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Childhood exposure to violence and lifelong health: Clinical intervention science and stress-biology research join forces

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Abstract

Many young people who are mistreated by an adult, victimized by bullies, criminally assaulted, or who witness domestic violence react to this violence exposure by developing behavioral, emotional, or learning problems. What is less well known is that adverse experiences like violence exposure can lead to hidden physical alterations inside a child's body, alterations that may have adverse effects on life-long health. We discuss why this is important for the field of developmental psychopathology and for society, and we recommend that stress-biology research and intervention science join forces to tackle the problem. We examine the evidence base in relation to stress-sensitive measures for the body (inflammatory reactions, telomere erosion, epigenetic methylation, and gene expression) and brain (mental disorders, neuroimaging, and neuropsychological testing). We also review promising interventions for families, couples, and children that have been designed to reduce the effects of childhood violence exposure. We invite intervention scientists and stress-biology researchers to collaborate in adding stress-biology measures to randomized clinical trials of interventions intended to reduce effects of violence exposure and other traumas on young people.

Everyone knows violence is bad for children and adolescents. It is harmful for them to be mistreated or abused by an adult, to be victimized by bullies, to witness serious domestic violence, or to be criminally assaulted. Many young people who are exposed to violence react to this adverse experience by developing behavioral, emotional, or learning problems. What is less well known is that adverse experiences such as violence exposure can also lead to hidden physical alterations inside a child's body. This article discusses why this is important for the field of developmental psychopathology and for society, examines the evidence base, and recommends that stress-biology research and intervention science join forces to tackle the problem.

When a child experiences violence, adults tend to focus on the child's learning in school and anxiety, depression, or aggressive reactions because these are pressing psychological needs after the child is restored to safety. However, recent research indicates there is also room for concern about less visible adverse effects on a child's physical health for decades into his or her future (Krug, 2002; Lupien, Paulozzzi, Melanson, Simon, & Arias, 2009; Shonkoff, 2012; Shonkoff, Garner, & the Committee on Psychosocial, Developmental, and Behavioral Pediatrics, 2012). These hidden effects are under study in stress-biology research, a multidisciplinary research area that is rapidly gaining ground because of advances for measuring stress-sensitive biomarkers in young people. These biomarkers are interesting because in midlife adults these same biological alterations are known to be associated with elevated risk for heart disease, metabolic diseases, immune diseases, stroke, and even dementia (Danese & McEwen, 2012; Miller, Chen, & Parker, 2011; Taylor, Way, & Seeman, 2011). Stress-biology research asks what biological (and psychological) alterations to brain and body can account for the long-term connection between a stressful childhood and ill health that only emerges 40 to 70 years later? What

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is it that changes? Here we look at potential changes in often-studied indicators of the health of the body (inflammatory reactions, telomere erosion, epigenetic methylation, and gene expression), and brain (mental disorders, neuroimaging, and neuropsychological testing).

Why is it important to know that stressful experiences during childhood might start a child on the long road to heart disease or dementia? This information is important for developmental scientists because it opens the door to early prevention, which is imperative today because of current demographic shifts. Life expectancy is growing longer and longer. Demographic trends suggest the possibility that the current generation of children will live an average of nearly 100 years (Vaupel, 2010). Policymakers and citizens are concerned that these many extra years of life should be healthy, productive, and enjoyable, not extra years of disease, disability, and dependence on others. Past medical research has shown that treating adult patients after they have contracted illnesses such as cardiovascular disease, diabetes, or dementia generally does not fully restore their quality of life (Jansson, 2005; McGill & McMahon, 2003; Wellcome Trust, 2006). Therefore, the hope of increasing children's lifelong productivity, health, and well-being calls for research to identify prevention targets that can be tackled successfully in early life, well before disease takes hold.

At the same time that life expectancy is growing longer for today's children, worldwide birth rates are dropping. There are fewer young people, even in developing nations. Simultaneously, baby boomers are becoming senior citizens. The ratio of young to old is shifting heavily toward older people. The math is compelling: soon each young person who is able to work will be depended on to support the healthcare and social security costs of more older people than today. This is called the *support ratio,* and it has been changing alongside the young to old demographic balance, and it is expected to continue changing worldwide (http://en.wikipedia.org/wiki/Potential_support_ratio). This ratio means that children are an increasingly valuable economic commodity. Insuring the lifelong health and productivity of each child-citizen is becoming more important for the world economy than ever before. We want today's children to have lifelong good health because we love them, but we also want them to be able to keep the economy going and support us in our own old age.

Great strides have been made toward designing treatments that work for children and adolescents who have learning, emotional, and behavioral problems as well as programs to prevent such problems among children at risk. However, today only a small fraction of young people have access to these effective treatments and preventions (Mihalopoulos, Vos, Pirkis, & Carter, 2011; National Research Council and Institute of Medicine, 2009). If preserving and promoting the psychological health of children were understood to be essential for worldwide economic security, child mental-health intervention might well become a key weapon in the fight to improve quality of life over the entire life course. Public awareness of the connection between childhood stress and adult physical health and age-related disease has the potential to galvanize political will toward prevention and treatment (e.g., see Tough, 2011). In contrast, we have noticed that listeners who seem inured to news of maltreated children's emotional problems are surprised and fascinated when told that maltreated children have elevated blood proteins that convey risk for heart disease.

On the 25th anniversary of *Development and Psychopathology*, there is an opportunity for the field of developmental psychopathology to bring together two of its strongest scientific themes: stress-biology research and clinical intervention science. If the hypothesis is true that stressors such as violence that precipitate psychological problems for young people also undermine their lifelong physical health, this would imply that the burden of adult and late-life diseases could be reduced by successfully improving the psychological health of children. First, we examine the evidence that violence exposure causes alterations in stress biomarkers. How good is it? This is not an exhaustive technical review but, rather, an overview of evidence for causation. Second, we envisage ways that clinical intervention researchers could incorporate stress biomarkers into their clinical trials to discover if invidious effects of ch1ildhood stress can be prevented or even *reversed* by psychosocial treatments. We note a handful of studies that have reported pre- versus posttreatment or treatment versus control group differences in stress-sensitive biological measures and make recommendations for more such research. Readers can find briefing papers with more in-depth coverage of the sections of this article at http://www.moffitt-caspi.com/content/klaus-grawe-think-tank-2012.

Childhood Violence Exposure

This article focuses on violence exposure for four reasons. First, violence exposure is one of the most common and severe sources of human stress. Second, the hypothesis is that stress in general affects health and studying violence exposure in particular provides a strong test of it. Third, violence exposure can be measured with fairly good reliability and validity, which is an advantage over many other adversities and stressors. Fourth, violence victimization is already a clear target of public-health and law-enforcement prevention efforts, as well as many clinical psychosocial intervention programs, providing opportunities for research into reversibility of putative effects of violence on stress biology. For this article, we defined violence exposure as personal exposure to physical acts of intentional harm in the first 18 years of life. We considered physical or sexual maltreatment by parents or other caregivers, physical or sexual assault by other adults, exposure to parents' or caregivers' domestic violence, bullying by peers or siblings, and violence within the context of an adolescent romantic relationship. These forms of victimization can be defined according to recent comprehensive reviews (Gilbert, Kemp, et al., 2009) and guidelines (Leeb, Paulozzzi, Melanson, Simon, & Arias, 2008). Other (nonviolent) adversities and forms of trauma undoubtedly have health implications but were omitted (Boyce, Sokolowski, & Robinson, 2012).

About 25% of children experience some form of violence exposure as juveniles (Koenen, Roberts, Stone, & Dunn, 2010). A comprehensive review of population-based studies in developed countries concluded that 5%–35% of children were physically abused and 5%–30% of children were sexually abused, whereas 10%–20% had witnessed domestic violence during childhood (Gilbert, Widom, et al., 2009). Subsequent national estimates agree. A nationally representative survey in the United States sought reports of exposure to violence from children under age 17 and their parents (Finkelhor, Turner, Ormrod, & Hamby, 2009; Turner, Finklehor and Ormrod, 2010). American estimates for exposure across the duration of childhood were 20%–29% for bullying, 2%–9% for dating violence, 5%–19% for physical maltreatment, 7%–33% for physical assault, 3%–11% for sexual maltreatment/assault, and 13%–27% for witnessing adults' domestic violence. This survey was repeated in the United Kingdom, yielding very similar prevalence estimates (Radford et al., 2013). The World Health Organization World Mental Health Survey provided estimates from 21 countries based on retrospective reports of adults looking back to their childhoods. Physical abuse was recalled by 5%–11% of respondents whereas 1%–2% reported contact sexual abuse and 4%–8% reported exposure to family violence (Kessler et al., 2010). Varying rates are partially due to differences between boys and girls, young children and adolescents, and to varying definitions and ascertainment methods across studies.

Prevalence rates that count victims conceal the fact that children who are exposed to one incident of violent victimization are likely to be repeatedly exposed to the same type of violence, which is termed *revictimization*, and to experience multiple different types of victimization, termed *polyvictimization* (Finkelhor, Ormrod, & Turner, 2007, 2009). Furthermore, juvenile victimization increases risk of adult violence victimization (Widom, Czaja, & Dutton, 2008). Such long-term multiple-exposure patterns constitute cumulative stress experiences that exacerbate victims' subsequent mental health outcomes (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Teicher, Tomoda, & Andersen, 2006). Individual variation in these patterns of violence exposure should thus also be considered in future research into effects on stress biology and health. Despite individual heterogeneity in the extent of violence exposure, and variation in the population prevalence estimates, all sources agree that childhood violence exposure is more prevalent than it ought to be and sufficiently prevalent to be taken seriously as a contributing factor in population health and age-related disease burden.

How Good Is The Evidence That Childhood Violence Exposure Influences Stress-Biology Measures?

It may seem heartless to challenge the hypothesis that violence exposure is harmful to lifelong health, as there is a moral imperative to prevent violence against children. However, there is also a scientific and societal imperative to evaluate threats to causal inference. Epidemiologists calculate population attributable fractions to estimate how much of the disease burden in the population could be reduced if certain causal factors were eradicated. For example, some estimates suggest that eradicating childhood adversities could reduce psychiatric disorders by nearly 30% (Kessler et al., 2010). Such estimates are intended to inform public policies and guide intervention efforts, but ". . . the population attributable fraction is of most use when the risk factor of interest is clearly causally related to the end point" (Rockhill, Newman, & Weinberg, 1998). Is it possible to say that childhood violence exposure causes poor health?

Experimental research in nonhuman animals has documented that stress causes alterations in body and brain measures. In contrast, the requisite evidence for causation in human children is weaker. Most studies reviewed for this article made an attempt to support causal inference by statistically controlling for other risk factors correlated with violence exposure (such as low socioeconomic status or family structure) that might have generated abnormal scores on health measures. However, children exposed to maltreatment and violence are statistically likely to experience a whole host of additional adversities that could diminish their health, and it is difficult to control for all of them (Cicchetti & Toth, 2005). Worse yet, because children inherit both their genotypes and environments from their parents, environmental risks such as violence exposure are known to co-occur with genetic predispositions to health outcomes, such as mental disorders and neuropsychological dysfunctions (Jaffee & Price, 2007). It is not known whether this gene–environment correlation extends to other health outcomes or stress biomarkers, but we should assume that it does.

Several study designs that could assist with causal inference are off limits to researchers who study children. For example, the hypothesized causal effect of violence exposure on health could be confirmed by experimental designs exposing children to violence (which is unethical) or by longitudinal designs taking biomarker measurements before and after violence exposure to use each child as his own control (which is impractical, although not impossible). This causal hypothesis could also be tested by comparing the stress biomarker status of siblings who are discordant for the experience of violence exposure. Twins are particularly good for this contrast, although in most twin pairs studied as young children when one twin is maltreated so is the other. As a result of these research limitations, we may never be able to rule out the possibility that biomarker abnormalities observed in violence-exposed children were caused by some other kind of adversity. Nevertheless, if we accept that the *key* hypothesis is that childhood stress in general affects health, then studying violence exposure in particular provides a reasonable test of this hypothesis, whether or not effects can be narrowed to violence per se. The main caution here is that this field of inquiry is far from being able to state how much of the disease burden in the population could be reduced if all violence-exposed children were successfully treated. Treatment studies will be useful to tackle this question, more about which appears later in this article.

The next sections of this article briefly review the state of the evidence that childhood violence exposure affects indicators of the health of the body (inflammatory reactions, telomere erosion, epigenetic methylation, and gene expression), and of the brain (mental disorders, neuropsychological testing, and neuroimaging). This set is not exhaustive; for example, studies of cortisol (Gunnar & Quevedo, 2007) and electroencephalography (Cicchetti & Curtis, 2005; Pollak, 2005) in maltreated children are important but not reviewed here.

Childhood violence exposure and inflammatory outcomes

Inflammation is part of the innate immune response, a defense mechanism that enables recognition of microorganisms' antigens, and triggers rapid response against them. Inflammation is triggered by "inducers," which can be both exogenous and endogenous (Medzhitov, 2008). Exogenous inducers include microbial factors and factors such as allergens, irritants, foreign bodies, and toxic compounds. Endogenous inducers include biological signals produced by stressed, damaged, or otherwise malfunctioning tissues. In response to these signals, the innate immune system develops a response involving blood vessels, white blood cells, and the so-called acute-phase proteins: the inflammatory response (Medzhitov, 2008). A successful inflammatory response achieves the elimination of the signals that originated the response, the resolution of the response, and the repair of damaged tissues.

If the inducers become chronic and the resolution phase cannot occur, the otherwise protective, acute inflammatory response can become a detrimental, chronic inflammatory state. Because the inflammatory response is nonspecific, it does not discriminate between inflammation inducers (e.g., invading microorganisms) and surrounding tissues. Collateral damage during chronic inflammatory states may therefore lead to significant tissue damage leading to age-related disease, such as cardiovascular disease, Type 2 diabetes, and dementia (Hotamisligil, 2006; Nguyen, Julien, & Rivest, 2002; Ross, 1999). In humans, a meta-analysis of longitudinal–epidemiological studies suggests that even mild elevation in plasma inflammation biomarkers, such as C-reactive protein, fibrinogen, and white blood cell count, predicts elevated risk for cardiovascular disease (Danesh, Collins, Appleby, & Peto, 1998). Elevated inflammation levels have also been linked to risk for psychopathology (Soczynska, Zang, Kennedy, & McIntyre, 2012). Although inflammation has been associated with several psychiatric disorders, a causal relation is most established with regard to depression, where evidence comes from meta-analyses, randomized controlled trials, and experimental animal models (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Howren, Lamkin, & Suls, 2009).

Many experimental findings from animal models document the effects of early life stress on long-term functioning of the immune system and particularly inflammation. Observational studies of humans also show that juvenile violence victimization is linked to abnormal immune system functioning with elevated inflammation levels (Danese et al., 2011; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Kiecolt-Glaser et al., 2011; Shirtcliff, Coe, & Pollak, 2009; Slopen et al., 2010; Surtees et al., 2003; Widom, Czaja, Bentley, & Johnson, 2012). For example, in the Dunedin Study, children who had been exposed to maternal rejection, harsh parenting, disruptive caregiver changes, physical abuse or sexual abuse were almost twice as likely as nonmaltreated children to show elevated levels of multiple clinically relevant inflammation biomarkers, such as C-reactive protein, fibrinogen, and white blood cell count, in adulthood (Danese et al., 2007). These findings were independent of the influence of other co-occurring early-life adversities, stress in adulthood, adult health and health behavior, and current active infections. Among 12-year-old participants of the UK Environmental Risk (E-Risk) Longitudinal Twin study, physically maltreated children experiencing current depression already exhibited elevated inflammation levels in childhood (Danese et al., 2011). This finding too could not be explained by potential confounders, such as family socioeconomic circumstances, obesity, or current infections. Another study reported that both postinstitutionalized children living in adoptive homes and children with substantiated cases of physical abuse still residing with their families showed elevated secretory immunoglobulin A for herpes simplex virus compared to controls, indicating impairment in the acquired immune response that normally contains the reactivation of this latent virus (Shirtcliff et al., 2009).

This effect of juvenile violence victimization on inflammation has thus been replicated in independent studies, appears to be independent of correlated risk factors, and is present when victimization is ascertained prospectively during childhood. Furthermore, the inflammatory alterations of juvenile violence victims have been observed to onset in childhood and also to be present in adult life. Some studies suggest that the connections between childhood stress and inflammation measures are strongest among individuals with depression (Danese et al., 2008, 2011). Because juvenile violence victimization could influence long-term disease outcomes through the mechanism of elevation in inflammation levels, reversing the effect of victimization on inflammation could potentially reduce health burden.

Childhood violence exposure and telomere erosion

Telomeres are the repetitive TTAGGG sequences that cap and protect the ends of chromosomes. They play a major role in regulating cellular replication and shorten progressively with each cell division in replicating human tissues. Upon reaching a critically short length, cells enter a state of replicative arrest called senescence. In recent years, telomeres have emerged as a promising new candidate in epidemiological research. Shorter telomere length and increased erosion rate are both associated with higher risk of morbidity and mortality

(Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003; Ehrlenbach et al., 2009). Studies in animal models have provided support for the predictive utility of telomere length early in life on the animal's subsequent lifespan (Heidinger et al., 2012). The advent of high-throughput and cost-effective laboratory techniques that measure telomere length, in buccal cells or peripheral blood cells, opened the gate to new studies linking shorter telomere length with a broad range of risk factors that predict disease morbidity, including smoking, obesity (Buxton et al., 2011; Nordfjall et al., 2008; Valdes et al., 2005), schizophrenia (Yu, Chang, Lin, & Cho, 2008), mood disorders (Simon et al., 2006), and psychosocial stress (Epel et al., 2004; Kiecolt-Glaser et al., 2011).

In the past 2 years, studies have provided initial support for an association between childhood stress and telomere length. Adult participants who reported physical abuse, emotional neglect, or other adverse life events in childhood had significantly shorter telomere length, regardless of key potential confounding factors such as age, sex, smoking, or body mass index (Kananen et al., 2010; Kiecolt-Glaser et al., 2011; O'Donovan, Epelm et al., 2011; