

Retrospective Recall and Prospective Observations of Childhood Adversity: Challenges and Opportunities in Their Use in Aging Research

Meeting of the Reversibility Network

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Managing Editors:
David Reiss and Andrea Danese

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Abbreviations and Acronyms

Acronym	Definition
ACE	Adverse childhood experience
CECA	Child Experience of Care and Abuse
CLEAR	Computerized Life Events Assessment Record
CPP	Child-Parent Psychotherapy
CPS	Child Protective Services
CTI	Comprehensive Trauma Interview
CTQ	Childhood Trauma Questionnaire
MCS	Maltreatment Classification System
PFC	prefrontal cortex
PI	previously institutionalized
PPI	Psychoeducational Parenting Intervention
PTSD	Post-traumatic Stress Disorder

Executive Summary

Background

Early life adversity confers a significant risk for mental and physical disease later in life. Many severe disorders that are influenced by early adversity, including metabolic syndrome, diabetes, and heart disease, may not be apparent until midlife or later; yet the effect is of sufficient magnitude that a targeted public health intervention could have a substantial impact on disease prevalence in adults.

An important early life adversity of considerable magnitude—the adversity of special interest here—is child maltreatment. Unfortunately, it is beyond the capacity of even the best health system to deliver prevention or intervention to all maltreated children at an early age. However, it may be possible to prevent or alter the course of disease in midlife or later. The Network on Reversibility was established in 2012 to focus the research community on developing interventions that could accomplish this goal. Its fifth meeting was held on November 1-2, 2016, and brought together researchers whose work covers the spectrum of development from infancy through late life to discuss the use of retrospective and prospective measures of early life adversity.

Comparing Retrospective and Prospective Assessments

To design effective interventions, it is essential to know who is at risk and for what. Childhood maltreatment takes many forms—no two experiences are the same, and details of an individual case, such as the type and severity of abuse or the identity of the abuser, can influence health outcomes. To further complicate matters, official records that provide detailed prospective accounts of childhood treatment are not available for most adults. Rather, it is often necessary to rely on their own retrospective accounts, recalled decades after the events they describe.

Speakers in this session included several who described comparisons of prospective and retrospective accounts of childhood adversity, focusing on the accounts' relations to health outcomes for two longitudinal cohorts, one being the Midwestern (United States) cohort and the other being the cohort recruited from Dunedin, New Zealand, for whom relevant data exist. Although there are some significant differences, data obtained from these cohorts reveal striking similarities. In both cases, prospective and retrospective reports identify overlapping but distinct groups, and there is a correlation between report type and health outcome. Retrospective reports of adversity associate more strongly with poor mental health in adulthood, whereas prospective reports from childhood predict worse physical and cognitive health in adulthood. In the U.S. cohort, prospective reports of physical abuse or neglect correlate with increased allostatic load and a variety of health problems. These studies also reveal that retrospective reports of adversity are associated with facets of ill health in adulthood regardless of whether the event itself can be proven to have occurred.

A comprehensive research review has identified additional cohorts in the literature, some of which may be ripe for further data collection or analysis.

Approaches to Ascertaining Past Adversity

In addition to the memory of abuse or other early hardship, childhood adversity leaves its mark on the mind and the body, and accurate ascertainment would benefit from a multifaceted approach. One place to look for evidence of adversity is in the developing brain. Compared to children raised in a conventional household, children adopted from orphanages demonstrate differential pacing in brain development in the amygdala and prefrontal cortex. This brain phenotype correlates with a distinct pattern of behaviors including separation anxiety and learning-associated anxiety.

Research suggests that early caregiving shapes the neurobiology of emotion regulation, perhaps by slowing the pace of development, and that children deprived of such care undergo more rapid maturation in the emotion regulation brain regions. This suggests that it might be possible to determine the amount of adversity that an individual experienced in childhood based on a combination of brain imaging and behavioral phenotypes.

At the core of this meeting is the question of how to obtain reliable data about past abuse. Detailed retrospective assessments have promise in ascertaining diverse types of exposure and may, when perfected, enable researchers to examine the impact of maltreatment on multiple areas of functioning. These assessments, as currently conducted, require a skilled interviewer and take considerable time to administer, limiting their use to relatively small studies. However, use of these tools has enabled the identification of phenotypically distinct subgroups associated with particular combinations of exposures—something that could not be obtained with a more blunt instrument.

In recent years, researchers have been able to further refine these assessments by focusing on the extremes, producing much stronger effect sizes in longitudinal studies and enhancing agreement between prospective and retrospective reports. Purification of the phenotype in this way has enabled the collection of epigenetic data and revealed DNA methylation patterns correlated with phenotypic subgroups.

Childhood amnesia (perhaps better termed “infantile amnesia”) creates challenges for retrospective reporting. Autobiographical memory can be demonstrated in toddlerhood, but most adults cannot recall verifiable autobiographical events prior to the age of approximately 3.5 years (that said, some adults can accurately recall significant events that occurred when they were in their second year of life), and especially in young children, both suggestibility and forgetfulness are serious concerns. Furthermore, many factors can influence memory, including the circumstances, timing, and severity of abuse itself. Errors of omission occur far more frequently than false reports, although both can be reduced with appropriate interviewing techniques.¹

¹ Even adults are suggestible and forgetful, and several studies show that the worse witnesses are actually the elderly (not children). There are individual differences at all ages, with some children being highly accurate and some adults being very inaccurate.

It is not known whether there is any way, as a person enters later childhood or adulthood, to access accurate memories formed during the period of childhood amnesia. Moreover, even if a person remembers an event, the person needs to be willing to recall it to another. Facial signals can at times reveal information that individuals attempt to conceal, but it is not known whether early childhood memories can be revealed in this way. Nonetheless, the enhanced precision that can be achieved by refinements of retrospective reporting, along with the association of brain phenotypes, physiological indices, and personality traits with particular exposures and health outcomes, suggest that it may be possible to obtain valid adult reports based on a combination of careful interviewing and biological and psychological markers.²

The Impact of Adversity on Course of Illness and Response to Treatment

Studies that test interventions at any age can provide insight into both the mechanism behind disease and the plasticity of the system. In a randomized clinical trial, two forms of therapeutic intervention yielded dramatic effects in maltreated infants, raising the number who had secure attachments from 0 to 50 percent. However, only one of these interventions, which focused on enhancing the mother-child relationship, produced a lasting effect that was still observed one year post-intervention.

This result highlights the enormous potential for intervention during early childhood, but it also reveals the extraordinary ineffectiveness of more typical care of these children: maltreated children in the control group, who received typical interventions showed virtually no improvement in attachment over the study period. If evidence-based interventions are to benefit public health, they must be translated into real-world clinical settings. A special problem may be the application of these approaches to children who were so severely maltreated that they have been placed in foster homes.

Salivary cortisol is an indicator of the stress response, and can be used as a marker for the effectiveness of therapy. Prior to therapy, maltreated infants had reduced cortisol function, as did their mothers. Attachment therapy restored cortisol to normal levels. A separate research group focusing on hormone regulation in postpartum women found strikingly similar results to the infant study. A mouse model demonstrated effects of early adversity on maternal cortisol and behavior that paralleled those seen in humans, suggesting that useful molecular information may be obtainable from this system.

Inflammation is associated with early maltreatment and compounds its deleterious effects. In depressed individuals, high levels of inflammatory biomarkers correlate with past maltreatment. The combination of early adversity and high levels of inflammatory cytokines correlates with worsening cognitive performance during the menopause transition.

² Many significant memories from early childhood are still available to young children, and there are ways to help retrieve some of the early memories, but later they become largely inaccessible. That said, many early memories, such as for events in the first year of life, present as familiarity and behavioral predispositions (“implicit memories”), not as explicit, verbalizable, consciously accessible memories

Given its lasting biological effects, recognition of childhood adversity could improve diagnosis and treatment of disease. For example, depression can be broken down into multiple subtypes, and some of this heterogeneity may be explained by early life stress. Childhood maltreatment is associated with a subtype of depression that is recurrent and resistant to treatment with tricyclic antidepressants.

It is particularly important to account for childhood adversity in drug trials: the few that have attempted to do so have found significant associations. In a randomized clinical trial that tested a psychostimulant to facilitate executive functioning in women undergoing premature menopause, only individuals who had experienced high levels of childhood adversity demonstrated a treatment effect.

