

National Institute of Aging/ ESRC/BBSRC
**Research Network on Later Life Interventions to Reverse Effects of
Early Life Adversity**

Network Meeting III:

*Childhood Adversity, Adult Health, and Preventive Interventions:
The Potential Role of New Findings on Neuroplasticity*

MEETING SUMMARY

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**April 19-20, 2017
The Rockefeller University
New York, NY**

MEETING GOALS

The brain is now recognized as a malleable and vulnerable organ of the body, capable of adaptive plasticity but also vulnerable to damage. Opening windows of plasticity in the developing, adult and aging brain is a major challenge in order to overcome the consequences of severe adversity, including poverty in early human development and subsequent adverse experiences. Of special interest are the possible long-term damaging effects of adversity on health promoting lifestyle, on the liability for a broad range of serious physical illnesses and—for some adversities—on rapid cognitive aging. Childhood, probably including adolescence, is a time when the brain is particularly sensitive. When periods of sensitivity or malleability begin to close, later in development, the effects of these adversities cannot easily be undone either by naturally occurring or therapeutically provided favorable experiences.

The long line of causal links from childhood adversity to rapid cognitive aging remains difficult to trace. This has prompted the search for “intermediate nodes of causality” that may in turn be linked mechanistically to forms of severe early adversity and—in turn—are linked mechanistically to lifestyles undermining health and to rapid cognitive aging. There are several possible candidates for “intermediate nodes” and all should be considered carefully. However, of particular promise, and vital national interest, are various components of the metabolic syndrome (MetS). While there is some debate about definition this syndrome is generally thought to be defined by a combination of central obesity, dyslipidemia (raised triglycerides, reduced HDL cholesterol), leptin resistance, elevated blood pressure and fasting blood glucose and insulin resistance in brain and body.

MetS, as exemplar of the “intermediate node,” is of special interest because:

- First, many of its components are being recognized very early in life.
- Second, both prospective and retrospective studies of severe child adversity have replicated associations with MetS.
- Third, potentially malleable pathways are being mapped from metabolic syndrome to mortality, to major impairments in health including and to rapid cognitive aging through the way stations of diabetes, cerebrovascular disease, depression and the brain biology underlying these clinical conditions
- Fourth, there are newly discovered links between brain physiology and the MetS.
- Finally, the impact of some strategies for intervention in adults—strategies that might interrupt the link between MetS and its long-term impact on rapid cognitive aging—may be moderated by recalled (and perhaps actual) child adversity. The literature is strongest for the moderation of treatment of depression. Thus, childhood adversity may constitute a “double risk:” a contributory cause in the etiology of MetS and a moderator of intervention attempts to ameliorate the risk of MetS to cognitive health.

Other candidates for “intermediate nodes” might include: a) inflammation and infectious disease resistance; or b) behavioral syndromes that include impulsive behavior, disrupted social relationships, difficulties in relationships and poor self-care; or c) alterations in the structure and function of cortical and subcortical processes or d) depression and loneliness or d) transitions in adulthood:(e.g., becoming a parent, moving, retirement) How people navigate these transitions may be greatly affected by early trauma and may have significant consequences on future health.

We recognize that the observed links between early adversity, on the one hand, and the intermediate and long-term outcomes, on the other, are derive—in most instances from

associational studies. Some of these are prospective studies diminishing the likelihood of reverse causation. However, the causal nature of the majority of prospective associations remains to be established in human studies although there are important intimations of causality from animal models. Thus, one function of a workshop that focuses on interventions, and the increasing literature on neuroplasticity that is an invaluable resource for their development, is to consider how interventions might provide experimental evidence for causal links between severe early adversity and “downstream” outcomes.

DAY 1

Welcome and Introduction

The day started with the meeting chair, Dr. Nim Tottenham, welcoming the participants and highlighting the primary goals for this network meeting. The main goal was to identify what questions need to be answered in order to ultimately understand how early life events may affect both mental and physical health outcomes later in life, and how we can leverage current knowledge of behavioral and neural plasticity to design interventions to enable compensatory adaptation or recovery from those impacts on health. This meeting was particularly focused on metabolic syndrome and its components as potential targets for reversibility interventions, using it as an exemplar for how researchers might tackle such questions in other domains. In addition, the meeting aimed to bring together researchers who study aspects of early adversity from various angles, therefore stimulating formation of potential collaborations. [Dr. Lis Nielsen](#) from the National Institute on Aging (NIA) provided a brief overview of the history of the Reversibility Network, which had been created collaboratively with the UK Economic and Social Research (ESRC) and Biotechnology and Biological Sciences (BBSRC) Research Councils in order to determine the extent to which it is possible to document any causal links between early adversity and health outcomes and to start identifying interventions, both biological and psychological, that could augment developmental trajectories of people affected by early adversity. She highlighted that this meeting – the third in a series of three - was the first of the network meetings focused on interventions. [Dr. Bruce McEwen](#), Co-PI of the Reversibility Network, noted that the word “reversibility” has to be used with caution, as truly “reversing” biologic processes that already occurred in early life is not possible, and suggested that words such as “recovery,” “redirection,” and “resilience” are more appropriate and reflective of our understanding of developmental processes and our abilities to affect them.

[Dr. Andrea Danese](#) gave an overview of the first network meeting, held in Bethesda, MD, on November 1-2, 2016 which had focused on the issues of measurement of early adversity and, specifically, on the utility of prospective vs retrospective assessment of early adversity for health research. The ACE study (Felitti et al., 1998) has been influential in identifying the important role of early adversity in adult health, but at the same time brought into light the question of validity of retrospective reports. The prospective Dunedin study then focused on this question specifically and suggested that association between retrospective and prospective measures of early adversity is generally low (Reuben et al., 2016). Therefore, it is likely that different participants are identified in studies that use prospective and retrospective assessment methodology. This could be due to measurement issues and/or criterion validity issues. Of note, in the Dunedin study, retrospective measures were more strongly associated with subjective health outcomes, while prospective measures were more strongly associated with

objective health measures – highlighting the potential for common method bias. Preliminary results from an ongoing systematic review identified a paucity of studies using both retrospective and prospective measures, and supported findings of low association between them in the studies conducted. However, the consensus of the first network meeting was that retrospective measures can be used pragmatically to predict course of disease (e.g., studies on depression, bipolar disorder), and treatment response, and may thus have clinical utility (Nanni, Uher, & Danese, 2012; Agnew-Blais & Danese, 2016). Future directions include further systematic studies, further investigation of criterion validity of retrospective vs prospective measures, the mechanisms underlying the difference between them, and how the retrospective measurements can be improved. Validity of assessment may also be increased by obtaining reports from multiple observers. A summary report for this meeting is available online: [Reversibility Workshop I Report](#)

[Dr. Teresa Seeman](#), Network Co-PI, gave an overview of the second network meeting, held in Bethesda, MD, on January 31-February 1, 2017 which had focused on the dimensions of early life adversity, their potentially differential effects on development through distinct processes of biological embedding, and their possible role as targets for interventions. The four broad categories or dimensions of adversity explored include: threat/trauma, loss, unpredictability/chaos, and deprivation. The workshop emphasized the value of re-focusing research from mere consideration of an accumulation of exposure approach (e.g., as used in ACE study) to studying co-occurrence of types of adversity and their clustering. The meeting reviewed current evidence on some of the already identified biological pathways underlying effects of early adversity on lifelong health, including epigenetics, inflammation, and metabolism. As an example, [Dr. Keith Godfrey](#), Network Co-PI, presented a program of multilevel research on obesity, which includes studying exposures, leading to mechanisms, leading to childhood obesity. Genome, epigenome, transcriptome, proteome, metabolome, and exposome data linked to a phenotype may provide understanding of the pathogenesis mechanisms underlying childhood obesity. For example, low birthweight is affected by environmental factors much more than by genetic factors (Lin et al., 2017). Considering implications for the current meeting, another important question concerns the best time points for interventions. A threatening vs secure environment plays a role in development early in life, but it is also an important health-relevant exposure over the whole life course. Arguably, the earlier the environment can change from threatening to secure, the better chance we have at changing the trajectory of development. However, effective interventions are possible throughout life course, and for example, adolescence may provide a good window for interventions to “reverse” or “redirect” processes set in motion by early adversity. Additionally, studying the interactions between early exposures to adversity and later environmental factors may help us identify the “biologic signatures” that can inform development of interventions.

[Session 1: Research strategies for clarifying the role of critical or sensitive periods in the apparent selective impact of severe adversity in childhood and adolescence rather than later in development](#)

[Dr. Nim Tottenham](#) reported on her work on the development of the amygdala, hippocampus, and prefrontal cortex to provide an example of critical and sensitive periods in the development

of neural systems for emotion regulation (e.g., Gee, Humphreys, et al., 2013; Gabard-Durnam et al., 2014; Gabard-Durnam et al., 2016). To demonstrate this concept, she described a study in which, using a paradigm built on music exposure at various stages of development, she was able to demonstrate a sensitive period for mPFC engagement in down-regulation of distress. She then turned to studies that suggest environment may shift the timing of development of these neural circuits. During childhood, regulated parents seem to be a buffer for amygdala reactivity (e.g., Gee et al., 2014), while dysregulated parents potentiate stress neurobiology and, specifically, the amygdala's responsivity to stress. In an extreme example of parental neglect, studying children in institutional care gives an opportunity to identify specific critical periods for development of this circuitry, as some children adopted after institutional care show a rebound on both the behavioral and neural level, suggesting continued plasticity in childhood. Mounting evidence from animal studies suggests that early life stress can accelerate development of emotion regulation neurobiology by establishing subcortical-to-cortical connections earlier in life. This phenomenon has been understood as developmental adaptation to environmental conditions. In Dr. Tottenham's human studies, children who had experienced severe form of neglect early in life show the shortening of the early amygdala sensitivity period and an earlier development of amygdala-mPFC-hippocampal connectivity, which more closely resembles adult connectivity (Gee, Gabard-Durnan, et al., 2013; Silvers et al., 2016). There seems to be an adaptive value to this shift as evidenced by lower anxiety experienced in a fear learning paradigm. However, a parental buffering effect was not observed in previously institutionalized children as compared to controls. Interestingly, this association was mediated by level of security of attachment. Therefore, early experiences may affect the pacing of development, having long-term developmental consequences. Timing and pacing should be taken into account when studying both short- and long-term consequences of early adversity.

[Dr. Takao Hensch](#) focused on critical periods from the bottom-up perspective with the goal of understanding what mediates the transition from a more malleable to a less malleable brain throughout development. In an example of vision studies with rodents, excitatory/inhibitory (E/I) balance in visual cortex determined a critical window for plasticity, which could be moved by manipulating this balance (Hensch, 2005; Bavelier, Levi, Li, Dan, & Hensch, 2010; Takesian & Hensch, 2013). This is especially relevant to the study of early adversity, as the development of the inhibitory system is particularly susceptible to stress. The second insight from this line of research was that plasticity closure is an active and necessary process. A number of molecular and cellular level mechanisms for the development of E/I balance have already been identified. Most current approaches to opening plasticity in adulthood have been focused on modifying inhibitory processes, including manipulating factors in perineuronal net, affecting the disinhibitory neurons, or transplantation of embryonic precursor cells (Werker & Hensch, 2015). Taking a broader look, the following questions remain: Why is the brain developing in a certain sequence, and are there consequences to mistiming? Using a model of critical periods for acoustic preferences in mice, Dr. Hensch was able to demonstrate two pathways to extend plasticity and shift critical period: a genetic approach by Nogo receptor blocking that affects myelination, and acutely with valproic acid (Gervain et al., 2013). Another clinically relevant aspect of this research focuses on sex differences. Human studies suggest sex differences in reaction to early life stress in that females tend to develop more internalizing behaviors, while males develop more externalizing behaviors. Dr. Hensch's lab replicated these sex differences in a fragmented care paradigm in mice and showed them to be associated with E/I balance in the prefrontal cortex. On a cell-subtype-specific level, one form of inhibition gets weaker in

females, while in males it gets stronger. In terms of reversibility of the effects of early adversity, in preliminary studies, slightly shifting a critical window for music preference development provided rescue of an anxious phenotype. In conclusion, Dr. Hensch stressed that while these studies suggest opportunities to reverse negative effects of early adversity, it is also important to consider potentially negative consequences of increasing neuroplasticity and shifting critical windows. In addition, there is a need to study prenatal windows of development, as different systems develop at different time points.

