylation was explained by genotype and 75% by an interaction between genotype and the environment.

Timing

- Timing is crucial in determining what sort of methylation has occurred and in determining the response to interventions (Lillycrop showed results of a study providing folic acid supplementation to juvenile vs adult mice and how responses varied).
- It seems that if methylation occurs in early life, the methyl group stays and lingers on that cpg site. However, if the methylation occurs in adulthood, that same methylated site might be affected, but methyl group will pop off (effects may not linger).

Future Research and Questions

- Research is needed to determine the stability of methylation patterns; longitudinal studies in humans are needed.
- Epigenetic markers may be used to identify people at high risk
- Timing of intervention is important to identify since plasticity may be different in different tissues and at different times across the life course.
- Whether methylation is causal or a consequence, can we use this to identify people at increased risk? Main obstacle in humans is readily available tissue (generally restricted to blood).
- In studies comparing methylation profiles, how does tissue-specific methylation compare? Found for the most part marked differences between methylation in different tissue types, but there is a subset of cpgs that overlap. Specific methylation markers may be able to be used as indicators of risk (example shown of methylation at RXRA promoter at birth and childhood fat mass, as well as other examples of studies searching for these markers using genome-wide approach).

Eric Loucks presented data on early life adversity (early life SES) and adiposity in the New England Family Study. Results indicated significant associations between methylation profiles and adiposity measures. There were stronger associations using fat tissue rather than blood. The data, however, are cross-sectional, so it is unclear if the fat adiposity was causing the methylation or vice versa. Major points raised in discussion:

Cell Type

- Miller asked if visceral fat might be even better to obtain (although harder to attain from epidemiologic studies, and more likely possible from surgical patients). Loucks added that the method of obtaining visceral fat is not more painful than phlebotomy. Miller suggested that photos of wound healing may be helpful to provide participants who are concerned.
- Miller pointed out as well that looking at the actual cell types might help determine functional consequences. For example, if a specific cell type is migrating, this may provide clues as to potential downstream effects. It would be best if studies banked blood samples to later extract both DNA and RNA.

Lack of Standardization

- McLaughlin asked about the available evidence in humans linking adversity and methylation patterns to specific phenotypes? Lillycrop responded that some of the problem in assessing the overall findings is inconsistent methodology. There are some original candidate genes, but regions may vary. For example, the original array chosen only reflects 1-2% of cpg sequences in

our DNA, but the ease of use leads to its use in many human studies. This array was preferentially chosen for cancer. In the current array that is now more in use (850k), about 6 cpg sites were linked to obesity. There has not been any focus on behavioral outcomes.

- Lillycrop also pointed out that many studies have been done with small sample sizes and various age groups as well as varying exposures. For good results, however, larger sample sizes are needed.
- Miller mentioned that this is difficult to do in human samples. The hypotheses have not been tested well, and the GWAS approach to analyses is vulnerable to type II error. The field is still in its infancy.
- Reiss suggested that we need to test replicability. The suggestion is that we form consortia to pool datasets, mostly using blood tissue. McLaughlin mentioned a consortium for PTSD where environment is measured as well, and where the investigators are pooling epigenetic samples mostly using saliva samples.
- McLaughlin asked what cell type is best to proxy brain function? Lillycrop responded that is the subset of cpgs conserved between blood and brain (see Jonathan Mills' work).

Steve Suomi presented data on a longitudinal study of rhesus monkeys. One group of monkeys staying with their mother and the other group was nursery-reared, with both groups separated at the natural weaning time (6-7 months); this study was repeated every year with a different cohort. Genome-wide methylation data was collected at 2 weeks of age, 6-7 months of age before weaning, 1-2 months after weaning, and at the end of 2 years (27-30 months of age). Results showed major sex differences in methylation patterns, despite no major gender differences in behavior change and cortisol patterns. One exception to this pattern is that after weaning, the gender differences disappear (all groups experience methylation). At 2 weeks of age, genes seem sensitive to rearing conditions (and absence of mother). These results show dramatic developmental changes that you can track at specific points in time; change relevant to behavior seems to be affected by particular types of environmental change at different stages of environmental development. According to these data, intervention is necessary during the weaning process.

- Reiss wondered if foster parenting might change this pattern?