Recommendations

The biological, psychological, and behavioral effects of early adversity vary widely among individuals. Meeting participants favored a comprehensive approach to data analysis that would test a collection of biomarkers and other phenotypes of maltreatment and create a probability atlas, based on clustering of phenotypes, that could reveal tighter links between early adversities and outcomes. This approach could make it possible to generate an assessment of risks for each individual and to recommend appropriate interventions.³

Existing prospective data sets may be a valuable resource for future research. These data sets offer an opportunity to investigate factors that moderate the relations between prospective and retrospective reporting. Researchers who have obtained prospective reports of adversity but lack follow-up data could be engaged and funded as a consortium. Where retrospective and outcomes data already exist, grants could target analysis using data-driven clustering to define phenotypes. Analysis of these studies should focus on identifying elements from prospective and retrospective accounts that add specificity to outcomes. In addition, smaller, focused studies could test aspects of retrospective reporting that have not been controlled for previously, such as rapport with the interviewer and approaches to questioning.

It is important to determine how detailed retrospective descriptions of adversity might be useful in clinical decision making, particularly because there is rarely enough time to complete an hour-long psychological assessment in a clinical setting. Several possible alternatives were mentioned, ranging from a simple, thermometer-like scoring of one's entire childhood to a comprehensive assessment tool that is performed on the computer or online. Defensive

³ Attachment theory suggests that there are two main dimensions of response to trauma, an anxiety response dimension and an avoidance response dimension (and some people have both). Yet those dimensions are often not differentiated in the research studies, sometimes wiping out or diluting effects. We may get more refinement in our measures if those dimensions are taken more into account.

processes and lack of knowledge to compare one's past with that of others may affect these measures.⁴

⁴ In Dr. Goodman's sample of African American adults from Chicago who were exposed to significant and multiple early traumas and removed from home due to child abuse, they often now as adults say that they had wonderful childhoods—that the "whoopings" and other abuses were deserved. They may remember what occurred but put a positive spin on the memories. Others realize the tragedy of their childhoods.

Meeting Summary

Research Review 1: Risk for Ill Health: The Relationship between Retrospectively and Prospectively Assessed Cohorts

Comparing Retrospective and Prospective Assessments of Adverse Childhood Experiences in the Prediction of Adult Health

Aaron Reuben, Duke University

In the overwhelming majority of adults, evidence of childhood adversity can only be obtained through retrospective recall. Although longitudinal studies have linked prospective reports of maltreatment to disease later in life, it is unclear how retrospective reports compare. Do retrospective reports reflect the same information that is obtained prospectively? And to what degree does the type of report (prospective vs. retrospective) influence its ability to predict specific health outcomes? Both questions must be addressed before retrospective reports can be incorporated into a risk model linking early life adversity to adult disease.

Aaron Reuben presented research from the Moffitt-Caspi lab at Duke University designed to address these questions through analysis of the Dunedin birth cohort, which represents all 1,037 individuals born in the town of Dunedin, New Zealand, in 1972-1973.⁵ Prospective adverse childhood experiences (ACEs) were measured biannually from ages 3 through 15. The researchers measured retrospective recall of individuals aged 38 of these same circumstances through written questionnaires and interviews. They also measured physical, mental, cognitive, and social health. Although the total number of events reported showed a moderate correlation between prospective and retrospective reports ($r = 0.47$), there was poor agreement for reporting of most of the nine types of adversity measured both prospectively and retrospectively.

Of interest, the researchers observed a significant relation between report type and adult health outcome. Adversity described retrospectively predicted nearly twice as much mental illness as that described prospectively. Furthermore, prospective adversity that was not also reported retrospectively did not correlate with increased risk of mental illness. In contrast, retrospective reports of adversity remained predictive of mental illness even in the absence of correlating prospective reports. These results suggest that unrecalled adversity does not associate with mental illness.

However, measures of physical and cognitive health followed a different pattern. Prospective reports predicted physical and cognitive health, measured both objectively and subjectively. This was the case whether the adversity was discovered in the adult assessment. By contrast, retrospective reports were more strongly associated with self-reported poor physical and

⁵ Reuben, A., Moffitt, T. E., Caspi, A., Belsky, D. W., Harrington, H., Schroeder, F., ... & Danese, A. (2016). Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry*, 57(10), 1103-1112.

cognitive health and were less predictive of objective measures of health compared to prospective measures.

Finally, the researchers noted striking differences in personality profiles between cohort members based on the congruency of their prospective and retrospective reports. Those who reported more childhood adverse experiences retrospectively than had been detected prospectively had a more neurotic and less agreeable personality profile than those who reported equal numbers of childhood adversities across time, while individuals who reported fewer childhood adversities than had been detected had a more agreeable, less neurotic, and more conscientious profile. Although personality discrepancies in the Dunedin subjects may reflect resilience, Reuben noted that they do not correlate with improved objective health measures for the more agreeable group.

Workshop attendees were particularly curious about additional factors that might affect resilience. Might the lack of mental illness in those who fail to recall adversity serve as a marker for the warmth of the home? Harsh punishment can be interpreted differently depending on emotional context. Might prospective indices provide an omnibus measure of favorable home context? For such information to be useful, it would need to be paired with the child's developmental state and perception at that stage of life.

Comparisons of Prospective and Retrospective Reports of Child Maltreatment and Physical Health Outcomes: Preliminary Findings

Cathy Widom, Ph.D., John Jay College of Criminal Justice, City University of New York

Many factors influence retrospective recall, including childhood amnesia and social factors. Recall also can be heavily influenced by information that is disclosed by parents and others later in life. Longitudinal studies of a diverse range of individuals, including crime victims and teenage boys, have demonstrated a surprisingly low ability to accurately recollect facts about one's past experiences years after the fact.

With that caveat, Cathy Widom presented preliminary results from The Midwest Study, a longitudinal study of 908 court-substantiated cases of abuse and neglect in children ages birth through 11 years.⁶ Retrospective reports were obtained at average ages of 29 and 39, along with medical exams and blood draws. Participants were assigned a score for allostatic load, an indicator of stress accumulated over time, based on nine biological markers.

Prospective (official) reports of abuse and neglect showed significant correlations with diabetes, anemia, hepatitis, and lung and vision problems; retrospective reports correlated significantly only with anemia and lung problems. In addition, prospective reports of physical

⁶ Widom, C. S., Czaja, S. J., Bentley, T., & Johnson, M. S. (2012). A prospective investigation of physical health outcomes in abused and neglected children: new findings from a 30-year follow-up. *American Journal of Public Health, 102*(6), 1135-1144.

abuse or neglect were strong predictors of increased allostatic load, whereas retrospective self-report was not.

In contrast to allostatic load, poor subjective health was predicted by both prospective and retrospective reports. Of interest, controlling for income eliminated nearly all differences in subjective health between individuals who had experienced abuse and those who had not. Pain, unique among measures of subjective health, was predicted by the retrospective report alone, and this relation was still highly significant after controlling for income.

Although Widom's study is still under way, the preliminary results suggest that assessments of childhood abuse and neglect in prospective and retrospective reports are not interchangeable and that the role of socioeconomic status is significant and needs to be better understood.

Identifying Cohorts That Have Collected Sufficient Data to Address Questions on the Separability and Comparability of Prospective and Retrospective Cohorts: A Systematic Review of Research with Prospective Measures of Childhood Adversity

Jessie Baldwin, Kings College London

A key purpose of the research discussed in this meeting is to establish the relation between prospective and retrospective studies and determine whether, and how, they may be brought into better alignment. Generalizable answers to these questions require data from a large and diverse set of cohorts. Jessie Baldwin described her effort to identify other cohorts, through a systematic survey of the literature, which could be mined to test the results obtained with the Dunedin and Midwest cohorts and to address additional questions.

Baldwin identified 386 independent cohorts, mostly from the United States but distributed globally, with prospective measures of childhood adversity. Most had small sample sizes of less than 10,000 participants, although a few studies were very large (the largest had 13 million participants). Most followed children only up to adolescence or early adulthood.

Twenty-two of these studies have been identified as having both prospective and retrospective measures of childhood adversity. Fourteen of the 22 studies reported on the agreement between prospective and retrospective measures. Overall, there was mild to moderate agreement; the weighted percentage of individuals with prospective adversity who reported it retrospectively was 54 percent, which is similar to the Dunedin results.⁷

Baldwin and colleagues plan to calculate the current age of subjects from all 386 prospective cohorts to determine whether it would be feasible to obtain more retrospective reports.

None of the 22 studies with prospective and retrospective reports appeared to test interventions. However, some of the research participants within Baldwin's collection of studies are likely to have received interventions. A great deal may be learned by following up on

⁷ Cohort effects may be important: older research participants may be less willing to disclose abuse and rape because social pressures—as they were growing up—favored silence on these topics.

outcomes in treated versus untreated children, and some of that information may even be available in extant publications.

Session 1 Discussion

Reuben noted striking similarities between his and Widom's presentations: Both determined that retrospective adversity associates more strongly with subjective assessment of cognitive and physical health, and more weakly with objective assessment, compared to prospective adversity. There also seems to be a personality bias influencing subjective assessment.

Widom noted the differences between the Dunedin and Midwest results. For one, there was a difference in degree: she found a much stronger effect of prospective adverse childhood events (ACE) on poor objective measures of health than did Reuben. She also saw more subjective health complaints associated with retrospective ACE reports. Widom's participants were roughly 8 years older than Reuben's at the last retrospective assessment, which might account for some of these differences.

Of particular significance to Reuben was his observation that participants with prospective ACEs who did not report them retrospectively nonetheless had poor objective health. The converse is also true: Those with retrospective reports of ACE who did not have prospective reports still had poor subjective measures of health.

On the individual level, what constraints might influence these results, and what is their predictive value? Many possibilities were suggested, a few of which are listed here:

- The self-rated health literature suggests that subjective reports of health or cognition may predict future objective reports.
- Individuals who subjectively report better health and do not retrospectively report adversity, who have more agreeable and less neurotic personalities, may have better health outlooks despite bad objective health measures.
- Priming (due to past interviews) can play a role in self-reports and subjective health measures. Widom noted that the second adult interview of her cohort matched the official report better than the first interview, raising the possibility that priming had occurred.
- At puberty, children may start to realize that some of their life experiences were abusive; there may be a delayed effect on health once this realization takes hold.
- While a reduced perception of abuse may be advantageous for the adult's mental health, the opposite may be the case when viewed from an intervention perspective because adults who do not recognize their own childhood experiences as abuse may be more likely to abuse their own children. It was also noted that individual appraisals could change as cultural views on abuse shift over time.

There are also societal issues that can influence perceptions and incidence of child abuse. Because 57 percent of the studies identified by Baldwin are in the United States, and data from these studies were collected over a long time period, it may be possible to test perceptions of abuse at different time periods or considering major policy experiments that had a substantial

effect on law and/or perception of abuse, including the federal Child Abuse Prevention and Treatment Act, enacted in 1974. Because child welfare is regulated at the state level, comparisons of neighboring states might prove revealing. In some states, laws criminalizing child sexual abuse are quite recent. A study from the University of Missouri in St. Louis has examined child abuse data state by state, investigating the effects of changes in policy, welfare, and other social metrics on rates of reported child abuse.

Retrospective reports of maltreatment have been shown to contribute to differences in drug response in randomized clinical trials. Some differences in brain imaging also correlate with retrospective reports. Nonetheless, Widom found that only prospective reports could predict physical and cognitive health. Attendees suggested that the key to this paradox might lie in the precision of retrospective assessments (the subject of the second session of the meeting).

The point was also made that it is not accurate to describe prospective reports as entirely “objective” and retrospective as “subjective.” There is a group of people who feel they had difficult childhoods, and these feelings have actuarial importance, whether or not abuse actually occurred. There may, however, be a different mechanism linking illness and the perception of abuse, compared to that which links illness to verifiable abuse. These may require different interventions.

As a possible corollary to the perception of an (undocumented) difficult childhood, it is very challenging to document emotional abuse of children by their caretakers. Emotional abuse may be a common cause of retrospective reports that lack prospective documentation. This could represent a common pathway that links these individuals and influences their adult mental health states.

It was noted that physical abuse also has an emotional component. Furthermore, the same physical act, such as corporal punishment, may be worse in an emotionally abusive environment than in an otherwise loving one where it is the accepted form of discipline.

Research Review 2: Risk for Ill Health: Improving Identification in Adulthood of Cohorts Identified Prospectively in Childhood

Early Adversity, Altering the Pace of Development and Compensatory Mechanism: Can We Fashion a Biological/Environmental Profile for Retrospective Ascertainment?

Nim Tottenham, Ph.D., Columbia University

Given the difficulty of correlating retrospective and prospective reports of childhood adversity, an ideal solution, if it were possible, would be to develop an objective profile of adults who had been maltreated as children. Indeed, the fact that one in five adolescents has a mental disorder that will persist into adulthood indicates a larger need to understand how the circuitry of the brain is altered during development.

Nim Tottenham studies the connections that form between the amygdala and medial prefrontal cortex (PFC) during development. This circuitry is very plastic, controls emotional regulation in adulthood, and is a candidate for linking early experiences to emotional function later in life. The architecture of this tissue may serve as a historical record of early experiences. As the amygdala-PFC system progresses across development, the connections that form in children are often qualitatively different from those seen in adults.

Tottenham's group is building a testable model to explain why early caregiving is important for the development of neurobiology. This model is based on the observation that the amygdala continues to develop postnatally and "tutors" the PFC via regulatory inputs throughout childhood. Ultimately the PFC becomes the regulator that buffers activity in the amygdala. Many disorders of emotional regulation emerge during this transition, in the period between adolescence and adulthood.

Animal studies suggest that parental care modulates amygdala activity in early childhood, before this role is assumed by the PFC. A regulated parent "buffers" amygdala responses to threat, whereas a dysregulated parent does the opposite. In chronically stressed animals, amygdala cells become larger and more reactive. In addition, overall neural development appears to accelerate in stressed rats. This may be a compensatory adaptation, changing brain development to meet immediate needs. But what are the long-term costs? And does a similar phenomenon exist in humans?

To test the role of parenting in development of amygdala-PFC connectivity, Tottenham worked with previously institutionalized (PI) children adopted internationally, with the orphanage serving as an example of extreme neglect. PI children showed significant heterogeneity in brain activity and behavior, with a subset demonstrating elevated separation (and other) anxiety, elevated amygdala activity, and atypical PFC-amygdala connectivity.

On neuroimaging, typically raised children showed an immature amygdala-PFC phenotype. However, the same brain region in a 6-year-old PI child resembled that of a typically raised 16-year-old, suggesting that early life exposure to adversity leading to hyperactivity of the amygdala may prematurely initiate adult-like connectivity with the PFC. If stress is abbreviating the period of plasticity, there is less time for elaboration of emotion-regulation circuits. Therefore, adults who experienced early adversity may rely more on emotion-reflexive than emotion-reflective regulation strategies.

Overall, PI children scored higher on separation anxiety than typically raised kids, but those with the adult amygdala-PFC phenotype had lower separation anxiety than their PI peers. However, PI children with the adult amygdala-PFC phenotype had higher anxiety associated with learning. Tottenham predicted that the different pacing of development observed in PI children would lead to different adult health and behavioral outcomes.

Given the heterogeneity of PI populations in terms of brain development and behavioral phenotypes, Tottenham has begun to employ data-driven analytic techniques that consider types of exposures as well as phenotypes in order to enable stratified predictions to be made

about the course of development. In a pilot experiment, she has defined a “compensatory” group of PI children with adult-like connectivity that appears to improve in emotional control over time. Another cluster with a different phenotypic profile worsens over time.

Tottenham concluded that early caregiving shapes the neurobiology of emotion regulation, perhaps helping to maintain an immature plastic neural state. Early caregiving adversity may change developmental pacing and lead to a reduction in plasticity in order to achieve compensatory adaptations.

Tottenham’s presentation raised the intriguing idea that it might be possible to determine the amount of maltreatment that PI children received based on brain imaging and behavioral phenotypes using machine learning algorithms similar to those used to model emotional states in social cognitive research.

Cross-Sectional and Longitudinal Ascertainment of Child Maltreatment

Jody Manly, Ph.D., University of Rochester

Our ability to understand, study, and develop effective treatments for adversity is limited by the quality of the data describing exposure and outcomes. Simply put, no amount of analysis can overcome bad data. Jody Manly and colleagues at Mt. Hope Family Center designed a Maltreatment Classification System (MCS) in 1993 that could distinguish among diverse types of exposure;⁸ in addition to improving data collection and analysis, this system has enhanced communication and enabled comparison of data across labs.

Using detailed physiological and psychological assessments, the MCS examines the impact of maltreatment on different areas of functioning. Researchers assess risk and protective factors at different levels of children’s environments in order to identify developmental processes that lead to different outcomes.

Manly and colleagues recruit maltreated children living with their biological parents and use the narratives of their experiences, along with parent interviewing, to classify them. They work with the same children for years and continue to monitor controls over time; the status and characteristics of maltreatment can change over time.

The researchers also study children in summer camps, analyzing psychology, brain function, genetics, epigenetics, allostatic load, stress, and other factors. Longitudinal studies have continued to collect data for two decades.

The MCS focuses on six dimensions of maltreatment:

1. Type of abuse (physical abuse, sexual abuse, physical neglect [most prevalent form, with four subtypes], emotional maltreatment [three subtypes])

⁸ Barnett, D., Manly, J. T., & Cicchetti, D. (1993). Defining child maltreatment: The interface between policy and research. In D. Cicchetti & S. L. Toth (Eds.), *Child abuse, child development, and social policy* (pp. 7–73). Norwood, NJ: Ablex.

2. Severity (coded based on potential for harm to child; 1 to 5)
3. Frequency/Chronicity (difficult to capture; may be calculated as number of developmental periods)
4. Developmental timing (acute vs. episodic vs. chronic; extent)
5. Separations/Placements (foster care, with relatives, residential treatment, group home)
6. Perpetrator (mother, father, step-parent, other relative, sitter/friend, stranger)

Each type of abuse has other dimensions nested within it (severity, timing, perpetrator) and the overlap can get complicated, but it is important to account for them when formulating research questions. For instance, multiple subtypes of maltreatment frequently occur together, and subtypes may change over time.

Frequency and chronicity are difficult to establish but may be considered in relation to the number of developmental periods that are affected. More chronic maltreatment across more developmental periods is related to increased internalizing and externalizing behavior and problems in socialization. The timing of experiences may have a significant impact on effect. For example, early maltreatment (prior to age 6) leads to higher internalizing symptoms and later maltreatment tends to cause externalizing behavior problems.

Phenotypically distinct groups can be identified by considering multiple dimensions simultaneously. For example, when Manly and colleagues examined timing, subtype, and severity together, they found that severity of emotional maltreatment in the early infant-toddler periods or physical abuse in the preschool period predicted aggression and externalizing behavior problems, whereas severity of neglect during the preschool period predicted more internalizing and withdrawn behavior.

Of importance, outcomes in children with chronic, low-severity maltreatment are as bad as those in children with higher severity maltreatment. However, these children tend to receive little or no response by the child welfare system.

By performing multilevel analyses, with dimensions of maltreatment and risk factors measured concurrently, researchers might be able to better tailor interventions that promote healing and foster resilience. To be effective, these results will need to be translated into public health decisions.

The MCS captures an enormous amount of information along several distinct dimensions. Meeting participants were curious to know how the MCS, with its daunting complexity, might be used to design a limited number of highly effective interventions. This question anticipated Sheree Toth's presentation, which describes an early intervention designed to change the trajectory of attachment. Keeping track of the dimensions can enable more accurate interpretation of the results. It can also explain why different studies fail to produce comparable outcomes.

Prospective and Retrospective Assessment of Childhood Maltreatment: Controlling “Contamination” and Improving Precision

Jennie Noll, Ph.D., Pennsylvania State University

In clinical trials, non-optimal randomization and non-compliance lead to contamination of control and test groups. When researchers work to remove contamination and “get the phenotype right,” effect sizes increase and outcomes are detectable. Jennie Noll emphasized the importance of attending to phenotype and contamination in studies on maltreatment, presenting work that she performed in collaboration with Chad Shenk.

Contamination occurs in the form of false negatives (participants in the control group who are maltreated) or false positives (participants in the test group who mischaracterize maltreatment). Noll and colleagues have developed strategies for identifying these individuals. The group performs long-term longitudinal studies of adolescents with confirmed maltreatment using the MCS.

Even studies done prospectively can suffer from contamination. In one 5-year study, 45 percent of children in the control group had experienced maltreatment. Meanwhile, a substantial number of children in the test group had Child Protective Services (CPS) records but no self-report of maltreatment. Effect sizes were much stronger when only children with both CPS records and self-reports of maltreatment were included in the test group and contamination was removed from the control group.

If this sort of contamination can exist in prospective studies, how can precision be gained in retrospective self-reports? Noll has developed the lengthy Comprehensive Trauma Interview (CTI),⁹ which requires interviewers to define the questions for participants and follow up with details: time, perpetrator, severity, etc. The CTI also obtains a subjective appraisal—that is, whether the subject thinks the treatment was bad. The interview process has been refined over two decades and requires a skilled interviewer. Participants quantify the severity of experiences by comparison to a benchmark that they establish (“the worst thing that ever happened to you”). Different follow-up questions are employed for different types of traumas.

Noll’s CTI method leads to enhanced agreement between prospective and retrospective reports.¹⁰ One prospective study has followed a cohort of sexually abused girls from their early teens to their 40s. Recollections 15 years after the event showed a high level of agreement with the initial caseworker report, likely a function of the precision of the interview. In another study, researchers found a high level of reliability of the Post-traumatic Stress Disorder (PTSD) component of the test. In this cohort the trust and rapport between participants and

⁹ Noll, J. G., Horowitz, L. A., Bonanno, G. A., Trickett, P. K., & Putnam, F. W. (2003). Revictimization and self-harm in females who experienced childhood sexual abuse results from a prospective study. *Journal of Interpersonal Violence, 18*(12), 1452-1471.

¹⁰ Barnes, J. E., Noll, J. G., Putnam, F. W., & Trickett, P. K. (2009). Sexual and physical revictimization among victims of childhood sexual abuse. *Child Abuse & Neglect, 33*(7), 412-20. PMCIS: PMC2723796.

researchers that grew across the years of the study may have contributed to more accurate disclosure.

Noll and colleagues are collaborating with a geneticist to obtain epigenetic data on their participants via microarray analysis. For this type of study, purity of the phenotype is crucial. Focusing on phenotypic extremes increases the power of genetic studies, and a similar approach to maltreatment research would likely improve the quality of results.

Improving the Reports of Childhood Maltreatment: Enhancing Narrative Skills, Understanding the Social and Personal Context of Maltreatment and Searching for Specific Effects

Antonia Bifulco, Ph.D., Middlesex University

Antonia Bifulco described research that seeks to improve the validity of retrospective reports. Bifulco examines diverse approaches that affect the quality of retrospective accounts of childhood, including witness corroboration, dose-response effects, added risks from adult adversity, and the degree of detail being measured.

False positives (over-reporting) may result from misclassification, hostility to one's parent, or a mental disorder. However, they are rare occurrences. False negatives are more common, resulting from childhood amnesia, an unwillingness to describe maltreatment, or an inability to access negative memories, which may occur as a result of poor attachment.

Bifulco's CECA (Child Experience of Care and Abuse) assessment is a detailed, semi-structured face-to-face interview.¹¹ To assess neglect, participants are asked to recount a typical day in their childhood. The interviewer inquires about parental or caregiver antipathy and physical and psychological abuse, as well as sexual abuse from anyone. Each experience is rated for severity on a scale of 1 to 4. Start and stop date and frequency are also recorded.

The CECA has been used in 44 studies and has shown positive associations with a range of disorders, including depression, anxiety, substance abuse, and psychosis. Recently, a screening questionnaire (CECA.Q) was validated against the interview.

To assess the utility of witness corroboration in enhancing accuracy of retrospective reports, Bifulco employed the CECA and two other tests (adult adversity [Alphi] and attachment style [ASI]) on community-based samples of high-risk individuals in pairs. These included mother-offspring pairs, adult sister pairs, and adolescent sibling pairs.

Although sister-sister pairs showed good agreement overall, corroboration of neglect was higher than that of sexual abuse. Corroboration was highest when both sisters had the same experience, but when they had different experiences, agreement was not significant. Among adolescent siblings, non-concordance of maltreatment was highest when mothers suffered

¹¹ Bifulco, A., Brown, G. W., & Harris, T. O. (1994). Childhood Experience of Care and Abuse (CECA): a retrospective interview measure. *Journal of Child Psychology and Psychiatry*, 35(8), 1419-1435.

from chronic or recurrent depression. In mother-offspring pairs, mothers under-reported abuse to their offspring.

The occurrence of depression increased with increasing severity of each type of abuse, indicating a dose-response effect; but it took detailed questions and some subtlety to assess a low level of abuse. Bifulco noted that comparison groups require careful screening, because the rate of maltreatment in the community at large is estimated at 28 percent.

Multiple types of abuse were associated with worse outcomes, manifesting as major depression in adults and as conduct disorder, deliberate self-harm, or substance abuse in adolescents.

The CECA also revealed specific outcomes associated with specific types of abuse and abusers. Whereas maltreatment from the mother was associated with depression, maltreatment from the father was associated with substance abuse. Anxiety and deliberate self-harm were associated with antipathy or neglect from the mother (but not the father).

As Manly noted in her presentation, looking at multiple dimensions simultaneously revealed new connections. Conduct disorder was more strongly associated with antipathy from the father than from the mother but was more likely to occur with physical abuse from the mother than from the father. Both substance abuse and conduct disorder were strongly associated with sexual abuse. Reliable classification of types of maltreatment can reveal different mechanisms of harm that lead to different disorders that can be addressed with different interventions.

Bifulco and colleagues developed an interview instrument that can be administered via a computer interface, the Computerized Life Events Assessment Record (CLEAR), which measures life events occurring in the past 12 months. The CLEAR has been tested on several groups and shows good test-retest results. It remains to be seen whether this online approach can be applied to the CECA for assessing a history of abuse. If so, it has the potential to vastly simplify data collection and analysis.

Remembering, Forgetting, and Creating Memories of Child Maltreatment

Gail Goodman, Ph.D., University of California, Davis

A particularly thorny question raised by retrospective reporting is that of childhood amnesia.¹² Many adults cannot remember events that occurred prior to age 3.5. In the legal arena, studies of children's memory with respect to abuse revolve mostly around child sexual abuse. To get a broader understanding of children's memory, Goodman tested children's recollection of events that did not involve abuse. When 3- to 13-year-old children were asked about an invasive

¹² Early childhood memories and infantile amnesia have been studied by experimental methods and animal studies. See, for example, Imuta, K., Scarf, D., & Hayne, H. (2013). The effect of verbal reminders on memory reactivation in 2-, 3-, and 4-year-old children. *Developmental Psychology, 49*(6), 1058-1065; Morris, G., & Baker-Ward, L. (2007). Fragile but real: Children's capacity to use newly acquired words to convey preverbal memories. *Child Development, 78*(2), 448-458; Travaglia, A., Bisaz, R., Sweet, E. S., Blitzer, R. D., & Alberini, C. M. (2016). Infantile amnesia reflects a developmental critical period for hippocampal learning. *Nature Neuroscience, 19*(9), 1225-1233.

medical procedure involving urethral catheterization, there were no definite memories if the procedure had occurred before the age of 3, but most children who were 3 years old or older at the time of the procedure did remember the event.

How the question is asked is important. During a full medical exam, a subset of children was assigned to have a doctor perform an anogenital medical exam. In free recall (“Tell me what happened during that exam”) or when given a doll to demonstrate on, such as might be done in the legal system, 60 percent of children failed to disclose the anogenital exam. However, employing a leading question (“Did the doctor touch you here?”) led to much greater accuracy. There was one caveat, however, particularly for use in legal settings: the leading question produced a small number (8 percent) of false reports among controls.

Studies find that details of events are lost over time, and this is accompanied by increased suggestibility. However, many false memory studies ask about relatively benign events, such as whether the child was ever lost in a mall. Other studies reveal that when there is low plausibility of the event occurring or it is a negative event, there is less suggestibility. Giving children a detailed explanation of a nose operation substantially reduced their susceptibility to implanting a false memory that they have had one. Around age 7, children develop metacognitive strategies that help to counter the implantation of false memories.

In a 15-year follow-up of child sex abuse cases, 81 percent disclosed the abuse, but 15.5 percent did not disclose and seemed to have no memory of the abuse. The researchers identified several predictors of accurate memory of abuse, including older age at the time of abuse (6 or over), higher severity, maternal support, and more criteria of PTSD, whereas poor memory of abuse was predicted by attachment avoidance (based on a self-report). Psychological therapy provided during the trial also increased the accuracy of memory of abuse.

In the 1990s, Goodman and colleagues studied more than 700 maltreated (abused and/or neglected) children ages 3-17 placed in a 5-day inpatient ward in Chicago for forensic, psychiatric, and medical evaluation to investigate maltreatment. On day 5, Goodman and colleagues evaluated memory and suggestibility for an anogenital exam performed at day 2. There were more errors of omission than commission, and both types decreased with age; children aged 11 and older made no commission errors to the false abuse-related questions about the anogenital exam.

Twenty years later, Goodman re-interviewed more than 100 of the children (now ages 23-35) and tested their recollections. Participants were randomly assigned to three interview conditions: a cognitive interview with context reinstatement (video of the inpatient ward), a cognitive interview with mental reinstatement (request to think back), and an FBI-type interview with no reinstatement. When participants were asked to recall the anogenital exam, the FBI-type interview elicited far more *denial* than either of the cognitive interviews. Adult reports of abuse were consistent with children’s disclosures of sex abuse, but far less consistent with children’s disclosures of physical abuse and neglect.

Meeting participants were particularly interested in discovering ways to access implicit memories that might have been formed before the age of 3 years, or formed later and forgotten. One study found that a history of abuse can alter startle response and interpretation of emotional faces. In another study, women with a history of child sexual abuse were asked the worst thing that ever happened to them and whether something sexual had ever happened to them. For those who said no, coding of their facial signals revealed shame, guilt, and anger.

The duration and frequency of abuse can have an influence on memory, as do age-related differences in cognitive processing. Most children cannot reliably report how old they were when something started and how often it happened. There could also be effects of stress on altering the onset of explicit memory formation. Avoidant attachment style predicts a later start of autobiographical memory. Abuse can also result in cognitive defects or traumatic brain injuries that impair memory.

Goodman noted that some children did not disclose abuse in the clinic but revealed it as adults. The attachment system is so strong in humans that it will often override avoidance learning, and some children will lie (e.g., denying maltreatment) to avoid separation from the abusive parent.

Session 2 Discussion

Returning to the question of whether adult accounts can be reconciled with the most accurate assessments of children, there are two separate problems:

1. When abuse occurs during the period of infantile amnesia, how can it be recovered with adult assessment?

Early abuse has a lasting effect on many systems, so it is important to identify adults who suffered this abuse in order to conduct interventions. There may be methods (such as facial expression, peer reports, or even brain scans) that can recover this information. This question requires further study.

2. Can events that occurred after infantile amnesia has resolved but were not reported be recovered, and, if so, how?

Data show that a conscientious but time-limited interview will have substantial inaccuracy (30-40 percent correspondence). Some of the presentations in the second session indicated that a very highly developed interview that takes the time and effort to restore context and detail can recover events that otherwise would have been lost (70-80 percent correspondence). After further correcting by eliminating unreliable data, this approach can yield a very good record.

Noll noted that long-term studies are, in their own way, a form of intervention. Her studies build trust over time, engendering an atmosphere that invites disclosure. Nonetheless, Noll and Widom agreed that it was much more difficult to get this level of accuracy for neglect and emotional abuse than for sexual abuse.

Different measures serve different purposes. If one's goal is simply to predict poor outcomes, then a risk indicator such as the Childhood Trauma Questionnaire (CTQ), which can be done in 5 minutes, might suffice. However, capturing an outcome that could have been prevented with a particular intervention requires a measure with good prospective and retrospective agreement. Similarly, brain imaging and epigenetic studies require a very clean phenotype.

There may be ways to improve the precision of the CTQ—for example, by asking follow-up questions of who and when. Based on Goodman's work, asking potentially leading questions about significant life events that occurred after the period of childhood amnesia will produce more complete and possibly more accurate reports, at least in older children and adults. Wherever possible, multiple methods should be used, including self-reports and objective records, to reduce contamination. Individual features at the time of recall, such as facial expression, attachment, and cognition, could increase confidence in the report.

Looking broadly, early life adversity presents several opportunities for intervention: primary prevention (of abuse), secondary prevention (of disease), and tertiary prevention (of disease progression). Even a perfect health system would not deliver prevention to everyone who needs it at an early age. But there are plenty of individuals in their 30's and early 40's who still have not developed metabolic syndrome, diabetes, heart disease, and other conditions that have been firmly linked to early adversity. Prevention of aging-related diseases must occur in midlife. This is where the public health system must intervene, and it is essential to identify the people who are at risk.

As suggested by Bifulco's reports, both verified and unverified early life stress may be linked to disease, but the treatments may be different. Timing of disease onset, severity of clinical course, and resistance to clinical treatment are all affected by the experience. The details of the adversity itself should not be neglected.

Animal models are ideally suited for establishing mechanisms and causal links. Researchers can manipulate timing, intensity, and other variables, and animals mature more quickly than humans. They can also be used to test epigenetics and intergenerational transmission.

For humans who have already shown signs of disease, randomized clinical trials should consider the role of early childhood stress, particularly in light of the heterogeneous responses to drug and placebo.

Research Review 3: The Relationship of Early Adversity to the Course of Illness and Response to Treatment: Special Problems for Ascertainment

Studies that test interventions serve an important research purpose, in that they help give a sense of the plasticity of the system. Interventions have revealed causal links in both human and animal studies. Therefore, the information offered in this session, which explores several

types of intervention, should be considered to inform not only treatment decisions, but also what it suggests about the developmental pathways that are affected.

Targeted Interventions in Childhood to Ameliorate the Effects of Maltreatment on Psychological and Physiological Functioning: Implications for Clinical Course or Treatment in Adulthood

Sheree Toth, Ph.D., University of Rochester

Child maltreatment increases the risk of failure to resolve developmental tasks from childhood into adulthood, with a range of socioemotional and neurobiological consequences. However, these developmental trajectories are modifiable with intervention. Sheree Toth's interventions are performed in randomized clinical trials and analyzed on multiple levels, including cultural, genetic, psychological, environmental, neurobiological, and social, to better understand what interventions work for whom and why.

Toth described a prospective study to test a preventive intervention for maltreated infants with officially documented CPS records. Two forms of intervention were compared: Child-Parent Psychotherapy (CPP), an attachment theory–informed method that treats the parent-child dyad; and Psychoeducational Parenting Intervention (PPI), which teaches parenting skills and treats only the mother. Each intervention was intensive and lasted for 1 year. The primary maltreatment was neglect, and the primary outcome measure was security of attachment.

Both interventions yielded dramatic effects. Secure attachments in children who received intervention rose from close to 0 percent at baseline to 50-60 percent after intervention, with PPI and CPP showing similar results. Attachments in non-maltreated children did not change over this time period, whereas children with CPS reports who received “community standard” treatment showed hardly any improvement, registering less than 10 percent attachment at the later time point. Only the group that received CPP showed sustained secure attachment at a follow-up 1 year after the intervention. Those who received PPI experienced a decrease of greater than 50 percent.

While demonstrating that preventive interventions for maltreated infants can promote secure attachment, Toth's work also highlights the need to export efficacious preventive interventions into real-world clinical settings. Particularly worrisome was the lack of effectiveness of community-standard treatment.

A second study examined the effect of intervention on normalizing regulation of the stress hormone cortisol, using infants and treatment groups similar to those described above. Morning cortisol levels showed no baseline differences across the four groups. However, although cortisol levels in the two groups receiving interventions were similar to those of the non-maltreated group throughout the yearlong intervention, the community-standard group diverged from the others over time. These results indicate that, in addition to affecting attachment and behavior, psychosocial interventions may normalize biological regulatory processes in maltreated infants.

A third study examined the impact of preventive interventions on cortisol in mothers. Only those mothers who received CPP evidenced decreased child-related parenting stress and had more normalized cortisol function 1 year post-intervention. Mothers receiving PPI had decreased parent-related parenting stress, but their cortisol function did not normalize post-intervention.

In a fourth study designed to investigate genetic and environmental influences on behavior, 548 school-aged low-income children with and without maltreatment were studied in a summer camp setting. Toth and colleagues examined methylation of the glucocorticoid receptor gene NR3C1 and links to developmental outcomes. Children who had experienced early maltreatment had hypermethylation at exon 1 of the NR3C1 gene compared to children who experienced maltreatment later or not at all. Chronic maltreatment was associated with more hypermethylation. Hypermethylation at NR3C1 was related to higher ego-undercontrol, higher emotional lability-negativity, and higher overall externalizing symptoms. This is one of very few studies linking epigenetics and child outcomes in maltreatment.

Toth noted that DNA methylation is potentially reversible, even in adults. Therefore, it is theoretically possible to design an environmental intervention capable of reversing DNA hypermethylation and alleviating adverse phenotypes.

The results of these randomized clinical trials can be seen as both gratifying and sobering. Plasticity is possible during early childhood and attachment, suggesting that preventive interventions may have effects into adulthood. By fostering secure attachment, costlier interventions (such as residential placement and treatment for mental illness) could be averted. However, these results also shed light on the harsh reality of the ineffectiveness of services currently being provided, at significant cost, in many communities throughout the nation. Evidence-based interventions may appear costly, but the long-term savings and benefits cannot be overstated.

This work also raises several questions for further study: Could DNA methylation changes early in life that predict risk and resilience be mapped to provide insight into the mechanisms involved? Is there a positive, supportive methylation pattern that places children on a positive developmental trajectory? How narrow is the window of opportunity for prevention? When is the best time to intervene? Could epigenetic markers be used to evaluate these interventions? Are there critical periods, or can later interventions be successful?

It was noted that becoming a parent is also a period of enhanced neural plasticity. Many parents who were maltreated want their children to have a better experience than their own, and this combination of motivation and plasticity could be leveraged for effective intervention. Targeting adults before they become parents might not be as effective.

Recalled Adverse Childhood Experiences: Impact on Reproductive Behavioral Health

Neill Epperson, M.D., University of Pennsylvania Perelman School of Medicine

There is sex bias in human disease, with women more likely than men to have affective disorders such as panic, anxiety, and depression, all of which tend to occur after puberty. Some women struggle during hormonal changes, such as those that occur during pregnancy/postpartum, natural menopause, and early menopause resulting from oophorectomy. Childhood adversity may impact the brain's response to hormonal changes, creating vulnerabilities that are unmasked at these reproductive time points.

To demonstrate the ways in which reproductive hormones affect brain activity, consider estrogen. Estradiol modulates synthesis and stability of serotonin and the density of the serotonin receptor. Overall, its effect is pro-serotonergic. Nonhuman primate work has demonstrated that early subordination, a stress condition, reduces the ability of estradiol to enhance serotonin production. Estradiol can also modulate the effect of stress on the architecture of cells in the prefrontal cortex.

Neill Epperson and colleagues study the impact of pre-pubertal adversity on affective disorders. They assay for effects on the woman during pregnancy and menopause, as well as on her offspring. Participants complete an ACE questionnaire twice and are then interviewed to generate a "reconciled" measure of ACEs.

Postpartum mothers and their 6-month-old babies were exposed to laboratory stressors, and salivary cortisol was measured to indicate the stress response. Both mothers and infants in the high-ACE group had lower baseline cortisol levels than those in the low-ACE group, and high-ACE mothers and infants showed a blunted response to stressors.

In a parallel experiment, researchers used mice to model human early life stress. Female mice that were stressed during the peri-pubertal window showed a lower corticosterone response than control females following separation from their pups and took longer to retrieve the pups after being reunited. Parallel observations of both behavior and hormone activity in stressed humans and mice suggest that useful molecular information may be obtained from this mouse model.

The Penn Ovarian Aging Cohort consists of 436 women who at the time of recruitment were premenopausal and had normal endocrine measures and menstrual cycles.¹³ These women were followed for 14 years, across all stages of the natural menopause transition. A subgroup of women developed depression only in the years leading up to menopause, with symptoms subsiding after menopause. Of interest, women who had experienced one prepubertal ACE had a reduced lifetime risk for major depression as well as reduced risk for new onset depression

¹³ Freeman, E. W., & Sammel, M. D. (2016). Methods in a longitudinal cohort study of late reproductive age women: the Penn Ovarian Aging Study (POAS). *Women's Midlife Health*, 2(1), 1.

during the menopause transition. Two or more ACEs conferred a risk similar to that of no-ACE controls.

To assay for cognition, the researchers monitored changes in immediate and delayed verbal recall, which declines across the menopause transition. Looking at blood samples collected over the years, they found significant relations between levels of inflammatory cytokines (hsCRP, IL-1 β , IL-6, and TNF- α) and cognition across the transition period.

During premenopause, there was no significant difference in levels of inflammatory cytokines between low-ACE (0-1) and high-ACE (2+) women. However, as they moved into perimenopause and postmenopause, high-ACE women demonstrated higher levels of IL-6 and IL-1 β , which were correlated with worsening cognitive performance. Neither high ACE nor high cytokines alone was significantly associated with cognition during the menopause transition; the effect was only seen when the two factors were combined. If this finding is replicable, it suggests that the perimenopause window might be a good time for intervention for high-risk women.

There is increasing evidence that childhood adversity affects response to medicine. In a randomized clinical trial, women going through premature menopause were given a psychostimulant to help with executive functioning. Women in the low-ACE group responded to both drug and placebo, to similar degrees. In contrast, women in the high-ACE group responded to the drug but had no response to the placebo. This result underscores the need to take childhood adversity into account when designing drug trials.

Meta-Analyses of the Associations between Retrospective Reports of Childhood Maltreatment and Course of Illness and Treatment Response in Affective Disorders

Andrea Danese, Ph.D., Kings College London

If retrospective reports of childhood maltreatment can be used to predict the course of illness and to identify treatments for individuals with affective disorders, this could facilitate “tertiary prevention” to identify the best treatments for patients who have already developed a condition.

To illustrate the problem of identifying appropriate treatments, Andrea Danese gave the example of depression—a single diagnostic category that conceals a great deal of heterogeneity. Researchers have identified six distinct classes of depression that vary with respect to number, duration, and severity of episodes. Likewise, there is considerable heterogeneity in the response to antidepressants.

Early life stress may explain some of the heterogeneity of the phenotypes associated with depression. For example, individuals with both early life stress and a history of major depression secrete higher levels of stress hormones and have greater increases in heart rate in response to stressors than those with either early life stress or major depression alone.

Danese probed the association between early life stress, major depression, and inflammation in the Dunedin birth cohort. With increasing likelihood of maltreatment, there was an increase in inflammatory biomarkers. The combination of current depression and past maltreatment was associated with the highest level of these biomarkers, raising the possibility that past maltreatment might identify high levels of inflammation in depressed individuals.

In a meta-analysis, Danese found that individuals who reported childhood maltreatment were twice as likely to develop depression that was recurrent and resistant to treatment, compared to non-maltreated depressed individuals.

Inflammation may also underlie the progression of bipolar disorder. Danese found that reports of maltreatment were associated with increased severity of bipolar disorder. Although the direction of causation between the illness itself and retrospective accounts of maltreatment is not clear, it was noted that a CTQ might be useful for predicting the course of bipolar disorder, whatever the actual history of maltreatment might be.

The potential implications of these findings are illustrated in a recent report of a randomized controlled trial of an anti-inflammatory drug. Overall, the drug (infliximab) showed no effectiveness over placebo at treating depression. However, patients with high levels of inflammatory biomarkers—in whom inflammation may have contributed to the pathogenesis of depression—did show a treatment effect.

Danese noted that administration of anti-inflammatory drugs to maltreated mice has been shown to prevent later cognitive effects. Taken together, these results suggest that it may be possible to stratify individuals with a variety of cognitive or psychological illnesses for therapeutic intervention, based in part on a retrospective account of early childhood maltreatment.

Session 3 Discussion

Workshop attendees were intrigued by the findings of Epperson and Toth, both of which identified the cortisol response as a potential biomarker for stress related to maltreatment. Although the two investigators measured cortisol under different conditions (Epperson's under stress, Toth's not), both observed a blunted cortisol response in mothers and infants in the maltreatment group, and Toth was able to reverse this response by treating mother-child pairs with CPP therapy.

Epperson noted that it was striking to observe cortisol differences among groups consisting of just 25 mother-infant pairs. Toth noted that control over children's diets and activities in the summer camp study may have given the study additional power to detect intervention effects.

One challenge of biomarker research is that adversity may affect different systems in different people. Tottenham suggested using a multivariate approach with a collection of biomarkers and creating a probability atlas based on biomarker responses, as is currently done with brain anatomy. This is the biological equivalent of including "probable" versus "definite" maltreatment.

Tottenham described one way this data-driven approach might work. In a population of individuals who experienced childhood adversity, there are many potential biomarkers and other phenotypes of maltreatment. Individuals can be grouped into clusters based on phenotype; these clusters are then submitted to a decision tree analysis that asks whether the report is prospective or retrospective, the type and severity of adversity, as well as other measures discussed at this meeting. This type of analysis could reveal tighter links between early care adversities and outcomes. Ultimately, this strategy could suggest a stratified approach to treatment, where groups are tracked over time, and it becomes possible to predict outcomes based on experiences and phenotypes. This type of risk assessment would move the field away from reliance on allostatic load and lead to the development of profiles based on a variety of biomarkers that could produce a fingerprint of risk.

Workgroup Reports

Participants divided into three workgroups, one for each session, to discuss ideas for further study. The groups delivered brief reports, summarized here.

Workgroup 1: Comparing Data across Longitudinal Data Sets

This group considered how to make the most of the data sets assembled in the systematic review by Baldwin, in which there is both prospective and retrospective assessment of ACEs.

The group identified several moderators of potential concordance that could be examined, including:

- Era of the study (for generational influence)
- Geography/Country/Region (for cultural influence)
- Reporters (are they the same in prospective and retrospective accounts?)
- Time difference (between prospective and retrospective ascertainment)
- Style of prospective measurement (official report, observational, etc.)
- Treatment +/- (this is not reported in most studies; however, the 2016 review of intervention studies by Toth et al.¹⁴ is a valuable resource)

The group recommended a consortium approach. Grants could target researchers with longitudinal studies that have ascertained adversity prospectively but do not yet have or could include additional retrospective or health outcome measures. When needed retrospective data already exist, grants could fund analyses using data-driven clustering to define phenotypes as described by Tottenham or include other state-of-the art approaches. The Child Neglect Consortium, which was headed by Widom and has succeeded in harmonizing research from diverse sources, provides a good precedent.

¹⁴ Toth, S. L., Petrenko, C. L., Gravener-Davis, J. A., & Handley, E. D. (2016). Advances in prevention Science: a developmental psychopathology perspective. In D. Cicchetti (Ed.) *Developmental Psychopathology* (pp. 815-873). Hoboken, NJ: John Wiley & Sons, Inc.

Workgroup 2: Enhancing Retrospective Analysis to Maximize the Overlap with Prospectively Ascertained Childhood Adversity

It takes intensive, one-on-one interviewing, while carefully controlling for contamination, to obtain a phenotype that is sufficiently detailed and accurate to address some questions. Nonetheless, this group sought a way to optimize retrospective reporting, including when intensive interviewing is not an option. Specifically, they considered how to achieve the following three goals:

1. Empirically derive, discover, or enhance the optimization of retrospective reporting.

This could be achieved by identifying existing studies that have both prospective records and retrospective accounts and leveraging these existing data to identify any details (age, perpetrator, etc.) from the prospective account that are predictive of physical and mental health outcomes. These details would then be included in an optimized measure of retrospective reports. Elements of the retrospective reporting experience such as timing, subjective appraisal, cultural components, psychopathology, and social support could then be evaluated with respect to whether they are predictive of outcomes. That specificity provided by prospective and retrospective records in predicting health outcomes could then be compared.

2. Demonstrate optimization of retrospective reporting.

This could be achieved by conducting new studies to test effects of the elements identified in step 1 and by validating these elements by applying them in new settings.

3. Increase confidence in retrospective reporting through small, focused studies.

Smaller studies could be performed to test factors that may influence the retrospective report but have not been examined or controlled for previously. These could include timing, rapport with the interviewer, approaches to asking a question, online versus in-person reports. These studies could increase confidence in retrospective reporting while remaining realistic about what is feasible in larger studies.

Workgroup 3: Making Pragmatic Use of Retrospectively Collected Data on Childhood Adversity

Given the difficulty in obtaining high-quality prospective data, it is crucial to understand how retrospectively collected data can be used for practical clinical decision making, such as for stratifying groups for intervention or predicting the course of disease. This group identified relevant gaps in knowledge and considered the types of studies that might be needed to address them.

1. Assuming that there is no way to verify the early life events described in retrospective reports, do subjective appraisals of early life adversity provide added value over other routinely assessed risk factors?

2. Retrospective data are useful for secondary or tertiary prevention interventions. Is it critical to get granular information on early life adversity via subjective appraisals when predicting the course of disease and response to treatment?
 - These appraisals may be extremely subjective. One could start with a feeling thermometer: “How difficult was your early life?” and follow with granular questions, then apply the thermometer again, much like the MacArthur ladder for social status. A study using this method could examine the added value of the interview, given that time is often in short supply.
 - Broad questions could capture people who do not know precisely what happened or are unwilling to share, but nonetheless feel comfortable saying “I did not have a good childhood.” The value of such a blunt instrument, which provides little information beyond a sense of perceived adversity, is not known.
 - Some individuals may have high discrepancy between broad and granular assessments of their childhood. These individuals may be most at risk.
3. Is it possible to stratify by (1) early life adversity and (2) by the combination of early life adversity and behavioral and biological phenotypes, to provide hypothesis-driven treatments?
 - This might take the form of a randomized clinical trial to test whether early adversity in the context of attachment difficulties responds better to one type of therapy, while adversity in the absence of attachment difficulties, but with other physiological indices, responds better to another therapy.
 - Assessing personality could help inform the type of care that is needed.
 - Evidence presented at this meeting by Widom, Danese, and others indicates that subjective appraisals can be predictive. Whether their predictive value is enhanced by additional factors remains to be seen, although Epperson’s study demonstrating a combined effect of ACEs and cytokines on cognition during menopause suggests that may be the case.

In general, research is needed to address the amount of information gained by adding additional levels of granularity, from a broad “feeling thermometer” measure, to additional more granular self-report measures, and finally to particular behavioral or biologic phenotypes.

Additional Questions Raised Before, During, and After Workgroup Discussions

Several key questions and comments were raised during the workgroup discussion session that were not directly addressed by the three workgroup reports. These are summarized below by theme:

The Utility of Retrospective Data

- How do different types of retrospective interviews and different therapeutic processes affect recall?
- What are the mechanisms behind the predictive value of retrospective data, and what interventions can best address these mechanisms?
- When using the CTQ as an independent variable, is it necessary to adjust for severity, social class, self-esteem, or other variables?

- Causality may not always be crucial in considering retrospective reports of adversity: it is important to understand the biological correlates of adversity reporting regardless of the direction of causality.

Improving Retrospective Measures of Childhood Adversity

- Research examining the role of relationship and context issues in interviews on child adversity reporting could be very useful in establishing a paradigm for the collection of retrospective data.
- Adversity questionnaires are often written with the assumption that two parents are initially involved in caretaking. This can be problematic for individuals raised in one-parent settings.
- Emotional abuse is not well defined and may not be well captured by current standard questionnaires or interviews.
- Attachment style could provide additional information when used together with current questionnaire or interview measures.
- Some childhood adversities, such as death of a parent, are likely to be accompanied by more support than others, such as neglect and abuse.
- Every individual experiences some early life stress. Risk groups can be identified on the basis of the amount of maltreatment that matters rather than the kind. A high count captures an early start and greater severity.
- The timing of an adversity could have a large impact on outcomes. In general, early maltreatment has the most deleterious effects, although it is less likely to be remembered.

Reconciling Retrospective and Prospective Accounts

- CPS records are discarded when children turn 18, limiting the availability of objective records of maltreatment for adult participants.
- No records are truly objective. It would be more accurate to categorize records as fully, partially, or not concordant.
- Can targeted treatments be effective for individuals who perceive they have been traumatized, despite lack of prospective evidence?
- Could biological data, such as the cortisol data presented by Toth and Epperson, be used to reconcile retrospective and prospective data?

Using Adversity Data in Treatments and Interventions

- Can new and existing targeted treatments utilize biological correlates of early life stress to improve outcomes?
- There is potential for translation of methods among diverse caregiving situations, including parenting, illness, and elder care.
- One medical approach to treating complex conditions is to develop interventions that stratify a broad illness phenotype into a finite number of clinically relevant subgroups for treatment; this can be effective even when the precise etiology of disease is unknown.

Using Adversity Data in Drug Trials

- If a drug study is truly randomized, there should be equal numbers of high-stress, high-adversity individuals in each group. Pharmaceutical companies could collect this information and consider these variables when examining treatment response.
- What proportion of people with early childhood adversity do not manifest problems early, but do manifest them in mid-life or later?

The Relations between Childhood Adversity and Later Outcomes

- What proportion of people with early childhood adversity do not manifest problems at all? What are the mediators of resilience?
- The use of retrospective data to stratify clinical trials has not been done in medicine. Nonetheless, retrospective reporting of maltreatment lends itself to random assignment in clinical trials.

Appendix 1: Agenda

Retrospective recall and prospective observation of childhood adversity: challenges and opportunities in their use in health and aging research

A meeting of the Reversibility Network in Bethesda, MD

Tuesday, November 1 • 9:00 am – 5:00 pm

Wednesday, November 2 • 8:30 am – 4:30 pm

Day 1, November 1, 2016

- 9:00 am Introduction
David Reiss and Andrea Danese
- SESSION 1 Risk for Ill Health: The Relationship between Retrospectively and Prospectively Assessed Cohorts**
- 9:30 am Comparison of the Associations between Prospectively or Retrospectively Assessed Childhood Adversity and Later Health Outcomes in the Dunedin Cohort
Aaron Reuben
- 10:00 am Comparison between Prospectively and Retrospectively Assessed Childhood Maltreatment and Later Health Outcomes in the Midwest Cohort
Cathy Widom
- 10:30 am Identifying Cohorts that have Collected Sufficient Data to Address Questions on the Separability and Comparability of Prospective and Retrospective Cohorts
Jessie Baldwin
- 11:00 am BREAK
- 11:15 am Group Discussion
- 12:15 pm LUNCH
- SESSION 2 Risk for Ill Health: Improving Identification in Adulthood of Cohorts Identified Prospectively in Childhood**
- 1:00 pm Early Adversity, Altering the Pace of Development and Compensatory Mechanism: Can We Fashion a Biological/Environmental Profile for Retrospective Ascertainment?
Nim Tottenham

- 1:30 pm Cross-Sectional and Longitudinal Ascertainment of Child Maltreatment
Jody Manly
- 2:00 pm Prospective and Retrospective Assessment of Childhood Maltreatment and the Impact of “Contamination” in Control Groups: Improving Assessments in Adults, Reducing False Negatives, Utilizing Contextual Cues, and Specifying Developmental Timing
Jennie Noll
- 2:30 pm BREAK
- 2:45 pm Improving the Validity of Retrospective Reports of Childhood Maltreatment: Enhancing Narrative Skills, Understanding the Social and Personal Context of Maltreatment and Searching for Specific Effects
Antonia Bifulco
- 3:15 pm Forgetting and Creating Memories of Childhood Maltreatment: Relevant Data from Studies of the Development of Memory and Strategies for Enhancing Recovery of Childhood Events
Gail Goodman
- 3:45 pm Group Discussion
- 4:45 pm Recap and Q&A
- 5:00 pm Adjourn

Day 2, November 2, 2016

SESSION 3 The Relationship of Early Adversity to the Course of Illness and Response to Treatment: Special Problems for Ascertainment

- 8:30 am Meta-Analyses of the Associations between Retrospective Reports of Childhood Maltreatment and Course of Illness and Treatment Response in Affective Disorders
Andrea Danese
- 9:00 am Memories of Childhood Maltreatment at Important Psychobiological Transitions: Menopause and Ovariectomy as Examples
Neill Epperson
- 9:30 am Targeted Interventions in Childhood to Ameliorate the Effects of Maltreatment on Psychobiological and Physiological Functioning: Implications for Clinical

Course or Treatment in Adulthood
Sheree Toth

10:00 am BREAK

10:15 am Group Discussion

SESSION 4 Workgroups

11:15 am Strategies for Comparing Data Across Longitudinal Data Sets with Prospective Ascertainment and Where Retrospective Ascertainment Has Been Obtained or Is Feasible.

12:15 pm LUNCH

1:00 pm How Can We Maximize the Overlap Between Groups of Individuals with Prospectively and Retrospectively Ascertained Childhood Adversity?

2:00 pm BREAK

2:15 pm The Pragmatic Use of Retrospectively Collected Data on Child Adversity

3:15 pm Moving Forward

4:30 pm Adjourn
David Reiss

Appendix 2: Participant Roster

Jessie Baldwin

Graduate Student
Department of Child and Adolescent
Psychiatry
Kings College London
jessie.baldwin@kcl.ac.uk

Antonia Bifulco, Ph.D.

Professor
Department of Psychology
Middlesex University
a.bifulco@mdx.ac.uk

Andrea Danese, Ph.D.

Clinical Senior Lecturer
Departments of Child & Adolescent
Psychiatry and Social, Genetic, &
Developmental Psychiatry
Kings College London
andrea.danese@kcl.ac.uk

Neill Epperson, M.D.

Professor
Department of Psychiatry
University of Pennsylvania Perelman School
of Medicine
cepp@mail.med.upenn.edu

Gail Goodman, Ph.D.

Distinguished Professor
Department of Psychology
University of California, Davis
ggoodman@ucdavis.edu

Jody Manly, Ph.D.

Clinical Director and Senior Research
Associate
Mt. Hope Family Center
University of Rochester
jody.manly@rochester.edu

Lis Nielsen, Ph.D.

Chief, Individual Behavioral Processes
Branch
Division of Behavioral and Social Research
National Institute on Aging
nielsenli@nia.nih.gov

Jennie Noll, Ph.D.

Professor
Department of Human Development and
Family Studies
Pennsylvania State University
jgn3@psu.edu

Christine Power, Ph.D.

Professor
Departments of Epidemiology and Public
Health
University College London
christine.power@ucl.ac.uk

David Reiss, M.D.

Clinical Professor
Child Study Center
Yale University
david.reiss@yale.edu

Aaron Reuben

Graduate Student
Department of Psychology & Neuroscience
Duke University
aaron.reuben@duke.edu

Teresa Seeman, Ph.D.

Professor
Departments of Medicine and Epidemiology
Geffen School of Medicine, University of
California, Los Angeles
tseeman@mednet.ucla.edu

Sheree Toth, Ph.D.

Director
Mt. Hope Family Center
and Professor
Department of Psychology
University of Rochester
Sheree_Toth@URMC.Rochester.edu

Nim Tottenham, Ph.D.

Associate Professor
Department of Psychology
Columbia University
nlt7@columbia.edu

Cathy Widom, Ph.D.

Distinguished Professor
John Jay College of Criminal Justice
cwidom@jjay.cuny.edu