Dr. Carmen Sandi focused her talk on the role of puberty in development. In rodent models, generally prepubertal exposure to stress (e.g., fear) leads to anxiety-like and depression-like behaviors, inattention, anti-sociality and highly aggressive behavior (Cordero, Ansermet, & Sandi, 2013; Cordero, Just, Poirier, & Sandi, 2016; Toledo-Rodriguez & Sandi, 2007; Toledo-Rodriguez & Sandi, 2011; Toledo-Rodriguez, Pitiot, Paus, & Sandi, 2012; Tzanoulinou, García-Mompó, et al., 2014; Tzanoulinou, Riccio, et al., 2014; Tzanoulinou et al., 2016; 2017; Veenit, Cordero, Tzanoulinou, & Sandi, 2013; Veenit, Riccio, & Sandi, 2014; Walker & Sandi, 2018). However, there are individual differences in these effects, and studies are underway to investigate them (Sandi & Haller, 2015). Mean diffusivity on MRI correlated with behavioral individual differences in aggression, and myelin-binding protein was associated with sociability. Polysialic acid (PSA) plays a role in myelination and distance between the cells in both animal and human studies and therefore plays a major role in neuroplasticity. Two enzymes with different developmental profiles control development of PSA. In Dr. Sandi's studies, prepubertal stress affected production of PSA in multiple areas of the brain, including the amygdala (Calandrea, Márquez, Bisaz, Fantin, & Sandi, 2010). Prenatal stress also affected development of PSA. Studies of the biomarkers of individual differences suggest that individual vulnerability is predicted by corticosterone adaptation to early stress. While all animals react to early stress, some of them adapt and develop less pathological aggression than others (Walker, Papilloud, Huzard, & Sandi, 2016; Walker, Zanoletti, de Suduiraut, & Sandi, 2017; Walker & Sandi, 2018). Currently, studies are under way to look at the brain and behavioral predictors of this adaptation. In terms of reversibility of the effects of peripubertal stress, Dr. Sandi presented data suggesting that a glucocorticoid receptor antagonist (mifepristone) in adulthood reversed pathological aggression induced by peripubertal stress (Papilloud et al., 2018). Focusing specifically on the metabolic syndrome, Dr. Sandi then presented data showing that peripubertal stress in mice alters fat metabolism, as well as food intake and efficiency (unpublished data). Based on the data presented, she suggested that the opportunities for interventions include: PSA neuroplasticity, glucocorticoid changes, and modulating fat metabolism.

Dr. Megan Gunnar started with an overview of several hypotheses regarding mechanisms of the effect of early experience on development of metabolic syndrome. First was the prediction from evolutionary-developmental psychology that harsh early environments will program earlier menarche. Second was a "mismatch hypothesis": poor early nutrition followed by food sufficiency may lead to obesity and a metabolic syndrome. To examine these hypotheses, 283 7-14 year-old children were studied, approximately half adopted from institutions (orphanages) in infancy or early childhood. There was no evidence, using nurse exams of Tanner stage, that the orphanage-adopted children were reaching puberty earlier, and this was also true when timing of menarche was examined in girls. Indeed, if the child was growth stunted at adoption, indicating a clearly harsh set of conditions prior to adoption, there was a suggestion of slightly delayed pubertal onset. Regarding the second hypothesis, there was also no difference between the orphanage-adopted children and those who did not experience harsh conditions

early in life for BMI or body fat percentage, yielding no evidence yet of a trajectory towards obesity. Indeed, the orphanage –adopted children were generally lean. Currently, there are further studies underway looking at adolescence and cardiovascular health. If early life adversity increases the risk of early onset puberty and obesity, it may take the double hit of not only starting out life in harsh conditions, but experiencing harsh, stressful conditions at a later point in development as well. This would be the “double-hit” hypothesis. On the other hand, it is possible that early removal from harsh conditions allows for a “reversal” of their impact.

Indeed, regarding the larger question of reversibility, evidence from orphanage-adoption studies suggest that different outcomes follow different patterns. Cognitive functioning is strongly depressed in deprived, orphanage conditions with later adopted children showing more deficits. However, many aspects of cognitive functioning improve with time in supportive environments, with improvement for the most impaired children continuing into adulthood (Sonuga-Barke et al., 2017). In contrast, for children adopted over 6 months of age, behavioral and emotional difficulties increase into adolescence and young adulthood (Gunnar & Van Dulmen, 2007; Sonuga-Barke et al., 2017). The following questions remain: Is this data suggestive of a sleeper effect? Double-hit hypotheses? Developmental cascades? Or are there specific turning points in development? Deprivation from birth to 6 months generally leads to few long-term effects, while deprivation beyond 6 months is associated with long-term impacts on working memory, sustained attention, cognitive flexibility, and perspective taking. Dr. Gunnar suggested that it was important to think about developmental tasks that characterize different age periods and their effects on emotional development. With regards to HPA axis functioning, prior to adolescence, adopted children showed hypo-response of the HPA axis to stress (Koss, Milner, Donzella, & Gunnar, 2016; McLaughlin, Sheridan, Tibu, Fox, Zeanah, & Nelson, 2015). This was supported by work of Capitano and colleagues (2005), who had showed that random assignment to deprivation of maternal care in monkeys also yielded low cortisol and blunted HPA axis responding. Currently, Dr. Gunnar is working on a hypothesis that puberty may be a neurobiological and psychosocial turning point as it is a period of reorganization/recalibration and it might be a second sensitive period for stress-system organization. The *pubertal recalibration hypothesis* may suggest a possibility of a shift to “normal” if the environment is less harsh, but development can be sensitive to a “double hit” if conditions continue to be harsh or threatening.

Discussion

A discussion led by Drs. Tottenham and Hensch focused on the ways in which the research presented can inform the development of interventions. Dr. Hensch suggested that in order to guide interventions, research has to reach a new level of precision and in-depth understanding of developmental mechanisms. For example, the field needs to define sensitive periods for various biomarkers and associated developmental milestones. There are biological triggers and breaks in development that come on board at different time points, and in the future, they may be targets of interventions. We also need to extend research on sensitive periods, currently mostly conducted in animal models, to infant research, which, though difficult, might be accomplished. For example, studying exposure to anesthesia or SSRIs in utero has provided some evidence on the topic. Participants discussed that the need for precision also included more careful characterization of the nature of exposure to early adversity (e.g., when studying exposure to SSRI, depression symptoms in the mother and other environmental factors have to be studied together). Dr. Hensch also urged researchers to reconsider their existing data in terms of the critical periods hypotheses. Dr. Tottenham brought up the issue of the hierarchical

nature of development and cascading effects of adversity on development and posed a question regarding at what level of this hierarchy we want to intervene. Participants discussed that one of the challenges was that the same mechanisms (e.g., same genes) may play different roles at various stages of development, and without knowing the consequences of their manipulation it might be difficult to implement these in clinical practice. Dr. Stephen Suomi brought up the possibility of differing sensitive periods for children who are genetically more susceptible to environmental influences vs those who are less susceptible (what is known as the “orchids and dandelions hypothesis”). These two types may also differ on sensitivity to interventions. A question was also raised whether more environmentally sensitive individuals have more flexibility in terms of sensitive periods. Participants highlighted that further study of individual differences in critical periods is important, and it is currently the focus of both animal and human studies.

Another direction of research that may provide insights into mechanisms underlying effects of early adversity on development is to focus on resilience. In this vein, Dr. Bruce McEwen spoke about further exploration of the epigenetic response to novel experience. Participants also discussed that psychological resilience does not always correlate with physiologic resilience and they may have different sensitive periods.

Another line of discussion focused on the idea that opening a window of plasticity is not enough to affect a change. Change requires an active learning/training during the reopened window in order for the intervention to work. It is also very important to take into account social environments while we attempt to modulate biology, as well as the interactions of the biologic and psychosocial factors. Social relationships are one of the most powerful modifiers of both subjective well-being and functioning of the nervous system and therefore might be an important and currently feasible class of interventions.

Dr. Seeman brought up the topic of identifying treatment targets for older populations. For example, we may better characterize - in terms of both biomarkers and psychological markers - people who had early adversity vs those who did not, which in turn may help target our interventions. Dr. Hensch proposed that, once the targets are identified, opening a window of plasticity could facilitate this work. Participants discussed that though more research studies have to be done in this area, some of the research presented at this meeting points to the potential utility of using “time travel via childhood stimuli”—that is, re-exposure to the stimuli experienced early in development (e.g., music) later in life potentially has an opportunity to open a window of plasticity that may be a powerful, yet safe, tool.

Session 2: Focusing on one of several intermediate nodes linking early adversity to health outcomes: the metabolic syndrome

[Dr. Natalie Rasgon](#) started this session by focusing on her neurobiologic research on insulin resistance and its association with early life adversity. She mentioned a growing interest in these concepts as evidenced, for example, by a recently established research network focused on studying insulin resistance and psychopathology as related to allostatic load across life span. In her presentation Dr. Rasgon presented data on HPA axis, telomeres, and inflammatory markers in at-risk populations. For example, a history of depression prior to pregnancy was associated with higher rates of gestational diabetes (Robakis, Aasly, Williams, Clark, & Rasgon, 2017). In another recent study of women at risk for postpartum depression, methylation of the

genes involved in regulation of insulin-stimulated signaling and regulation of glucose uptake was associated with the women's attachment style (Robakis, Williams, Crowe, Lin, Gannon, & Rasgon, 2016). In children and adolescents (ages 9-17) with untreated acute mood disorder, lower fasting insulin was associated with reduced negative functional connectivity between the striatum and posterior cingulate, as well as with a shift from negative to positive connectivity between the striatum and the frontal cortex (Singh et al., 2018). If insulin resistance is one of the nodes in the road from early adversity to mood disorders later in life, then treating depression with an insulin-sensitizing agent may be effective. In a study of adults with treatment-resistant depression, augmentation with a peroxisome proliferator-activated receptor gamma (PPARG) agonist, pioglitazone, significantly decreased depression as compared to placebo augmentation, in particular among younger patients (Watson-Lin, Wroolie, Robakis, & Rasgon, 2015). Of note, treatment with pioglitazone was less effective at blunting glucose response and decreasing symptoms of depression in individuals with histories of childhood abuse. In this study, another marker of allostatic load, telomere length, modulated treatment response in that patients with longer telomeres exhibited greater declines in depression severity in the active arm, but not in the placebo arm (Rasgon, Lin, Lin, Epel, & Blackburn, 2016). It still unknown whether telomeres are markers of depression or early adversity. Current thinking is that telomeres are markers of allostatic load and oxidative stress (see [report from recent NIEHS/NIA telomere workshop on telomeres](#) for a recent discussion of these issues). Dr. Rasgon suggested that more research needs to be done on the specific markers of insulin resistance, perhaps with better utility than metabolic syndrome markers.

[Dr. Peter Gianaros](#) presented his work, which focuses on inflammatory markers as they may be potentially related to cognitive aging. There is still an open question whether early adversity causes cognitive decline. In fact, there is not much evidence supporting this causal link, and there are not many studies on the predictive role of metabolic syndrome in premature cognitive aging (Everson-Rose, Mendes de Leon, Bienias, Wilson, & Evans, 2003; Fors, Lennartsson, & Lundberg, 2009; Ritchie et al., 2011; Melrose et al., 2014; Seifan, Schelke, Obeng-Aduasare, & Isaacson, 2015). For example, in the data from Dr. Lisa Barnes, prospective assessment of cognitive decline was not related to adversity (Barnes, Wilson, Everson-Rose, Hayward, Evans, & De Leon, 2012). Some methodologic interpretive issues are important to take into account when considering this research. A survivor effect may result in the most resilient people participating in studies of cognition in aging populations. Therefore, midlife samples may be more appropriate methodologically in order to account for this factor. In addition, very few studies of aging have data on early life cognition. In the studies that did take early cognition into account, no strong links between early adversity and early adulthood cognitive function emerged (Deary et al., 2006; Biessels, Deary, & Ryan, 2008; Danese et al., 2017). At the same time, consistently, the literature suggests that early adversity is related to systemic inflammation in adulthood (Danese & McEwen, 2012; Nusslock & Miller, 2016). There is also reasonably consistent evidence pointing to the association between inflammation in midlife an early cognitive aging (Weaver, Huang, Albert, Harris, Rowe, & Seeman, 2002; Yaffe et al., 2003; Rosano, Marsland, & Gianaros, 2012). Inflammation also seems to account for most components of metabolic syndromes (Marsland, McCaffery, Muldoon, & Manuck, 2010). In cognition research, inflammation is consistently reported to be affecting reasoning, short-term memory, verbal proficiency, verbal learning, and executive functioning. The latter findings are supported by those derived from the Adult Health and Behavior Project in Pittsburgh, a longitudinal study of otherwise healthy community dwelling adults focusing on aging and physical, mental, and cognitive health (Marsland et al., 2006; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008). Cortical volume, particularly in the prefrontal cortex and temporal lobes, accounts for the relationship between inflammation and these cognition markers (Marsland et al., 2015). In fact, models that link adiposity to inflammation to morphology to

cognition fit the data better than models built around metabolic syndrome components. Also, inflammation seems to have an influence on the brain independent of the metabolic syndrome. In a recent study of the neural correlates of systemic inflammation, higher levels of pro-inflammatory cytokine IL-6 were associated with lower default mode network (DMN) connectivity, particularly in the subgenual cingulate (Marsland et al., 2017). DMN is also relevant for Alzheimer's disease and early forms of dementia. Looking at the whole brain, high levels of IL-6 were associated with reduced connectivity in mPFC, medial temporal lobe, and hippocampal networks, even after accounting for multiple covariates. Recent review of the literature also suggests that these findings are consistent across studies and across types of inflammation biomarkers measured (resubmitted manuscript, under review). In terms of reversibility of these effects, interventions focused on mindfulness (e.g., Mindfulness-Based Stress Reduction) reduce IL-6 via changes in DMN, suggesting possibilities for neuroplasticity (Creswell et al., 2016). Dr. Gianaros suggested that for future studies, it was important to take a granular approach to measuring cognition as well as to account for early life cognition. He also proposed that inflammation might be a more useful concept to focus on rather than a more clinical construct of the metabolic syndrome. Dr. Nielsen added that based on the data presented at the recent [Cognitive Aging Summit III](#) on early life and cognitive decline, early life cognition and education seem to be strong predictors of lifelong trajectory. Motivational factors may be at play, and people who pursue education and professional achievement might have greater cognitive reserve and better functioning, which has implications for interventions. She also highlighted that everyday functioning is an important variable in studying cognitive decline in addition to the specific components of cognition.

[Dr. Karen Matthews](#) opened her talk by pointing out that both adolescence and midlife are important for understanding the development of metabolic syndrome. Low SES and child abuse and neglect are related to outcomes at both life stages. However, positive resources or “reserve capacity” have the potential of reversing earlier adversity. Psychological markers of successful transition through adolescence include: meeting the demands of school, fostering a sense of competency, developing a unique identity and sense of autonomy, and forming satisfying and enduring relationships. Attaining these goals can result in the development of a bank of psychological resources (“reserve capacity”) to meet the challenges of early life disadvantage (Matthews & Gallo, 2011). In Dr. Matthews's recent study, positive resources were inversely related to metabolic syndrome markers (adjusting for multiple factors such as age, sex, race, family SES, physical activity, smoking, and BMI percentile). These resources might help adolescents cope with low SES, with consequent health impacts (Midei & Matthews, 2014). In another study of adults, lower childhood SES was related to the prolonged recovery of heart rate and systolic blood pressure post-stress induction task. Prolonged systolic blood pressure recovery, however, was evident only in participants with fewer psychological resources. This association was stronger for people growing up with lower early childhood SES, suggesting a possible sensitive period conceptualization of these findings (Boylan, Jennings, & Matthews, 2016). In yet another study of middle-aged women (Montez, Bromberger, Harlow, Kravitz, & Matthews, 2016), the difference in the incidence of metabolic syndrome between women from the most and least advantaged backgrounds during childhood doubled across 10 years (between ages 50 and 60). And in a different study, positive resources (“resource capacity” and social relationships) protected women from development of metabolic syndrome (Matthews, Raikkonen, Gallo, & Kuller, 2008). Dr. Matthews noted that compensatory mechanisms can, however, be very complex, and we need to conduct more research studies to understand them. For example, in a study by Brody and colleagues, high social competence in high-risk, very low SES African Americans at ages 11 to 13 was related to higher “allostatic load” at age 19, and higher self-control at ages 17 to 20 was related to faster epigenetic aging, suggesting that adaptive advantages in one domain might be accompanied by costs in other domains (Miller,

Yu, Chen, & Brody, 2015). Going back to the importance of social relationships in development, referencing Dr. Danese's presentation, Dr. Matthews highlighted that children who had been rated as isolated during mid-childhood were at highest risk of developing metabolic syndrome on a number of biomarkers. These findings suggest an opportunity for interventions. Dr. Matthews concluded by mentioning a few questions for further research: Would enhancing personal and interpersonal resources reverse some of the effects of early adversity? And if yes, which ones? Do the timing and type of resources vary by sex and by ethnic group? And, would support mechanisms reduce the potential negative health impact of positive attributes among disadvantaged groups?

[Dr. Andrew Fuligni's](#) presentation focused on the importance of sleep in development, research on the association between sleep and inflammation in adolescence, and the implications of this research for potential ways to intervene. He prefaced the talk with the observation that many components of the models that describe the effects of early adversity on lifelong development are associated with sleep; however, it remains a question whether these links are causal or are just epiphenomena. Moreover, many of these links are likely bidirectional. A recent review by Irwin suggested an association of sleep duration and quality with immune markers (e.g., IL-6 and CRP), although methodologic factors in the majority of studies complicate the interpretation of the data (Irwin, Olmstead, & Carroll, 2016). In Dr. Fuligni's data, stronger associations between inflammatory markers and sleep duration and quality were observed in younger ages (Park et al., 2016). Sleep restriction, however, can also predict later immune marker changes. At the same time, it is promising that sleep may be a possible target for interventions. For example, a sleep-focused CBT—as compared to tai chi and to sleep education—significantly decreased CRP over a course of 16 months (Irwin et al., 2014). There are still a lot of unknowns about sleep early in life. In several studies on childhood and adolescence, shorter sleep duration was associated with higher CRP. In Dr. Fuligni's own studies, this association was observed only in younger ages (15 vs 16 or 17), which brought the younger teenagers with poor sleep to “older” levels of CRP (Park et al., 2016). Sleep variability is a separate, important variable that was related to CRP in the teenagers of all ages studied. This research has direct implications for sleep interventions in adolescence, as studies show that teenagers need to sleep and want to sleep, and that sleep and sleep interventions have implications for the levels of inflammation. The challenges in this field of research include: a phase-delay shift, gradual increase in circadian rhythms to beyond 24 hours over the course of maturation, suprachiasmatic nucleus becoming more “permissive” after puberty therefore allowing better tolerance for lack of sleep, the fact that adolescents live in a more chaotic family environment, and family sleep being a family practice. Sleep is an important target for intervention as it has opportunity costs: reduced sleep may lead to missing school, internalizing symptoms, and problems with other developmental tasks. The questions for future research include: Can CBT sleep interventions be used to affect inflammatory processes? Can we target sleep quality, variability, and duration? Is the immune system at puberty and adolescence characterized well enough to study its relationship with sleep? Is there a stability of individual differences in sleep over the life course? And, what is the role of a chronotype? In discussion, participants also mentioned that sleep interventions are very relevant in midlife as well and might be particularly relevant to females, as sleep deprivation is very common in early childrearing years.

Discussion

Dr. Rasgon summarized research presented at this session, highlighting that several transitional time points in the life course might be important windows for interventions - e.g. puberty and menopause. In order to integrate the data presented in this session, the question of relationships between insulin resistance and immune markers was posed. While data suggests that insulin resistance is associated with inflammation, other studies also point to the adiposity, SES, depression, and other conditions as also being associated with inflammation, which makes it difficult to draw cause-effect conclusions and narrow down the underlying mechanisms. It was suggested that large cohort studies may add post hoc analyses to help clarify relationships between variables of interest and provide a more nuanced understanding. For example, it might be possible to study the gender differences in the associations of BMI vs insulin resistance to the inflammatory markers. Overall, insulin resistance is emerging as an important target for interventions as it might be an earlier marker of metabolic problems than BMI.

Dr. Gianaros posed a question regarding what evidence is needed for investigating relationship between early adversity and cognitive decline. Dr. Nielsen mentioned NIA's interest in understanding these issues in more depth, especially within Alzheimer's disease research, including identification of the appropriate measures to be used, leveraging existing cohorts by reanalyzing the data, and bridging cognitive aging studies with studies that contain data on other health markers. There are, unfortunately not many cohorts with repeated multilevel measures – an area that might help future research. A number of methodologic challenges were highlighted by participants. One was that early prospective cohorts that have dense measurements are likely to be small, therefore, making it difficult to address the questions at hand. Another question of importance was differentiating between premature cognitive decline and failure to develop. Cultural factors need to be accounted for in studies of adverse exposures: for example, sleep practices or even what constitutes abuse or neglect may differ quite drastically from one culture to another. Cultural differences also have important implications for measurement of cognition. For example, studies suggest that measurements of cognition may vary in some cultures under varying contextual conditions. In fact, assessing functional cognition may be a better approach than standardized testing in studying some populations.

Participants then discussed the role of the effects of temporary environmental changes in affecting both insulin resistance and cognitive performance, and whether these observations may provide clues into the mechanisms of pathogenesis and inform interventions. For example, changes in diet or brief food deprivation may reverse insulin resistance. Optimizing the microbiome has been also shown to have quite fast effects on cognition, mental health, and other health markers. In a monkey colony, for example, aberrant behaviors among those with a history of early adversity, were reduced or even eliminated by probiotic treatments. It was noted that while microbiome is usually fairly established by the age of 4, it remains malleable afterwards, throughout adult life, presenting multiple good opportunities for interventions.

With regard to sleep interventions, participants discussed whether intervening effectively in later age results in a cascade of positive effects. Sleep is a very complex topic to study as it relates to multiple other biobehavioral markers. For example, is there direct sleep-inflammation link or does sleep affect inflammation through affecting other behaviors? Also, sleep is linked to disruption of circadian rhythms, which affects cortisol rhythms, which is linked to testosterone, all having effects on the brain, and sympathetic system. Therefore, we need more studies to isolate the effects of sleep, including leveraging animal studies, and intervention studies that look at the mechanisms of change.

Overall, there is a growing literature on sleep interventions, and on physical activity studies conducted throughout lifespan (from age 5 to adulthood) that show good effects on cognitive function, as well as health markers (e.g. diabetes), and mental health problems (e.g., schizophrenia, depression). The question however remains, whether there are interventions that target early life adversity. Participants discussed that perhaps going into the data from the large prospective and retrospective studies might help us see if they can inform interventions that would target effects of early adversity. Another issue discussed was the optimal timing for interventions. Is an intervention more effective in a time of stability or when there is a lot of change? In the latter case, midlife may be a good time for interventions, as there are many natural changes occurring in people's lives, and midlife sets the stage for development and health trajectories from age 60 onward. Of course, it remains a question whether midlife is too late to intervene or whether change is still possible? It also remains a question whether special approaches to intervention will be required for people who survived early adversity.

DAY 2

Session 3: Sketching strategies for interventions with adults

[Dr. Kirk Erickson](#) presented the work of his lab that focuses on physical activity interventions to illustrate that the field is moving closer to studying specific interventions that might work for addressing particular cognitive problems, in particular subgroups of people, and at particular time points during development. While much work still needs to be done, some questions already have answers. For example, do we need to apply interventions in childhood to change cognitive and brain function? The evidence demonstrates that this isn't necessary. In fact, the effect sizes of interventions conducted in childhood and adulthood are very similar. Are physical activity interventions more effective among healthy participants? Studies suggest that, no, meaningful improvements happen among both healthy and not healthy participants. At the same time, there are individual differences in the response to interventions. For example, women tend to benefit more from engaging in physical activity in terms of its effects on cognitive improvement (Colcombe & Kramer, 2003). Genetic factors may also be moderators of change. In at least two studies of genetic predisposition to cognitive problems (on APOe4 gene and BDNF Met polymorphism), physical activity decreased the negative effects of genetic predisposition on cognitive deficits (Erickson et al., 2013). Therefore, individuals at greater risk for cognitive changes might benefit more from an intervention. While generally most interventions show only moderate effects, we are starting to learn what interventions work better than others. For example, among interventions for obesity, exercise has more promising effects, compared to cognitive training and nutrition interventions. Exercise interventions may have multilevel benefits. In a recent study, one year of regular exercise resulted in an increase in hippocampal volume, which correlated with serum BDNF, had positive effects on white matter and connectivity, and was associated with improvements in cognition (Erickson et al., 2011; Voss et al., 2010). Preliminary results of a weight loss intervention showed effects on BMI, cognition, and cerebral blood flow, primarily in prefrontal regions. Dr. Erickson highlighted that, ideally, understanding mechanisms of pathogenesis and the individual differences should have a direct impact on the success of our therapeutic strategies. Otherwise, we could be targeting the wrong population with the least effective approaches for the weakest effects at the most inopportune times. A more targeted approach in terms of risk, brain phenotypes of interest, and projected outcomes is necessary to move this field forward. This includes conducting more

studies on early adversity. Even when an intervention is effective, there is a challenge to engage people in the intervention. However, there are creative ways to do it. For example, changing participants' perception of physical activity (e.g., from "physical activity" to "dance") may help engage participants in interventions. Dr. Erickson also outlined future directions of this research, including: standardization of manipulations and measures, targeting multiple populations and age ranges, harmonization of intervention approaches and outcomes, better understanding of the individual differences, studying populations with a gradient of risk, and studying the window-of-opportunity effects.

[Dr. Alison Adcock](#) outlined her research on learning and neuromodulation that targets interventional paradigms in mental health and behavioral change. The overall strategy for learning neuromodulation interventions includes the following steps: engaging physiologic neuromodulation, then tailoring the neural context to what needs to be learned, then putting regulation of plasticity under behavioral control. While there is a lot already known about learning (e.g., the role of dopamine), why people sometimes don't learn remains unknown. We are starting to understand that the physiologic relationship between dopamine and neuroplasticity is complex. In order to explore these questions, Dr. Adcock's research focuses on the neural bases of the motivation to learn. In an fMRI study, reward anticipation was associated with neural activity in the ventral tegmental area (VTA), a region high in dopaminergic cells, and hippocampus, also mapping onto behavioral effects: memory enhancements for upcoming events (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Murty, LaBar, & Adcock, 2016). Experimentally, there are two types of motivation: we can engage motivation by either anticipation of obtaining rewards or avoiding punishments. Reward and punishment seem to generate different states of the brain with regards to memory encoding, which has an impact on later memory for a novel stimulus or experience (Murty, LaBar, Hamilton, & Adcock, 2011). Dr. Adcock's studies suggest that only reward motivation results in enhanced long-term memory for a surprising novel stimulus (Murty et al., 2016). On the neural level, in reward-based learning, VTA to hippocampus connections become activated (Adcock et al., 2006). In contrast, in the case of avoidance-of-punishment motivation, amygdala activation influences encoding, and the contribution of cortical regions predominates in the memory trace (Murty, LaBar, & Adcock, 2012). In addition, we can relate these networks to psychological interrogative and imperative goal states, and putatively to dopamine and norepinephrine (Dickerson & Adcock, 2018). Understanding the neural bases of these types of motivation begs the next question: how can we engage the most optimal motivational state for the new learning required? Dr. Adcock conducted a study to teach people to learn to engage their VTA in learning. While at baseline people could not voluntarily engage VTA motivational system very well, neurofeedback training on VTA activity was successful in teaching people to voluntarily activate the VTA system (MacInnes, Dickerson, Chen, & Adcock, 2016). In this study, patterns of changes in the VTA connectivity also support the idea that learning was possible. Unlike a drug, or electro stimulation, this type of neural circuitry activation has no side effects; it is under behavioral control of an individual. This line of research has enormous potential for enhancing effects of various interventions including exercise and other sustained behaviors that require new learning or habit formation.

[Dr. Michelle Carlson](#) presented her research that suggests that social engagement is an effective way to modulate neurocognitive plasticity throughout life, including among older adults. A low-intensity (non-cardiovascular) physical activity may improve neurocognitive plasticity in aging adults. Neuroplasticity occurs throughout the life course, and it is feasible in late life. For example, it has been demonstrated that daily steps activity logs correlated with changes in hippocampal volume – a brain structure important for spatial and verbal memory, suggesting that lifestyle engagement may be important. Social enrichment is yet another mechanism with

positive effects on health as well as motivation, and those at greatest sociodemographic risk would benefit most from social enrichment programs. To investigate this, Dr. Carlson & colleagues conducted a study that involved both physical activity with social engagement among older adults. In the Experience Corps program, men and women age 60 and above were placed in elementary schools to volunteer in multiple roles. Each of these roles involved exercising executive function and memory, and had features that enabled these older adults to remain relevant, engaged, and active. This program improved executive function (Carlson et al., 2008) and related prefrontal networks functioning as measured in fMRI (Carlson et al., 2009). A larger scale 2-year program suggested that more exposure was even more beneficial. Moreover, women showed increases in physical activity even outside of the program (Varma et al., 2015). Men in particular showed duration-dependent increases in hippocampal volume, and there was a direct correspondence of this measure with memory performance (Carlson et al., 2015). The social engagement aspect of the program was associated with increase in surface area of the left amygdala, especially in women (Carlson et al., 2018). Children showed improvements in academic performance (Rebok et al., 2004). Dr. Carlson also presented approaches to studying mobility and how people navigate in their communities. Data from a pilot study suggest that activity in social spaces was most strongly associated with cognitive health in older adults. In yet another approach to look at the effects of early adversity, Dr. Carlson used geocoding of the residential locations of all participants (Adam, Varma, Harris, & Carlson, in press). While there was a lot of heterogeneity in socio-demographic neighborhood level risk, looking at the baseline cognitive performance, it became evident that participants with cognitive impairment were more concentrated in the most impoverished areas. These studies can be further extended to looking at early life adversity by utilizing census data. In yet another related line of research, using anthropometric measures (knee height, arm span, and maximal height) to characterize what person's early life might have been like, characteristics associated with deprivation of nutrition in early life were also associated with risk for dementia (Huang et al., 2008). At the same time, reported early life enrichment (engaging in activities such as learning a foreign language, volunteering at church, taking dance or singing lessons, playing a musical instrument, scouting, playing team sports, or going on vacation) was positively correlated with performance on cognitive measures among older adults (Chan, Parisi, Moored, & Carlson, 2018).

[Dr. Christina Hugenschmidt's](#) research is focused on the fact that brain plasticity is retained in aging, even in the presence of neurodegenerative disease, and can be harnessed to develop interventions. It has been suggested that aerobic exercise may promote a more neuroplastic physiological environment (Petzinger et al., 2013). If that is the case, there is a potential to overlay other interventions (e.g., CBT) onto an aerobic exercise program. In a study of obese older adults, an aerobic exercise intervention paired with a weight loss program was associated with improvement in physical function and improved connectivity of somatosensory regions in the brain, suggesting that neuroplasticity is possible in older adults at metabolic risk (even though cognitive change outcomes were not observed). Pilot data were presented from an improvisational dance intervention originally developed for people with Parkinson's disease, and adapted for older adults with cognitive impairment. Of note, this movement intervention includes family members, therefore involving two potential mechanisms: movement/physical activity and social engagement. In a case study of a patient with Parkinson's disease, improvements in movement in response to the dance intervention correlated with strengthening of basal ganglia-to-motor cortex connection. Data comparing older adults with mild cognitive impairment or early-stage dementia who completed the dance intervention with those who did not showed

modest improvements in balance among people with early-stage dementia and changes in functional connectivity in somatosensory cortex. Participants with cognitive impairment in the dance intervention also showed decreased depression and apathy scores that were associated with increased default mode network connectivity. These pilot data demonstrate that the aging brain retains plasticity even in the presence of neurodegenerative diseases. In addition, caregivers of people with dementia are also at great risk for health problems (Alzheimer's Association, 2013; Roepke et al., 2012; Gaugler, Yu, Krichbaum, & Wyman, 2009; Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012; Chattillion et al., 2012; Mausbach et al., 2012; von Känel, Mausbach, et al., 2012; von Känel, Mills, et al., 2012; Christakis & Allison, 2006), and both caregivers and people with dementia show elevated levels of cortisol (De Vugt et al., 2005; Wahbeh, Kishiyama, Zajdel, & Oken, 2008). While some work has been done testing whether supportive interventions can decrease stress and cortisol levels in caregivers (Danucalov et al., 2013), virtually no work has been done to test whether cortisol levels in people with dementia can be decreased. Dr. Hugenschmidt showed data from a separate pilot examining whether participating in a support group decreased self-reported stress and cortisol levels in caregivers and people with dementia. Both caregivers and patients with dementia decreased overnight cortisol levels after the support group intervention. Overnight cortisol was also associated with shorter telomeres among caregivers of people with cognitive impairment, which was in turn associated with allostatic load. Finally, Dr. Hugenschmidt mentioned work from the Wake Forest Memory Counseling Program where therapists see people with dementia and their caregivers. The therapists have noted that stress and early life adversity may be important in managing behavioral symptoms and caregiver stress in dementia patients. In particular, as patients lose cognitive control and compensatory mechanisms due to dementia, symptoms like re-experiencing may begin to occur again. These therapists have been finding ways to use therapies such as Eye Movement Desensitization and Reprocessing (EMDR) to address early-life adversity in dementia patients and caregivers.

Discussion

In discussion, participants focused on the finding that the effects sizes of physical activity interventions across ages were the same and discussed whether it was known if behavior change was more lasting if interventions are conducted earlier in life. Research suggests that while that is likely the case, it is never too late to start increasing physical activity in order to have positive effects on health. The most optimal times for interventions have not yet been identified. More research on timing of the interventions and sustained behavior change needs to be done. For example, studies are currently underway to investigate effects of Mindfulness Based Stress Reductions interventions (MBSR) in middle schools with a planned long-term follow-up.

Participants discussed the potential mechanisms for sustaining a behavior change. One such mechanism might be the intervention getting incorporated in a self-concept of a person. For example, studies show that one of the best predictors of maintaining activity levels is change in self-efficacy. The NIH Science of Behavior Change Program <https://scienceofbehaviorchange.org/> aims at precision targeting of psychological, behavioral, and interpersonal mechanisms to promote effective and sustained behavior change.

Motivational factors represent other potential intervention targets, and it would be important to identify motivational factors specific to midlife. Social engagement and responsibility seem to be two likely candidates. Overall, it might be helpful to design interventions tailored to the

developmental tasks of a particular life period. It would also be important to take into account that different types of early adversity may influence the development of different motivational systems. For example, there is evidence in the deprivation literature that the reward system of affected individuals is impaired, and therefore, it may be more difficult to engage this system in the deprivation-affected individuals.

The idea of a need for inducing increased plasticity in order to affect change and reverse effects of adversity, led to discussion of the timing of the combined interventions. For example, an exercise program may precede a cognitive training.

Reopening critical periods may, however, have its own costs. Dr. Hench presented some additional data on the potential dangers of reopening windows of plasticity. Recently, a specific mechanism for closing a critical period was discovered. A Lynx1 molecule seems to function to close critical periods, putting brakes on the open plasticity period. In mice, a pharmacologic manipulation of changing a cholinergic supply (e.g. with medication Aricept) supported this mechanism. Cholinergic plasticity was also induced by exercise in a mouse model. Currently, clinical trials are underway with Aricept and SSRIs that target reopening of the window of plasticity. In other studies, perceptually rich videogames are being used to reopen windows of plasticity with regards to perceptual learning. However, opening a window of plasticity can be a double-edged sword. Extending the window of neuroplasticity also led to oxidative stress and a neurodegeneration phenotype in mice. Another line of evidence suggests that perineuronal nets protect against oxidative stress. Destroying them in order to open a window of plasticity may cause mitochondrial DNA damage. In fact, animal models of schizophrenia include oxidative stress in perineuronal net complex. This has been confirmed in postmortem studies of patients with schizophrenia. There may be dangerous consequences in reopening critical periods.

Critical period closure may be neuroprotective. In cognitive aging research, it has been suggested that “lifting the brakes” may make people more susceptible to Alzheimer’s disease. (Omega 3 diet may preserve perineuronal nets by decreasing oxidative stress – suggesting that nutrition may be a good way to regulate plasticity.)

Session 4. Social/Contextual Forces at Play in Childhood and Throughout the Life-Course

In his talk, [Dr. Craig McEwen](#) proposed a necessary conceptual step back in our thinking on this topic: in order to study which mid-life intervention would be effective in ameliorating the effects of early life adversity, we first and foremost need to define very carefully and thoughtfully what do we mean by the term “childhood adversity,” and, consequently, what are the best ways to measure it. He called for the precision in our terminology and suggested that it has an enormous effect on the research we conduct. Dr. McEwen reviewed the original ACEs study by Felitti and Anda which defined 10 types of early adversities. Since the study was conducted, this classification has been widely used in research and in shaping policy, interventions, and clinicians’ education across the US. While the study raised the issue of importance of early adversity, its approach to what constitutes early adversity had severe limitations: in particular, its failure to acknowledge the importance of social context in families and households, as well as the adversities stemming from racial and economic inequalities. Taking the data of a recent National Survey of Children’s Health conducted by the Census Bureau in 2011-12, Dr. McEwen demonstrated how utilizing different dimensions of adversity changes the findings on its effects on health and wellbeing. Another important question in defining early adversity is whether we consider “adversity” the exposure itself regardless of person’s perception of it, or does “adversity” imply a subjective response to that exposure (e.g., stress, anger, disappointment).

Yet another dimension to consider is how an adversity is being transduced (e.g., does financial hardship affect an infant through the anxiety of a parent?). From this perspective, is poverty an adversity or a predictor of other adversities? Adversity is multidimensional and its effects are often indirect and cascading. Therefore, our measures of early adversity have to be multidimensional. Dr. McEwen suggested a wider list of early adversities which included such dimensions as individual experience, social context, parenting and community structures. He then also emphasized the importance of the protective factors that buffer the biological effects of early adversity, and their appropriate measurement. Understanding protective factors may help us build interventions. Therefore, understanding the interactions of adversity with protective factors may make a difference not only in the short, but also in the long run. In sum, we need much greater specificity of definitions of early life adversity in order to understand their mechanisms and potential for reversibility (please see [report from Workshop II](#)).

Workshop Discussion

The workshop discussion started by taking a wider angle look at the field. Participants posed the following questions: Should we perhaps be looking at psychological processes or behavioral domains as a targets for intervention, as opposed to diagnostic categories? Would it be helpful to conceptualize this research from the perspective of normal development and articulate what can go wrong in cases of early adversity? To what extent are early adversities transmitted through generations? Does exposure to adversity or the individual's perception of that exposure matter more for development, and would the answer to this question affect our interventions? Can we build on the interactive nature of development, in that by intervening at parental level we may affect development of a child?

Summarizing multiple discussions of neuroplasticity during the meeting, several participants highlighted that opening the window of plasticity is not enough for change – it needs to be coupled with exposure to supportive environments and interventions. Opening a window of plasticity may be accomplished in multiple ways (e.g., pharmacologically, or behaviorally, e.g., with exercise, or by targeting natural windows of plasticity for example by intervening with teenage mothers or with adolescents; Brody et al., 2017).

Studying resilience may also help us better understand the effects of early life adversity. Children who are exposed to the same environments often do not suffer the same health and behavioral effects, owing not only to genetic predispositions but also to epigenetic effects of experiences in utero and postnatally. However, it is important to remember that compensation later in development is not the same as recapitulating development since we cannot “roll back the clock”. On an evolutionary level, redirection of neural development in response to early adversity may also be part of preparation for later adversity and challenges which may or may not occur, e.g., the effects of the Dutch Winter Famine on later obesity in a food-rich environment as opposed to a food-poor one. This also needs to be taken into account in intervention studies.

Several questions remain, that were only beginning to be explored at the meeting: Would individuals with early adversity benefit from same interventions as those not exposed to adversity, but simply need a stronger “dose”? Or do they require an intervention coupled with an opening of neural or behavioral plasticity? Or do they require additional interventions (such as those developed for working on comorbidity issues)? We also need more studies on how early

life adversity differs from other adversities throughout life, and on whether we need special interventions for affected individuals, as well as on whether response to intervention depends on early adversity.

In addition to conducting further research in this field, researchers need to better communicate these ideas of public health relevance to the public. Explanation of the neurobiology of mechanisms underlying the effects of adversity on health, perhaps using good metaphors may be helpful. As we are gaining more specific knowledge, some ideas are ready for public health awareness, for example: “No matter what has happened to you in your life, or what your current circumstances are, there are things you can do to turn your life in a new direction. Science is beginning to reveal what is possible and to understand how to help you more easily do those things. The brain is a pivotal organ that will help you achieve that.”

Participants offered the following ideas for future directions. Some of the approaches suggested for human studies included: 1) studying people with metabolic syndrome with and without early adversity in order to investigate whether there are additive effects; 2) distinguishing more carefully between reported retrospective early life adversity vs prospective assessments of early life adversity; 3) in the studies that were already conducted, looking for other indicators for retrospective measures of adversity; 4) better definition of phenotypes; and 5) investigation of what are best periods in a person’s life to intervene.

Crossing subfields of research may be needed to answer many of the questions of interest: for example, can the microbiome be changed with exercise? Furthermore, it would be helpful to better understand the effects of early life adversity on the prediction of the course of illness and pathophysiology, in order to stratify risk, and understand trajectory of pathophysiology if adversity adds risk. At the same time, we need to study interaction of early life adversity and protective factors.

Basic science research is revealing the importance of mitochondria for maintaining efficient metabolism and controlling production of free radicals both in brain and systemically. It is also illuminating the limits and possibilities of opening windows of plasticity. We need further studies on epigenetic modifications, energy metabolism, and free radicals; their relationship with stress; suppression of neurogenesis; and the protective effects of mitochondrial function. The effects of repeated impact of trauma need to be investigated further, as well as the effects of repeated reopening of critical periods.

At the same time, more needs to be done to understand mechanisms of critical periods in humans; and to accomplish that, looking for signatures that are shared in animals and humans may be helpful. For example, we need to develop methods to measure peri-cellular nets—the macromolecular structures around cell bodies—in a noninvasive way, and to first study their normal development.

Methodologically, what kind of studies can bring us to a better understanding of whether there is a unique brain signature for early life adversity? Translational research approaches will be helpful (for example, pairing large-scale studies with animal models). Smaller-scale studies that can characterize phenotypes on a deep level are also needed, including studies that can take into account the complexity of constant re-updating of the meaning of early trauma during life. To accomplish all this, we need to study risk factors on both individual and population levels, as well as across levels of analysis.

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APPENDIX A. AGENDA

DAY 1	April 19
8:00 - 8:30 AM	Breakfast
8:30 - 8:45 AM	Welcome and Introductions <i>Nim Tottenham - Chair</i> <i>Bruce McEwen, Steve Suomi, Lis Nielsen, David Reiss</i>
8:45 - 9:15 AM	Recap of Prior Reversibility Network Meetings <i>David Reiss, Andrea Danese, Teresa Seeman, Chris Power, Keith Godfrey</i>
9:15 - 10:30 AM	<p>Session 1: Research strategies for clarifying the role of critical or sensitive periods in the apparent selective impact of severe adversity in childhood and adolescence rather than later in development Co-chairs: Nim Tottenham, Takao Hensch</p> <p><u>Major questions.</u> We know that a broad range of early childhood adversity is associated with a range of adverse physical health outcomes, including the metabolic syndrome (MetS). We presume that underlying such an association are special features of the nervous system in children: these features make them either especially vulnerable to adverse circumstances or, alternately, adverse circumstances fail to permit a child to acquire certain skills or adaptive capacities including self-regulation, trust in others, cognitive growth. Can our understanding of neurodevelopment and the mechanisms that “open” and “close” critical periods for the acquisition of adaptive capacities contribute to our understanding of the apparent vulnerability of young children? In what ways might mechanistic research on these early vulnerabilities enhance our appraisal of the causal role of some early adversities on later diminished health, the components of Mets in particular? Might this work help isolate specific dimensions of adversity—such as relational /cognitive deprivation or interpersonal threat and danger—they play a pre-eminent role in establishing liability? Might work in this area provide clues for intervention in childhood and, more pertinent, in adulthood? Are there important “counterfactuals” to be weighted in these analyses (e.g., the apparent long term, delayed effects of <i>adult</i> trauma on health outcomes)?</p> <p>9:15 - 9:30 AM General Findings in Humans (Possible Accelerated Development of PFC Following ELS, Childhood Music Use in Adulthood) Nim Tottenham</p> <p>9:30 - 9:45 AM ELS Data Effects on PFC (Sex Specificity) - Use of Juvenile Music as Possible Reversibility - GABA Mechanisms Takao Hensch</p> <p>9:45 - 10:00 AM</p>

	<p>Developmental Processes Underlying ELS Effects - PSA ncam/Myelination - P29-P30 Exposure and Body Fat Effects Carmen Sandi</p> <p>10:00 - 10:15 AM ELS in Humans - PFC Effects, Metabolic Phenotypes/Puberty/Recalibration - Potential Need for "Double It" for Effects? Megan Gunnar</p> <p>10:15 - 10:30 AM Discussion</p>
10:30 - 10:45 AM	Break
10:45 AM - 12:15 PM	Session 1 Discussion – Nim Tottenham & Takao Hensch , moderators
12:15 - 1:15 PM	Lunch
1:15 - 2:30 PM	<p>Session 2: Focusing on one of several intermediate nodes linking early adversity to health outcomes: the metabolic syndrome Co-chairs: Pete Gianaros, Natalie Rasgon</p> <p><u>Major questions:</u> What might be the prenatal and postnatal origins of MetS, particularly insulin resistance, dyslipidemia and obesity? What role do adverse environmental factors play in these developments and how early in development do these appear? Do we understand what role genetic factors play as confounds, main effects or moderators on these pathways? What are other major factors that moderate risks? As the mechanism accelerating development towards MetS unfold, are there consequences for cognitive development? How central is MetS as an intermediate node between adversity and a range of health outcomes? Altered immune function and alteration in the microbiome as well as structural and functional changes in the brain are underscored in recent literature as potential and related mediators; are their research strategies for integrating these findings with the role of Mets? What are the mechanistic links between MetS and its major consequence for adult health including rapid cognitive aging and how do we understand the malleability of such links. In what ways do these processes linking MetS to health outcomes constrain neuroplasticity at mid-life and beyond? In what ways, if any, does a history of severe adversity in early childhood moderate these links?</p> <p>1:15 - 1:30 PM From ELA to IR: Unwinding the Long Road Natalie Rasgon</p> <p>1:30 - 1:45 PM Adversity and brain aging: a focus on inflammatory pathways Pete Gianaros</p>

	<p>1:45 - 2:00 PM Role of positive resources in the development of metabolic syndrome <i>Karen Matthews</i></p> <p>2:00 - 2:15 PM Adolescence, inflammation, & sleep: Opportunity for reversibility? <i>Andrew Fuligni</i></p> <p>2:15 - 2:30 PM Discussion</p>
2:30 - 2:45 PM	Break
2:45 - 4:15 PM	Session 2 Discussion – <i>Pete Gianaros & Natalie Rasgon</i> , moderators
4:15 - 4:30 PM	Day 1 Wrap-up

DAY 2	April 20
8:00 - 8:30 AM	Breakfast
8:30 - 9:45 AM	<p>Session 3: Sketching strategies for interventions with adults <i>Chair: Kirk Erickson</i></p> <p><u>Major questions:</u> What are the major obstacles to successful intervention in aging individuals and does a history of severe child adversity (either prospectively or retrospectively ascertained) provide additional obstacles? To repeat a question from session one proposed here: does our increased understanding of the mechanisms underlying critical periods provide clues to intervention? “Plasticity” and “motivation for change” appear to be important rubrics informing the selection of targets and intervention strategies for older individuals. From the perspective of “plasticity” who is likely to benefit more from intervention in mid- and late life: those on a rapidly declining trajectory or those whose decline is more gradual decline? Is there an age window for the most effective intervention in adults or perhaps such a window can be defined by “biopsychosocial” transitions such as a first pregnancy or major changes in social role such as retirement? Conceptually and technically, can we separate preparatory strategies (for example exercise) that may enhance “plasticity” from strategies that target specific mechanisms of health liability (particularly those linked to adversity decades before in childhood)? From the perspective of “motivation,” are there--by analogy to plasticity--general strategies for enhancing motivation for older people to engage in more specific interventions? Again, are these separable (and do they enhance) more targeted interventions? Returning more specifically to MetS, what do we need to know to decide whether those with MetS and a history of early abuse are different from those without? In other words, would we design interventions to forestall the consequences of MetS differently for those with a history of early adversity in comparison to those without? What research would clarify decisions of this kind? And before we</p>

conclude this complex session, are there low-lying fruit for intervention research in this domain that commend our immediate attention (e.g., probiotic trials)?

Themes:

- Life course effects of interventions
 - Efficacy of interventions in children, versus young adult, versus midlife, versus older adults
 - Window-of-opportunity effects at certain age ranges when the long-term effects of an intervention might be optimized?
 - Could we extend or re-open the window-of-opportunity by the right type of intervention? What magnitude of effects could be found?
 - Linking early-life to late-life interventions – for example, weight loss interventions in mid-life and their impact on prevention of dementia
- Gradients of risk
 - Those at greater risk (based on age, SES, gender, etc.) might benefit more (or less) from an intervention.
 - These variables create heterogeneity in the response to an intervention
 - Does it depend on the type of intervention and the outcome?
- Moderators
 - The issues described above – life course, windows-of-opportunities, and gradients-of-risk can all be considered as potential moderators of a particular intervention.
 - Challenges with studying moderators in intervention studies – logistical issues

8:30 - 8:42 AM

Interventions: For Whom, What, and When?

Kirk Erickson

8:42 - 8:54 AM

Learning and Neuromodulation in Interventional Paradigms for Mental Health

Alison Adcock

8:54 - 9:06 AM

Social Engagement (over the Life course) and Neurocognitive Plasticity

Michelle Carlson

9:06 - 9:18 AM

Movement and Social Engagement in Dementia

Christina Hugenschmidt

9:18 - 9:30 AM

Discussion

9:45 - 10:00 AM	Break
10:00 - 11:30 AM	Session 3 Discussion – <i>Kirk Erickson</i> , moderator
11:30 AM - 1:00 PM	Lunch
1:00 - 1:15 PM	Social/Contextual Forces at Play in Childhood and Throughout the Life-Course <i>Craig McEwen</i>
1:00 - 4:00 PM	Workshop Discussion – <i>Nim Tottenham</i> , moderator <u>Major Questions:</u>

APPENDIX B. BIOSKETCHES

Reversibility Network – Neuroplasticity Workgroup

Participant Biosketches

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R. ALISON ADCOCK

Duke University

I am an Associate Professor of Psychiatry and Behavioral Sciences, Neurobiology, and Psychology and Neuroscience, and the Associate Director of Center for Cognitive Neuroscience at Duke. Our laboratory has been continuously funded by NIDA, NIMH, and NSF, as well as Alfred P. Sloan and Klingenstein Fellowships in the Neurosciences, and the Brain & Behavior Research Foundation. Our work has been honored by NARSAD awards, the 2012 National Academy of Sciences Seymour Benzer Lectureship, the 2015 ABAI BF Skinner Lectureship, and 2016 Duke Health Scholars award. The overall goals of my research program are to understand how brain systems for motivation support learning. We hope to use mechanistic understanding of how behavior changes biology to design and enhance interventions, particularly to meet the challenge of new therapies for early interventions in mental health.

The Adcock laboratory has three main lines of work. Our foundational research demonstrated that interrogative and imperative motivational states engage distinct neuromodulatory transmitter systems to accomplish adaptive memory formation in the medial temporal lobe. Our basic human neuroscience is currently focused on biological mechanisms of intrinsic motivation to learn. Recent translational work has used our understanding of motivated neuromodulation and learning (the I/I model) to develop real-time functional MRI neurofeedback methods for training human participants to sustain activation of dopamine-containing regions of the midbrain; this application is currently being tested in populations with ADHD, depression, and nicotine dependence.

Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JDE. "Reward-motivated learning: Mesolimbic activation precedes memory formation." *Neuron* 50,3 (May 04 2006): 507-17. [pdf](#)

Shohamy D, **Adcock RA**. "Dopamine and adaptive memory." *Trends in Cognitive Sciences* 14,10 (October 10 2010): 464-472. [pdf](#)

Murty VP, LaBar KS, **Adcock RA**. "Distinct medial temporal networks encode surprise during motivation by reward versus punishment." *Neurobiology of Learn & Memory* (February 05, 2016) [pdf](#)

MacInnes JJ*, Dickerson, K*, Chen NK., **Adcock RA**. "Cognitive Neurostimulation: Learning to Voluntarily Sustain Ventral Tegmental Area Activation." *Neuron* 89, 6. (March 16, 2016): 1331-42. [pdf](#)

MICHELLE C. CARLSON

Johns Hopkins University

Dr. Carlson is an Associate Professor in the Department of Mental Health at the Johns Hopkins Bloomberg School of Public Health (SPH) in Baltimore, MD, core faculty member in the Center on Aging and Health at the Johns Hopkins Medical Institutions, and holds joint appointments in the Johns Hopkins SPH Department of Epidemiology and the School of Nursing. Dr. Carlson has published 120 papers to develop tools and examine factors related to cognitive risk and resilience for their downstream impacts on risk for functional difficulty and Alzheimer's disease. She has been continuously funded by NIA, NHLBI, NCCAM, the Alzheimer's Drug Discovery Foundation, AARP and other foundations to examine environmental and pharmacologic risk modifiers of cognitive aging and dementia. Dr. Carlson leads

these investigations using both observational studies, such as the Women's Health and Aging Study II (WHAS II) and the Cardiovascular Health Study (CHS), and intervention trials. She currently serves as the Johns Hopkins site principal investigator (PI) of the CHS study, now entering its 29th year. Dr. Carlson has over 14 years of experience leading large-scale randomized trials having served as Johns Hopkins site PI of the Ginkgo Evaluation of Memory (GEMS) randomized, controlled trial. Dr. Carlson has co-designed and evaluated the Baltimore Experience Corps program since its inception in 1998 and initial pilot trial in 1999-2001. The Experience Corps program trained and placed teams of seniors to support teachers in mentoring and tutoring children in elementary schools. Dr. Carlson served as project co-leader on the P01-funded Baltimore Experience Corps Trial (BECT) initiated in 2006 to evaluate the impact of on older adults' cognitive, and functional health. She incorporated a nested Brain Health Substudy (BHS) to evaluate the mechanisms through which the Experience Corps (EC) Program impacted older adults' cognitive and physical health using neuroimaging, objective step activity, and salivary cortisol. Dr. Carlson has expanded on the success of evaluating social engagement through mobile technology to determine how socially and cognitively enriching activity in daily life helps to promote neuroplasticity, delay dementias of aging and help individuals age in place, particularly in underserved populations at elevated risk for health disparities. Dr. Carlson recently served on the AARP/Age UK Global Brain Health Initiative's (GBHI) expert panel to develop a report on the state of the science on the role of social engagement in delaying age-related neurocognitive decline and risk for Alzheimer's disease.

[Carlson, M.C., Kuo, J.H., Chuang, Y., Varma, V.R., Harris, G., Albert, M.S., Erickson, K.I., Kramer, A.F., Parisi, J.M., Xue, Q.L., Tan, E.J., Tanner, E.K., Gross, A.L., Seeman, T.E., Gruenewald, T.L., McGill, S., Rebok, G.W., & Fried, L.P. \(2015\). Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes. *Alzheimers Dement*, 11\(11\), 1340-8.](#)

[Varma, V.R., Tang, X., & Carlson, M. \(2016\). Hippocampal sub-regional shape and physical activity in older adults. *Hippocampus*, 26\(8\), 1051-60.](#)

ANDREA DANESE

King's College London

Dr Andrea Danese is Senior Lecturer in Developmental Psychobiology and Psychiatry at the MRC Social, Genetic and Developmental Psychiatry (SGPD) Research Centre and the Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London. He is also Consultant Child & Adolescent Psychiatrist at the National and Specialist CAMHS Trauma and Anxiety Disorders Clinic, South London & Maudsley NHS Foundation Trust, a Tier 4 service for children and young people for complex and treatment-resistant forms of Post-Traumatic Stress Disorder and Anxiety Disorders generally emerging after childhood violence victimisation. He leads the Stress & Development Laboratory, a team of clinical and non-clinical researchers interested in understanding and preventing the harmful effects of traumatic stress and violence victimisation in children and young people.

Dr Danese is co-investigator of the Environmental Risk (E-Risk) Longitudinal Twin Study, which will provide the data for the proposed research. He is also co-investigator of the Dunedin Multidisciplinary

Health and Development Study. His research on traumatic stress and violence victimisation in children has been funded by grants and fellowships from the Wellcome Trust, the U.K. Medical Research Council, the U.K. Department of Health, the U.S. Brain and Behaviour Research Foundation / NARSAD, and the U.S. National Institutes of Health. His team's research has been published in all top-tier journals in psychiatry, psychology, neuroscience, and child health including the Proceedings of the National Academy of Sciences U.S.A., JAMA Psychiatry, the American Journal of Psychiatry, the Lancet Psychiatry, Molecular Psychiatry, the Annual Review of Psychology, Neuropsychopharmacology, the Journal of Child Psychology and Psychiatry, and JAMA Pediatrics. He has also contributed to key textbooks including the Child Maltreatment chapter in the Rutter's Textbook of Child & Adolescent Psychiatry.

For his work, Dr Danese received several awards listed below. He sits on the U.K. Department of Health (DH) and National Institute for Health Research (NIHR) Steering Committee for a Strategy for Mental Health in Children & Young People, the MQ Advisory Committee on Adolescent Mental Health, the U.S. NICHD / NIA Network on Reversibility of Childhood Adversity, and the Penn State University Center for Multidisciplinary Research in Child Abuse and Neglect. He has been as invited speaker on topics related to traumatic stress and violence victimisation in children at several international conferences and universities.

[Reuben, A.R., Moffitt, T., Caspi, A., Belsky, D., Harrington, H., Schroeder, F., Hogan, S., Ramrakha, S., Poulton, R., Danese, A. \(2016\). Lest we forget: Comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *The Journal of Child Psychology and Psychiatry*, 57\(10\), 1103-1112.](#)

[Danese, A. & Baldwin, J.R. \(2017\). Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. *Annu Rev Psychol*, 68, 517-44.](#)

KIRK I. ERICKSON

University of Pittsburgh

I am an Associate Professor in the Department of Psychology and a Faculty Member for the Center for the Neural Basis of Cognition and Center for Neuroscience at the University of Pittsburgh. I have been intimately involved in, and helped to execute, several randomized interventions of physical activity. I have published >140 articles on cognitive and brain changes which occur as a function of physical health and aging as well as in the development of training and physical activity and exercise trials. The main message from these studies is that cognitive function, brain morphology, and brain function remain modifiable throughout the lifespan and that physical activity training can take advantage of brain plasticity. This idea has spawned several grants including a multi-site Phase III randomized clinical trial (PI: Erickson; R01AG053952) a multi-site study that added brain imaging to the Look AHEAD diabetes intervention trial (PI: Espeland; R01-DK092237) and several other R01's to study the effects of weight loss and physical activity on brain and cognitive health during midlife (PI: Erickson; R01-DK095172) and for breast cancer patients (PI: Bender/Erickson; R01CA196762). I currently run a laboratory of about 30 students and staff to investigate these questions. I take a very hands-on approach to mentoring and have served on 12 Master's degree committees, 17 comprehensive exam committees, and 22 dissertation committees. I've also mentored 8 post-docs in several capacities including supervising T32

and K awardees. My research is highly mechanistic and I have examined multiple mediators for the effects of exercise on brain and cognitive outcomes.

[Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., & Kramer, A.F. \(2011\). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A.*, 108\(7\), 3017-22.](#)

[Prakash, R.S., Voss, M.W., Erickson, K.I., & Kramer, A.F. \(2015\). Physical activity and cognitive vitality. *Annu Rev Psychol*, 66, 769-97.](#)

TERRENCE FORRESTER

The University of the West Indies

More than 25 years of experience in the conduct of whole body metabolic and physiological studies exploring both intermediary metabolism on the one hand and cardiovascular risk on the other provide tools the interaction of cardio-metabolic risk and neurological/neuropsychological status. Understanding mechanisms in order to define new interventions to improve cardiovascular risk is a primary research goal. Specific research activities I have engaged in that are relevant to this Network include, i). description of the epidemiology of overweight and cardiovascular risk in populations of the African Diaspora, ii). exploration of the components of energy balance and their contribution to body composition in these populations (ongoing NIH Funded project), iii). using developmental biology frameworks (early life origins of disease) to define cardiovascular risk, iv). including in adult survivors of childhood malnutrition by exploring the defects in protein and amino acid metabolism in severe malnutrition to first, inform therapy and second, identify mechanistic underpinnings of the increased cardiometabolic risk that is associated with childhood malnutrition. v). We are completing our NIH RO1 examining mechanisms of exercise in the context of ischaemic stroke to reduce cardiovascular risk through muscle structure and metabolism and reduction in insulin resistance. Many of the exercise based techniques to improve cardio metabolic risk modulate neuro plasticity and in principle have a role to play in reversibility.

[Forrester, T.E., Badaloo, A.V., Boyne, M.S., Osmond, C., Thompson, D., Green, C., Taylor-Bryan, C., Barnett, A., Soares-Wynter, S., Hanson, M.A., Beedle, A.S., & Gluckman, P.D. \(2012\). Prenatal factors contribute to the emergence of kwashiorkor or marasmus in severe undernutrition: evidence for the predictive adaptation model. *PLoS One*, 7\(4\), e35907.](#)

[Sheppard, A., Ngo, S., Li, X., Boyne, M., Thompson, D., Pleasants, A., Gluckman, P., & Forrester T. \(2017\). Molecular Evidence for Differential Long-term Outcomes of Early Life Severe Acute Malnutrition. *EBioMedicine*, pii: S2352-3964\(17\), 30088-9.](#)

ANDREW J. FULIGNI

University of California, Los Angeles

I employ multiple methods to study the interaction between sociocultural experience and biobehavioral development during adolescence and young adulthood, with particular attention to teenagers from Latin American, Asian, European, and immigrant backgrounds. In several studies, I have examined how stress and daily experience shape family relationships, peer relationships, educational adjustment, psychological well-being, and health. This work has been funded by NICHD, a Faculty Scholars Award from the William T. Grant Foundation, the Mac Arthur Foundation, the Russell Sage Foundation, and the Haynes Foundation. I have worked with biobehavioral scientists in order to examine the health implications of daily experience in adolescents' lives. I also have collaborated extensively with neuroscientists to examine the linkages between social experiences and neural development during the adolescent years. Most of my work follows an explicitly transdisciplinary approach, involving collaborations with multiple scholars in order to better understand adolescent development.

[Chiang, J.J., Tsai, K.M., Park, H., Bower, J.E., Almeida, D.M., Dahl, R.E., Irwin, M.R., Seeman, T.E., & Fuligni, A.J. \(2016\). Daily family stress and HPA axis functioning during adolescence: The moderating role of sleep. *Psychoneuroendocrinology*, 71, 43-53.](#)

[Park, H., Tsai, K.M., Dahl, R.E., Irwin, M.R., McCreath, H., Seeman, T.E., & Fuligni, A.J. \(2016\). Sleep and inflammation during adolescence. *Psychosomatic Medicine*, 78, 677 -685.](#)

PETER J. GIANAROS

University of Pittsburgh

My work focuses on the neurobiology of psychological stress, emotion, and socioeconomic health disparities. This focus has encompassed studies of how the brain (i) regulates and represents autonomic, immune, and cardiovascular stress responses, (ii) how the brain influences and is influenced by biological and behavioral risk factors for chronic illnesses, including atherosclerotic cardiovascular disease (CVD), and (iii) links socioeconomic inequalities to mental and physical health across the lifespan. These studies have used a wide range of approaches, including the integrated use of functional and structural brain imaging, psychophysiological, epidemiological, behavioral, and basic laboratory approaches.

The overall goals of the NIA reversibility network are relevant to work we have been conducting for the past 10 years, specifically on the neurobiological pathways by which early life disadvantage and adversity may relate to physical health outcomes in later life (e.g., cardiovascular disease).

[Gianaros, P.J., Kuan, D.C., Marsland, A.L., Sheu, L.K., Hackman, D.A., Miller, K.G., Manuck, S.B. \(2017\). Community Socioeconomic Disadvantage in Midlife Relates to Cortical Morphology via Neuroendocrine and Cardiometabolic Pathways. *Cereb Cortex*, 27, 460-473.](#)

[Marsland, A.L., Gianaros, P.J., Kuan, D.C., Sheu, L.K., Krajina, K., Manuck, S.B. \(2015\). Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun*, 48, 195-204.](#)

KEITH MALCOLM GODFREY

University of Southampton

My research is characterizing pre- and postnatal exposure periods, risk factors and mechanisms that programme long-term health effects, and interventions to prevent/remediate these. My 25 years clinical research experience in the field of developmental influences on later health and disease commenced with an MRC Clinical Training Fellowship, and ongoing adult and pediatric clinical commitments have allowed me to retain a sharp focus on translational research for patient and population benefit. I am a principal investigator on major mother-offspring cohort studies internationally, and have close involvement with three studies examining developmental programming of neuropsychological function. We have made major progress in determination of the optimal diet and body composition for women before and during pregnancy, and optimal paths of growth for fetuses, infants and children. The research is also leading to greater understanding of the epigenetic mechanisms and pathways underlying relationships between early environment and later phenotype observed in epidemiological studies. The aim is to strengthen the evidence base for pre- and postnatal policy measures to improve health throughout the lifecourse. I have published 285 peer reviewed papers, and 55 reviews/book chapters (>20,500 citations, H-index 66), and have been an invited speaker at >100 national and international scientific meetings.

My research programme underpins UK government policy (Foresight Tackling Obesities 2007; SACN Early Nutrition & Chronic Disease 2010; CMO Annual Report, Our Children Deserve Better 2013; CMO Annual Report, Women's Health 2014) and NICE guidance (Maternal & Child Nutrition 2008; Pregnancy Weight Management 2010). It has led to a lifecourse approach to prevention of non-communicable diseases, now recognised by the World Bank, World Health Organisation (2008-13 Global Strategy for Prevention & Control of NCDs; UN General Assembly resolution 64/52, 2010; WHO Ending Childhood Obesity Commission 2014) and other NGOs.

As Director of the NIHR Southampton Biomedical Research Centre, I administer a broad programme of mechanistic, observational and interventional projects in the field of nutrition, developmental influences on health, and their reversal in later life. The programme has produced numerous peer-reviewed publications from each project, and has led to collaborations with major research groups internationally in the US, Europe, Asia and Australasia.

[Lin, X., Lim, I.Y., Wu, Y., The, A.L., Chen, L., Aris, I.M., Soh, S.E., Tint, M.T., Maclsaac, J.L., Morin, A.M., Yap, F., Tan, K.H., Saw, S.M., Kobor, M.S., Meaney, M.J., Godfrey, K.M., Chong, Y.S., Holbrook, J.D., Lee, Y.S., Gluckman, P.D., Karnani, N. \(2017\). Developmental pathways to adiposity begin before birth and are influenced by genotype, prenatal environment and epigenome. *BMC Medicine*, 15\(1\), 50.](#)

[Mandal, S., Godfrey, K.M., McDonald, D., Treuren, W.V., Bjørnholt, J.V., Midtvedt, T., Moen, B., Rudi, K., Knight, R., Peddada, S., Brantsaeter, A.L., Eggesbø, M.Å. \(2016\). Fat and vitamin intakes during pregnancy have stronger relations with a pro-inflammatory maternal microbiota than does carbohydrate intake. *Microbiome*, 4\(1\), 55.](#)

MEGAN R. GUNNAR

University of Minnesota

For over 35 years my research has focused on the factors affecting the reactivity and regulation of stress-mediating systems, including the hypothalamic-pituitary-adrenocortical (HPA) axis in infants, children and adolescents. I have published over 200 peer-reviewed papers covering various aspects of stress and development and have received three life-time achievement awards, one from the American Psychological Association, one from the Society for Research in Child Development and one from the American Psychological Society for my research and mentoring in this area. In the last 15 years I have focused on the impact of early deprivation on neurobehavioral development, including stress reactivity/regulation, emotion regulation, executive functioning, and deprivation-related emotional and behavioral problems. In my current work with this population I am examining whether puberty opens a window for the recalibration of stress reactivity and regulation so as to reflect current life conditions. If those are more benign than those in early life, this may allow a reversal of early life stress effects.

[Hodel, A.S., Hunt, R.H., Cowell, R.A., Van Den Heuvel, S.E., Gunnar, M.R., & Thomas, K.M. \(2015\). Duration of early adversity and structural brain development in post-institutionalized adolescents. - *Neuroimage*, 105, 112-9.](#)

[Koss, K.J., Mliner, S.B., Donzella, B., & Gunnar, M.R. \(2016\). Early adversity, hypocortisolism, and behavior problems at school entry: A study of internationally adopted children. *Psychoneuroendocrinology*, 66, 31-8.](#)

[Quevedo, K., Johnson, A., Loman, M., Lafavor, T., & Gunnar M. \(2012\). The Confluence of Adverse Early Experience and Puberty on the Cortisol Awakening Response. *Int J Behav Dev*, 36\(1\), 19-28.](#)

TAKAO K. HENSCH

Harvard University

We aim to understand how early life experience shapes brain function. Pioneering the use of a molecular / genetic approach, we revealed that specific GABA circuits orchestrate the functional and structural rewiring of neural networks during "critical periods" of cortical plasticity (Hensch, 2005, 2014) which are later limited by 'brake'-like factors (Bavelier et al, 2010). Ongoing work is aimed at 1) confirming to what extent mechanisms generalize across brain regions and species (Werker & Hensch, 2015), and 2) translating basic animal studies into therapeutic strategies for devastating neurological disorders in humans. Our animal work has inspired pilot clinical trials for the treatment of amblyopia at Boston Children's Hospital and novel insight into the nature of brain plasticity across the lifespan.

CHRISTINA E. HUGENSCHMIDT

Wake Forest School of Medicine

The motivation for participating in the reversibility meeting stems from two lines of work in my career. One is work examining the effects of type 2 diabetes on the brain and cognition, and how exercise and weight loss might remediate these effects. The other is my background as a child and family therapist, and current pilot work examining the effects of support groups on biomarkers of stress in older adults with dementia and their spouses. Prior to entering my doctoral, I began a career as a child and family therapist. I completed an internship at the Program on Childhood Trauma and Maltreatment at UNC Chapel Hill, worked for 3 years in public mental health in South Carolina, and worked briefly as an assessment therapist for a non-profit agency serving abused and traumatized children. Given my background in counseling, in the past 2-3 years I have worked with the Memory Counseling Program at Wake Forest to collect pilot data examining the effects of their support groups on allostatic load and telomere length in people with dementia and their spouses participating in support groups. My doctoral work provided me with a background in cognition and analysis of multiple neuroimaging modalities, and my postdoctoral fellowship added to this by investigating the relationship between diabetes and the brain in a large, family-based genetic study. My current career development award examines the effects of aerobic exercise and diet-induced weight loss on the relationship between diabetes risk factors and cognition and the brain in sedentary obese older adults, a population at risk for metabolic disease. To date, I have collected and analyzed images from multiple brain imaging modalities (see 1, 2 below as examples) and authored 40 manuscripts (11 as first author).

ALLA LANDA

Columbia University Medical Center

My research bridges clinical psychology and neuroscience, and focuses on the interface of emotion regulation, interpersonal well-being and physical health, with the goal of informing development of new effective treatments informed by the psychosomatic developmental perspective. I have formulated a translational-research-based conceptual approach for understanding centralized chronic pain and effects of early interpersonal experience on its lifelong development. This Developmental Theory of predisposition to centralized chronic pain proposes mechanisms of symptom formation and maintenance in this disorder, pointing to a crucial role of early and lifelong interpersonal experience on development. We have been conducting studies to investigate this theory further, using multilevel methodology, including psychologic, psychophysiologic, brain imaging (fMRI), immune markers, and neurotransmitters data; and both human studies and animal models in collaboration with colleagues at our university. Currently, I am also investigating these processes in a clinical population - a career development award from NIA to investigate the role of early interpersonal experience in neural predisposition to chronic pain later in life. Trained as a Clinical Psychologist (at LIU, and NYU-Bellevue Hospital), I then pursued postdoctoral training in Developmental Neuroscience at CUMC. I continue clinical work with patients with somatic symptom disorders, conversion disorders and chronic pain, which informs my research. In 2015, in order to further multidisciplinary work in this area and to inform clinicians of the latest advances in translational research, I started annual Columbia Psychosomatic

Conferences, held on CUMC campus, which have attracted international multidisciplinary audience of researchers and clinicians as well as presenters from the US and Europe.

[Landa, A., Peterson, B.S., & Fallon, B. A. \(2012\). Somatoform pain: A developmental theory and translational research review. *Psychosomatic Medicine*, 74, 717-727.](#)

[Landa, A., Wang, Z., Russell, J.A., Posner, J., Duan, Y., Kangarlu, A., Fallon, B.A., & Peterson, B.S. \(2013\). Distinct neural circuits subserve interpersonal and non-interpersonal emotions. *Social Neuroscience*, 8, 474-488.](#)

[Landa, A., Bossis, A., Boylan, L. & Wong, P. \(2012\). Beyond the unexplainable pain: relational world of patients with somatization syndromes. *Journal of Nervous and Mental Disease*, 200, 413-422.](#)

KAREN MATTHEWS

University of Pittsburgh

Relevant to the reversibility conference is my work on psycho-social and -biological factors that lead to the development of cardiovascular risk in adolescence and the influence of menopause on cardiovascular risk and aging more generally in women of diverse socioeconomic and ethnic backgrounds.

Adolescence is a unique period in the life course and a time when many of the traditional risk factors for cardiovascular disease increase substantially. Our studies have shown remarkable similarities between the psychosocial factors related to cardiovascular risk in adolescence and in adulthood. For example, we found that high levels of depressive symptoms, hostility, and anxiety are associated with elevated pulse wave velocity, a marker of vascular stiffness in black and white healthy teenagers; positive attributes, such as general positive affect, can protect adolescents from risk for metabolic syndrome. Elevated nighttime blood pressure, a hallmark of future hypertension, is associated with low family income and high levels of negative emotions and few positive attributes, especially in blacks. Furthermore, elevated nighttime blood pressure and insulin resistance are associated with short, fragmented sleep in adolescents. Our most recent work has focused on the influence of child abuse on later risk factors in adulthood. Women who report child abuse are at higher risk for central adiposity, metabolic syndrome, and elevated C reactive protein, primarily through obesity. We are now examining the role of early life experience measured prospectively on the development of cardiovascular risk and sleep in black and white men.

When we began our research on menopause and cardiovascular risk, there were hints in the epidemiological literature that early menopause conferred risk for CVD but the field at that time was focused on the potential protective effect of hormone therapy. We decided that it would be most useful to track changes in CVD risk factors across the menopausal transition in women in observational cohort studies. Using data from the Study of Women's Health across the Nation (SWAN), we have found that (a) dramatic changes in lipids and apolipoproteins occur during the years surrounding the final menstrual period and these changes are similar in all ethnic groups, (b) changes in cardiovascular risk factors during natural menopause are similar in magnitude to changes that occur with surgical menopause, with the exception that women who undergo a bilateral oophorectomy gain more weight

than comparison women; (c) the magnitude of changes in lipids around the final menstrual period predicts carotid plaque and carotid intima media thickness, markers for later clinical coronary events; and (d) occurrence of vasomotor symptoms are related to a number of cardiovascular risk factors and to carotid atherosclerosis. These findings are important because of the ongoing controversy on whether menopause has an effect of women's risk for cardiovascular disease. Our research indicates it does.

[Matthews, K.A. & Gallo, L.C. \(2011\). Psychological perspectives on pathways linking socioeconomic status and physical health. *Annu Rev Psychol*, 62, 501-30.](#)

Matthews, K.A., Boylan, J.M., Jakubowski, K.P., Cundiff, J., Lee, L., Pardini, D.A., & Jennings, J.R. (in press). Socioeconomic status and parenting during adolescence in relation to ideal cardiovascular health in Black and White men. *Health Psychology*.

BRUCE S. MCEWEN

The Rockefeller University

My laboratory discovered adrenal steroid receptors in hippocampus and this provided a gateway to the ongoing discovery that circulating steroid hormones and other systemic mediators affect cognition, mood and many other neural processes and the further discovery that there is structural and functional plasticity of the adult as well as developing brain, which these hormones mediate. Translational studies throughout the world are extending these findings to the human brain. Dentate gyrus neurogenesis was "rediscovered" in my laboratory and we went on to show that chronic stress reduces neuron number in dentate gyrus, and remodels dendrites and granule cell neurons in ways that differ between the sexes. Indeed, we have also led the way in demonstrating mechanisms of action of gonadal steroids via the entire brain, starting with the hippocampus, via both genomic and non-genomic mechanisms. Beyond the hippocampus, we have demonstrated stress-induced remodeling of neurons of the medial prefrontal and orbitofrontal cortex as well as basolateral and medial amygdala, in which the health brain shows resilience after stress is over. Glutamate and glucocorticoids play a major role. This work has led translationally down a conceptual path, namely, that stress hormone effects are biphasic – protective in the short run and potentially damaging in the long run – embodied in the now widely used concepts of allostasis and allostatic load/overload that we helped to develop. We are currently looking at epigenetic effects of acute and chronic stressors on depression- and anxiety-related behavior, as well as cognitive functions, in order to investigate the actions of putative rapidly acting antidepressant drugs in which glutamate overflow plays a role. We find that slowing glutamate overflow by enhancing reuptake has a protective role in aging and may slow the rate of neurodegeneration in Alzheimer's disease. Collaborative transdisciplinary research has also been a priority in my career as shown by my membership in the MacArthur Foundation Research Network on Socioeconomic Status and Health and the National Scientific Council on the Developing Child. For 40+ years, I have mentored and trained many young scientists who have gone on to productive careers as researchers in basic and translational neuroscience. These include Robert Sapolsky, Michael Meaney, Elizabeth Gould, Victoria Luine, Neil MacLusky, Roberta Brinton, Catherine Woolley, Heather Cameron, Carl Denef and Ron de Kloet, all Professors or the equivalent at their respective institutions. I have also mentored scientists who do clinical and epidemiological work, including, Teresa Seeman, Professor at UCLA; Elissa Epel, health psychology, Professor at UCSF; Cheryl Corcoran at Columbia University and Marty Altemus at

Weill/Cornell, both practicing psychiatrists; and, currently, Ana Pereira, neurologist, Assistant Clinical Professor at Rockefeller. I have also co-mentored M.D.-Ph.D. students in the Tri-Institutional program: Dan Rosell and Xenia Protopopescu, both practicing psychiatrists; Conor Liston, psychiatrist and researcher, now an Asst Prof at Weill/Cornell; and Joanna Spencer-Segal, reproductive neuroendocrinologist, currently at Michigan.

CRAIG MCEWEN

Bowdoin College

Over the past decade I have become deeply involved in community initiatives addressing poverty and early childhood development with the United Way of Mid Coast Maine particularly. For example, I chair the implementation committee for a home visiting initiative that expands those resources in the region and another initiative focused on expanding parenting resources. My scholarly interests have followed my community-engaged teaching and community work and now focus particularly on the impact of poverty on child development, integrating neuroscience and sociological perspectives. That has culminated in three articles with Bruce McEwen. Currently, I am writing critically about the imprecise understanding of adversity, and examining in particular the widespread misuse of the Adverse Childhood Experiences study (Felitti and Anda) in public policy and professional training. My early research and writing examined community corrections. Over the next 30 years my research and commentary focused largely on the legal profession, courts and mediation programs – small claims, community, corporate, family and general civil – and has been published widely in books, law reviews, social science journals and professional magazines.

McEwen, B.S. and McEwen, C.A. (2015). Social, Psychological, and Physiological Reactions to Stress. In R. Scott and S. Kosslyn (Eds.) *Emerging Trends in the Social and Behavioral Sciences* (pp. 1–15). New York, NY: Wiley.

LIS NIELSEN

National Institute on Aging

Lis Nielsen is Chief of the *Individual Behavioral Processes* (IBP) Branch in the *Division of Behavioral and Social Research* (BSR) at the *National Institute on Aging* (NIA). This branch develops programs of broad scientific scope, encompassing research on behavior change and behavioral interventions, cognitive and emotional functioning, behavior genetics and sociogenomics, technology and human factors, family and interpersonal relationships, and integrative biobehavioral research on the pathways linking social and behavioral factors to health in mid-life and older age. Nielsen manages a portfolio of transdisciplinary research in affective science, health psychology, and life-span developmental psychology. She coordinates NIA research initiatives on midlife reversibility of risk associated with early life adversity, conscientiousness and healthy aging, and stress measurement. Since joining NIA in 2005, Nielsen developed programs in Neuroeconomics and Social Neuroscience of Aging, Subjective Well-being, as well as trans-NIH initiatives for the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) and the Science of Behavior Change (SOBC). Nielsen has a BA in Philosophy from Rhodes

College, MA in Psychology (cand. Psych.) from the University of Copenhagen, and PhD in Cognitive Psychology from the University of Arizona. She was an NIA-supported NRSA Post-Doctoral Fellow in Psychology of Aging at Stanford University.

LISA ONKEN

National Institute on Aging

Lisa Onken directs the Behavior Change and Interventions Program at the National Institute on Aging (NIA). The goal of this program of research is to develop and test interventions that promote the health and well-being of individuals as they age. Prior to joining NIA, Dr. Onken served as Chief of the Behavioral and Integrative Treatment Branch and the Associate Director for Treatment at the National Institute on Drug Abuse (NIDA). She has championed a conceptual framework for behavioral intervention development that stresses the integration of basic science within the intervention development process to produce potent and maximally implementable behavioral interventions (<https://www.nia.nih.gov/research/dbsr/stage-model-behavioral-intervention-development>). Dr. Onken received her Bachelor's degree from Tufts University and her Master's and Ph.D. degree in clinical psychology from Northwestern University. She completed her clinical internship at Cook County Hospital and has subsequently held a variety of academic, clinical and research scientist positions at Northwestern University, the University of Illinois Medical School and Walter Reed Army Institute of Research. In addition to her current involvement in the NIH Common Fund SOBC initiative, she has taken the lead in numerous trans-NIH initiatives related to behavioral intervention development. She is a "Fellow" of the Association for Psychological Science and a consulting editor for the journal, "Clinical Psychological Science."

[Onken, L.S. \(2015\). Cognitive Training: Targeting Cognitive Processes in the Development of Behavioral Interventions. *Clinical Psychological Science*, 3\(1\), 39-44.](#)

[Onken, L.S., Carroll, K.M., Shoham, V., Cuthbert, B.N., & Riddle, M. \(2014\). Reenvisioning Clinical Science: Unifying the Discipline to Improve the Public Health. *Clin Psychol Sci*, 2\(1\), 22-34.](#)

CHRISTINE POWER

University College London

Having trained in epidemiology, working on the distribution of 'diseases of affluence', I began a new phase of my research career that was transformative, based on longitudinal data from the 1958 British birth cohort. Investing in the scientific value of this cohort study, I have: developed the field of life-course epidemiology in terms of conceptual frameworks that integrate social and biological influences at different life-stages in relation to later health; planned, designed and implemented as PI, a biomedical survey in mid-adulthood of the cohort to create one of Britain's most important and widely used repositories of data and biosamples for research users both nationally and internationally; provided empirical evidence on links between early life exposures and adult health outcomes. I am at the

international forefront in developing conceptual frameworks for life-course research, going beyond an emphasis on early life influences on adult health to encompass the whole lifespan, empirically testing alternative processes and timing of influences. My past and ongoing research contributing to wide acceptance of life-course as a crucial scientific perspective emphasises the role of both social and biological influences. In relation to social inequalities in health, I have established that factors contributing to inequalities do not emerge exclusively in adulthood but accumulate over decades of life, with effects on adult health of adverse early experiences only partially offset by subsequent favourable circumstances. My work has influenced debates on the causes of health inequalities, directed attention towards early life origins explanations rather than social selection. Exploring how social and biological influences are interwoven, my recent work suggests a well-defined epigenetic signature associated with living conditions in childhood opens up the prospect of further advances in understanding early life 'biological embedding'. These contributions are highly relevant to the Network. My experience of interdisciplinary working in fields that require cross-cutting scientific input is also highly relevant. Examples include: the European Science Foundation programme on Social variations in health expectancy (as scientific lead on 'Life course influences'); as Fellow of the Population health and Human development groups of the Canadian Institute for Advanced Research; as co-I for the Public Health Research Consortium and the New Dynamics of Ageing Programme on 'A life course approach to healthy ageing: capitalising on the value of UK life course cohorts'.

NATALIE RASGON

Stanford University

My lab (Stanford Center on Neuroscience in Women Health) is focused on neuroendocrine correlates in various models of affective and cognitive neuroscience. Specifically, this research builds upon my investigative experience on the role of insulin resistance in brain function. Vascular illnesses such as type 2 diabetes (DM2) and CVD are well established as risk factors of cognitive decline, vascular dementia and AD. An estimated 57 million or 25.9 % of American adults aged 20 or older had pre-diabetes (e.g. IR) in 2007. I was first to propose a hypothesis linking insulin resistance (IR) with mood and neurocognitive disorders. In my research on women with mood disorders, I and my colleagues have demonstrated: 1) high rates of IR, independent of medication status; 2) increase in IR with duration of treatment; 3) high rates of depression in women with primary IR syndrome (PCOS), 4) significant association between IR and depression severity; 5) mood enhancing effects of PPAR-gamma agonist in treatment resistant patients with major depression, and recently sex differences in lipid profiles in patients with bipolar disorder.

In my research on aging, since 1999, I have utilized structural (sMRI) and functional brain imaging (FDGPET), and cognitive testing in studying the effects of reproductive steroids on biomarkers of brain function in persons at genetic risk for AD in association with the Center on Aging at UCLA (PI: Gary Small) and subsequently at Stanford since 2002. Recent published work from my lab supports a negative association between hippocampal volume and IR in women at risk for AD, as well as produced pilot data on compensatory regional hypermetabolism and disrupted connectivity in default mode network in IR women in comparison to IS women. Over the years, I have accumulated a record of successful and productive research projects in areas related to insulin resistance and demonstrated substantial

scientific and administrative leadership experience, as well as a publication record that has prepared me to contribute meaningfully to this research.

[Rasgon, N., Lin, K.W., Lin J., Epe, I E., & Blackburn, E. \(2016\). Telomere length as a predictor of response to Pioglitazone in patients with unremitted depression: a preliminary study. *Transl Psychiatry*, 6, e709.](#)

[Rasgon, N.L., & McEwen, B.S. \(2016\). Insulin resistance-a missing link no more. *Mol Psychiatry*, 21\(12\), 1648-52.](#)

DAVID REISS

Yale University

I serve as a coordinator of a workgroup consisting of experts in the associations between early life adversity and adult health. The focus of the workgroup is enhancing the ascertainment of early adversity when data collected in childhood is not available. The work will center on analyses of research cohorts where data is available from both childhood and adulthood will consider social, psychological and genetic factors that may influence correspondence between childhood and adult reports. I bring to this effort experience with long-term, longitudinal studies of infants, children and adolescents as well as extensive experience on the interplay of genetic and family social factors on child and adult development. For example, I led the design team and was first PI of the longitudinal Early Growth and Development adoption study following infants to adolescence. I have broad experience in integrating the study of social and genetic processes having led the design team and was PI of two major and very productive NIH-supported twin studies (The Nonshared Environment in Adolescent Development study and the Twin and Offspring Study in Sweden) See relevant publications below.

[Eley, T.C., McAdams, T.A., Rijdsdijk, F.V., Lichtenstein, P., Narusyte, J., Reiss, D., Spotts, E.L., Ganiban, J.M., & Neiderhiser, J.M. \(2015\). The Intergenerational Transmission of Anxiety: A Children-of-Twins Study. *Am J Psychiatry*, 172\(7\), 630-7.](#)

[Fearon, R.M., Reiss, D., Leve, L.D., Shaw, D.S., Scaramella, L.V., Ganiban, J.M., & Neiderhiser, J.M. \(2015\). Child-evoked maternal negativity from 9 to 27 months: Evidence of gene-environment correlation and its moderation by marital distress. *Dev Psychopathol*, 27\(4 Pt. 1\), 1251-65.](#)

CARMEN SANDI

École Polytechnique Fédérale de Lausanne

Research in Carmen Sandi's laboratory aims to understand how stress and personality traits affect brain function and behavior. One of their ultimate goals is the identification of neurobiological mechanisms underlying vulnerability or resilience to psychopathology. Her lab is currently developing an integrative research program combining approaches in rodents and humans focusing on the effects of stress on the social brain. A special emphasis is placed on the regulation of brain bioenergetics in the long-term programming of behavior and peripheral metabolism by early life stress, and on the understanding of

the neurobiology of individual differences in behavior and vulnerability to psychopathology. Recently, her lab has identified a key role for mitochondrial function in the nucleus accumbens as a mechanism that links anxiety with social behaviors.

[Calandreau, L., Márquez, C., Bisaz, R., Fantin, M., & Sandi, C. \(2010\). Differential impact of polysialyltransferase ST8Siall and ST8SialV knockout on social interaction and aggression. *Genes Brain Behav*, 9\(8\), 958-67.](#)

[Márquez, C., Poirier, G.L., Cordero, M.I., Larsen, M.H., Groner, A., Marquis, J., Magistretti, P.J., Trono, D., & Sandi, C. \(2013\). Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. *Transl Psychiatry*, e216. doi: 10.1038/tp.2012.144.](#)

TERESA E. SEEMAN

University of California, Los Angeles

Trained as a social epidemiologist with post-doctoral training in neuroendocrinology, my research career has been interdisciplinary in focus throughout, seeking to elucidate the biological and other pathways through which SES and other social and psychological factors impact on trajectories of health and aging, including work specifically focused on factors affecting cognitive aging. I have published widely on socio-economic status, social relationships, behavioral and biological risk factors in relation to a range of major health outcomes of aging, including incidence and recurrence of cardiovascular disease, patterns of cognitive and physical functioning, frailty and overall longevity. I have also been one of the leading contributors to empirical research on the concept of allostatic load (a multi-systems approach to biological risk), contributing the original work documenting links between allostatic load and subsequent health risks as well as evidence linking differences in both socio-economic and social relationship histories to differential accumulation of allostatic load and its associated health risks. The research underpinning this work has entailed considerable experience in the design and implementation of large, multi-site community- as well as clinic-based data collection protocols. I currently serve as one of 4 PIs for the Research Network on Early Life Adversity and the Reversibility/Compensation of Its Negative Health Effects at Older Ages.

[Friedman, E.M., Montez, J.K., Sheehan, C.M., Guenewald, T.L., & Seeman, T.E. \(2015\). Childhood Adversities and Adult Cardiometabolic Health: Does the Quantity, Timing, and Type of Adversity Matter? *J Aging Health*, 27\(8\), 1311-38.](#)

STEPHEN SUOMI

Eunice Kennedy Shriver National Institute on Child Health and Human Development

Stephen J. Suomi, Ph.D. is Chief of the Laboratory of Comparative Ethology at the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), National Institutes of Health (NIH) in Bethesda, Maryland. He also holds research professorships at the University of Virginia, the

University of Maryland, College Park, the Johns Hopkins University, Georgetown University, the Pennsylvania State University, and the University of Maryland, Baltimore County. Dr. Suomi earned his B.A. in psychology at Stanford University in 1968, and his M.A. and Ph.D. in psychology at the University of Wisconsin-Madison in 1969 and 1971, respectively. He then joined the Psychology faculty at the University of Wisconsin-Madison, where he eventually attained the rank of Professor before moving to the NICHD in 1983.

Dr. Suomi's initial postdoctoral research successfully reversed the adverse effects of early social isolation, previously thought to be permanent, in rhesus monkeys. His subsequent research at Wisconsin led to his election as Fellow in the American Association for the Advancement of Science "for major contributions to the understanding of social factors that influence the psychological development of nonhuman primates." His present research at the NICHD focuses on 3 general issues: the interaction between genetic and environmental factors in shaping individual developmental trajectories, the issue of continuity vs. change and the relative stability of individual differences throughout development, and the degree to which findings from monkeys studied in captivity generalize not only to monkeys living in the wild but also to humans living in different cultures.

NIM TOTTENHAM

Weill Cornell Medical College

My research has been dedicated to studying the role of early experiences in neurodevelopmental processes associated with affective and cognitive development. I have examined this topic both behaviorally, using computerized tasks and parent reports, and at the neurobiological and physiological level, using structural and functional magnetic resonance imaging, physiological and hormonal assays, both in typical developmental samples and following early life adversity. My program of research has focused on human subcortical regions (e.g., amygdala, hippocampus, ventral striatum) and developing connections with cortical regions (e.g., prefrontal cortex). With support from the NIMH BRAINS R01, I have examined the developmental construction of limbic-cortical connections and associated emotional behaviors during childhood and adolescence, conducting large, longitudinal and cross-sectional studies on emotional and cognitive development in children.

[Gee, D.G., Gabard-Durnam, L.J., Flannery, J., Goff, B., Humphreys, K.L., Telzer, E.H., Hare, T.A., Bookheimer, S.Y., & Tottenham, N. \(2013\). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proc Natl Acad Sci U S A*, 110\(39\), 15638-43.](#)

[Callaghan, B.L. & Tottenham, N. \(2016\). The Stress Acceleration Hypothesis: effects of early-life adversity on emotion circuits and behavior. *Current Opinion in Behavioral Sciences*, 7, 76-81.](#)