Future Research Ideas

Epigenetic Clock

- Power asked whether there is much evidence of work on the epigenetic clock regarding aging. Are there things we can start to think about in this regard? How do the changes in early life relate to longevity in later life? Lillycrop responded that Steve Horvath has done some work on setting up a "methylation clock." This work was based on a methylation signature found using the 450K array, and using it to age people. There has also been work looking at methylation markers and cancer, which is indicative of premature aging. Godfrey mentioned that this methylation clock shows a stronger association with age than telomere markers.
- Power asked whether this association has been found with early life adversity (and premature aging). Lillycrop responded that when exploring ELA in terms of nutritional challenges, there

have been associations with epigenetic and metabolic aging. There is a metabolic link, but the data is unclear with regard to behaviors.

- Danese mentioned that data from biomarkers, telomeres and the epigenetic clock do not correlate clearly. Miller mentioned that these independently predict mortality even though they may not be correlated.
- Miller mentioned that the work done by Horvath was done in a data-driven way, and there is a need for more *in vitro* research.
- Godfrey asked whether we can use the samples we have to see if effects of early life adversity are related to the speed of the epigenetic clock.
- Danese mentioned that an ESRC/BBSRC network based in Bristol is considering this.
- Nielsen asked whether there is a possibility of collaborating with the network. Power will attend the next meeting and assess this.

Nutrition

- Reiss said that the field of nutrition contributed a great deal to the field of early life adversity. Based on Lillycrop's work, early life nutrition has been linked to early life metabolic pathways, and they have identified specific gene expression pathways that can be altered. While there is some skepticism about obtaining biological markers later in development, given the tighter links between nutritional deficiency and gene expression profiles, perhaps we can design a study linking gene expression profiles much later in development with sensitive and specific nutrients that might be missing later on? Lillycrop responded positively, noting that you can look at genes involved in metabolism and see a genetic signature. In humans, the data will be noisier, but should be possible. Danese asked whether results from Dutch famine can be generalized to the general population. Godfrey responded that the exposure was "dirty" (includes both nutritional deprivation and stress, and did not affect people similarly), and thus individual exposures to nutritional deprivation and stress could not be quantified from the data available.

Epigenetic Profiling

- Seeman asked whether we should assess whether different ELA types are associated with different epigenetic profiles in kids. Godfrey responded that in 9 months he will have these data on kids in his study (approximately n=400). [Post meeting KG note: some of data relating different types of ELAs to methylome changes are now published – [Lin et al, BMC Medicine 2017; 15\(1\):50](#).]

10:30-12:00: Pathways – Inflammation

Overview: Greg Miller

Additional contributors: Andrea Danese

Danese and Miller presented on the inflammation pathways related to early life adversity. The focus of this research is on the response elements of inflammation, those that can measure the whole system well and are easy to collect (for example, CRP). The impetus for this research began with coronary heart disease and was related to plaque formation; however, the process of inflammation can affect other outcomes and predict other diseases. CRP and IL6 are robust biomarkers that predict CVD; systemic inflammation can also moderate the metabolism of key neurotransmitters and affect the balance of monoamine and glutamate systems. Inflammation in early life can affect brain development, as well as moderate the influence of exposure later in life. Some additional discussion included the following points:

- Distinctions should be made between the various inflammatory markers used. CRP is a marker of inflammation, but does not seem to be a causal factor in disease pathophysiology, rather, CRP is expressed by the liver in response to IL6, that is produced by fat cells. While 30-50% of IL6 is fat derived, there are other sources for IL6 (approximately 25 different cells), which makes it difficult to determine etiology despite its use as a prognostic tool.
- Non-resolving inflammation has been shown related to many different health problems. There may be multiple reasons for initial increased inflammation. CRP is not really a causal factor in understanding these various complex mechanisms.
- Those exposed to low SES have increased inflammation and are less responsive to pathways that shut down that process (e.g., glucocorticoid hormones).
- Chronic conditions (rather than short-term responses to challenge) seem better predictors of long term health outcomes.
- Miller described longitudinal data on adolescents that include challenges to in vitro cells examining the response profiles of how these cells respond to stimuli. It seems that after exposure to the ELA of harsh parenting, the cells are more reactive to bacterial stimuli and less sensitive to glucocorticoids.
- Danese described results from studies on childhood trauma and inflammation.
- The issue at hand seems to be high inflammatory response that goes beyond what is needed for short term adaptive purposes (for example, in clearing an infection). The question is, does overload of this system response over the life course increase one's risk for cardio-metabolic problems?
- Danese mentioned how we should also consider other mechanisms linking ELA and potential inflammatory targets. One potential pathway is through the effects of ELA stress on the gut biome. The change in different bacterial compositions in the gut can, in turn, be associated with increased levels of inflammation. Other pathways may involve behavioral mechanisms. For example, substance abuse is likely related to the biggest production of IL6 in fat cells and associated with inflammation; sleep is associated with inflammation and psychopathology. There is also a role for genes related to these pathways; one of the key findings from GWAS is the association between inflammatory genes and psychopathology.

- What do we know about the timing of assessing these relationships? The link between ELA and inflammatory biomarkers appears in adolescence and later.
- What about the stability of these biomarkers? CRP and IL6 seem to track over decades, possibly reflecting the chronic influence of body composition (adiposity) or smoking. Power suggested then perhaps we do not have a need for temporal data (exposure and outcome). Danese responded that we still want to be sure the biomarkers are not related to acute infections. It was then suggested that obesity and smoking might be better markers of inflammation, avoiding the “noise” due to acute infection. Danese responded that it depends on the hypothesis; BMI is a good marker of chronic inflammation, but it will not capture the effects of stress on inflammation.
- What can we do in terms of large observational studies where you may only have certain biomarkers available? Perhaps we can complement these studies with some additional methods? Danese suggested taking advantage of experimental animal studies and new techniques to measure inflammation. Since animal studies have found that inflammation is not only measurable in the blood, but in the brain as well, perhaps we can focus on reversing those brain effects. To this end, perhaps we should focus on measures related to neuro-inflammation.
- Power asked, regarding interventions, whether there is information on mindfulness and how it might lead to improvement. Danese responded that an intervention with mindfulness was conducted on foster children in Georgia. This was a small study and showed some reduction of IL6 measured in saliva over a 10-week period.

Greg Miller presented data on a study done in collaboration with Gene Brody on children in high risk communities in rural Georgia (low SES and mostly African American). The intervention took place during transition from middle school to adolescence, age 11, with the initial goal to change mental health outcomes and behaviors. The intervention plan included 7 weekly meetings in the evenings, consisting of separate parent meetings on parenting and caregiving and child meetings on coping and setting goals; communication skills were emphasized at both sets of meetings. The child participants were followed up 8 years after this intervention and biomarkers were assessed; findings show lower inflammation in treatment group (although no “pre-test” biomarker levels available). Follow-up continued until age 25, and metabolic syndrome was assessed (lower prevalence in group with intervention). These findings suggest improvement with the intervention on later metabolic outcomes (although there is only post-test data). These findings suggest that this “post-weaning” window in children might be a potentially useful time to intervene with lasting health effects.

1:00-4:00 Final Discussion

Nielsen opened the discussion with a summary of the major objectives of the Reversibility Network. Each of three working groups is holding meetings to advance understanding of the links between ELA and health outcomes, and identify short and long-term research needs and opportunities to advance the Network's overarching goal: to explore potential interventions that can "reverse" or compensate for the health risks associated with ELA in midlife or older age. There is also a need for additional multi-disciplinary research, merging behavior and biology, in order to understand how interventions may be behavioral or socially based, rather than only pharmacological. The NIA is particularly interested in how collaborations between researchers across disciplines - including researchers working with both children and adults - can move forward to build or test causal hypotheses that can lead to the identification of malleable targets for later life interventions, while recognizing that early life interventions may be a critical step in this research. Dr. Matt Gillman, the Environmental Influences on Child Health Outcomes (ECHO) Program Director, was invited to join the meeting and discussion to discuss potential synergies between ECHO and the Network's goals. Dr. Gillman and Network members noted the potential for collaborations to build research infrastructure, identify measurement initiatives and generally, to stimulate and move this research forward. The discussion identified the following opportunities:

Dimensions

- Gillman mentioned the need for harmonizing early life measures across studies. McLaughlin agreed that there is a strong need for assembling large cohorts with similar measures to maintain consistency and to be able to establish patterns.
- There is a similar ongoing effort at the NIA's network on stress measurement, to try to bridge lab and survey measurements of stress. It may be worth reviewing this effort and establishing a similar one for this Network with regard to ELA measures.
- Seeman suggested a particular need, and a possible goal for the Network, is to present suggested early life measures that can be useful in adult studies. This would be a worthwhile and productive goal for the Network.
- Reiss brought up the significant and fundamental problem regarding measures: the difference between prospective vs. retrospective measures; this issue has to be addressed when we determine ideal ELA measures for use in studies. There seems to be 2 major issues:
 - The validity of retrospective measures (Danese added that at least we can increase reliability).
 - The possibility of developing retrospective measures in adulthood that are good indicators of early adversity. This is especially important since we often only have the option of retrospective measures.
- How do we obtain better measures moving forward? Two actionable short-term ideas:
 1. Tools for retrospective and prospective measures are applied more consistently to adequately cover multiple domains of early life adversity.
 2. Use existing data to test these pathways and domains.

Elucidating Pathways/Interventions

In order to better understand the mechanisms of the pathways and to test causal inference, we need more specific measures of the actual processes that we would like to change via interventions. On the other hand, Seeman suggested that it may not be necessary to fully understand the disease mechanisms to implement intervention. So, the question remains, what else might you gain by understanding pathways and processes connecting ELA to later disease? One answer is that this knowledge may be used to target high risk individuals before symptoms occur. Danese also suggested that if we understand the disease mechanisms, we may also understand the heterogeneity in outcomes (i.e., why some people do not develop the disease while others do). Some specific pathways were discussed:

Inflammatory Pathways

- Nielsen suggested that obtaining more indicators of behaviors might enhance our understanding of the pathways leading from ELA to disease. Danese agreed that these would be helpful, since likely to be on the pathway linking ELA an inflammation.
- It is important to remember that just focusing on which inflammatory markers are more associated with disease may not be enough information to inform intervention; there is still a need to increase knowledge of the actual process driving inflammation and not just the biomarkers.

Metabolic Pathways

- Malnutrition can serve as a proxy for adversity; significant and severe malnutrition can lead to CVD and cognitive sequelae.
- Forrester suggested that the relationship between nutrition and adversity may be the simplest area to explore in terms of pathways and interventions. This area of research is more malleable in animal models and may be the best way to seek new pathways and contribute to the existing investigation of pathways.
- Lillycrop suggested that 'Omics' research can be very useful in teasing out aspects of nutrition that would be crucial in these relationships.

Focus on Specific Disease Models

- Focusing on specific diseases can lead to general insights. Certain disease should be identified for programmatic research. Miller suggested that considering that the evidence of an association between cancer and adversity is more unclear, cardiovascular disease is likely a better candidate.
- Seeman suggested bringing together experts on CVD research and adversity research, and Miller suggested convincing ongoing CVD studies to go back to participants and ask about childhood adversity. The major problem with this is retrospective measures that cannot be validated. However, Miller mentioned that retrospective measures are essentially perceptions of adversity
 - in adulthood (for more complete discussion on retrospective measures: [see notes for Retrospective/Prospective working group meeting](#)).

Epigenetics

- The area of epigenetics is promising in furthering our understanding of the plasticity of methylation changes. Why do some genes respond (when others do not), and what governs that in different tissues and at different times?
- Use of the epigenetic clock, or epigenetic aging, may be used for specific phenotypes, and possibly tissues, to better understand behavioral changes. Godfrey suggested exploring how these clocks operate in different tissues and how they can be sped up or slow down based on ELA.
- Godfrey discussed how the epigenetic process, as well as structural processes and the microbiome, might provide a “memory” as to how the effects of ELA can influence health.

Timing

- Godfrey offered a hypothesis for timing of ELA and subsequent health consequences: during the developmental phases, it seems that there is a memory component associated with environmental exposures. In adulthood, a similar set of exposures may influence structure, biome, and epigenome, but there is likely a need for ongoing exposure to maintain those changes because the maintenance memory component is diminished.
- This hypothesized model is testable and the challenge we have is to attempt to answer some of these questions.

Interventions

Parents/Children

- Reiss suggested a potentially effective “two for one” intervention strategy aiming interventions at children, while also affecting the parents via those same interventions. While we are confident that childhood is an area of plasticity, parenthood might afford such a window of ideal time as well. Parents should thus be part of the assessments aimed at child participants.

Physical and Neurocognitive Interventions

- A promising type of intervention is the coupling of plasticity openers with other components. For example, a combination of physical activity/exercise with mindfulness (and other neurocognitive interventions). There are also other more sophisticated approaches to the neural component of the intervention that can be an exciting in terms of future research.
- Nielsen mentioned a list of all NIA funded non-pharmacological trials related to cognition/Alzheimer’s disease. This might be a useful resource moving ahead.

Inflammation-Related

- Miller suggested promising evidence of breastfeeding and other interventions across the lifespan that might also be good candidates (SES would also play a major role when considering such interventions).

Microbiome

- This is a very promising area of research, especially with regard to interventions.

Availability of Data

Intervention Studies vs. Observational Studies

- Loucks mentioned the importance of increasing cross-talk between intervention and observational studies. The observational studies have the biological sophistication, while the intervention-focused studies can increase the potential for causal inference.
- Systematic Reviews: A systematic review of the cardio-metabolic area of this research would be worthwhile and helpful. There was mention of reviews already done regarding malnutrition and brain outcomes, as well as decades of research evaluating cognition and behavior of survivors of severe and acute malnutrition and stunting.
- Some of the questions we have about disease process and pathways may be directly addressed in observational studies (like CARDIA and MESA), but it is not always simple to obtain access to those data, and many researchers unaware of what is available. Nielsen suggested cataloging available datasets so that we can identify what is available. Danese may be able to share their list developed for the mini-project (retrospective vs prospective data list). A pilot project may be developed to produce this catalog.

Animal vs Human Research

- It is important to encourage interaction between clinical and preclinical research in this area; there has not been enough cross talk between animal vs. human research. It would be helpful to harmonize the efforts between animal and human research to improve future translatability and cohesion. This interaction should begin by at least talking to each other to address their research objectives.
- Nielsen mentioned a planned workshop at the National Academies on animal models and social behaviors: <https://www.nia.nih.gov/sites/default/files/2017-11/animal-models-of-socialaging.pdf>. Nielsen also mentioned a prior NIH initiative to stimulate cooperation between animal and human researchers, where investigators spent a short sabbatical in another lab to facilitate cross-fertilization of research methods.

Imaging Data

- Nielsen mentioned the value of adding neuroimaging measures to examine, in adulthood, the neural pathways associated with different dimensions of ELA. One challenge is that adding imaging is difficult for participant retention in many large studies. Perhaps subsamples are the best way to obtain images that would validate the measures without having to obtain for all participants. Two existing NIA-funded studies are collecting relevant measures: The Dunedin study is collecting imaging data on all participants to assess function in “four neural circuits and the core behavioral capacities each supports: (1) the amygdala and emotion/threat, (2) the ventral striatum and motivation/reward, (3) the hippocampus and memory, and (4) the dorsolateral prefrontal cortex and executive control.” The project is testing whether prospectively ascertained early- life adversity is linked to midlife neural measures. The Midlife in the United States (MIDUS) study collects data on a subsample of participants who complete a clinical visit at the University of Wisconsin. Participants complete psychophysiological and MRI

protocols assessing emotional reactivity and recovery, as well as assessments of individual differences in brain morphology.

Collaboration with ECHO: Environmental Influences on Child Health Outcomes (Matt Gillman)

- ECHO includes observational and intervention datasets and efforts.
- Cohorts included start at different stages of life course, at different calendar time, with varying intervals of data collection and different measures. The goal is to create an ECHO-wide cohort, a data platform used to answer question about broad array of early factors and how they might affect health. The efforts include setting up working groups related to various outcomes, and plans for new data collection as well as harmonizing old data with new data.
- A major goal is to set up an inventory of datasets and assess what has been collected and what data can be harmonized, and, ultimately, to provide public access to these data.
- One major advantage of ECHO cohorts is that they cover a wide range of the life course.
- Ideas for collaboration between ECHO and Reversibility Network:
 - Reversibility Network can provide guidance to ECHO regarding relevant data collection on ELA. This area has not been well developed in ECHO and an opportunity for the Reversibility Network to provide valuable input.
 - The Network might form a sub-working group to focus on ELA dimensions.
 - While data access may not be complete and available yet, the Network may function as an “early consumer,” assessing the list of measures and data that might be available via ECHO.
 - Suggestion to access ECHO datasets themselves, but this should wait until harmonization/standardization is complete.
- Actionable items in the short-term:
 - Suggestions were made to keep the lines of communication open between Network and ECHO to ensure collaboration.
 - Network should follow up on some ideas for future collaboration.

Miscellaneous

Translation to Public

- Loucks mentioned that one difficulty in terms of interaction with the public and potential participants is how to describe and explain (and “brand”) this work. There are different terms we use: ELA, ACE, and perhaps we should think about what terms we use. What wording would help in translating or explaining this research to the public?

Papers

- Godfrey suggested that the Network publish papers.
- Nielsen hopes that each meeting can produce a paper. The hope is that the ideas stimulate research and identify deficiencies.
- Seeman mentioned that the Dimensions working group is planning to present an outline for a paper.

Other Ideas Moving Forward

- Seeman and Merkin can work on putting together a list of observational studies and what measures might be available (including outcomes; for examples CARDIA and MIDUS).
- Pilot project would be useful for this. Danese suggested that a list of studies start with prospective measures that are available, and then retrospective measures as well.
- Sheridan suggested starting with studies including good measures of mediators and then going back to see if they have ELA and age range.
- Gillman asked whether the types of exposures that matter remain the same over time, or whether there are cohort effects, for example, related to a change in the perception of maltreatment.
- Danese mentioned some new measures, including cyber-bullying. Danese mentioned the need for norms on a range of measures, i.e., growth charts of biological measures, growth function. It is difficult to detect abnormalities without normative patterns for comparison.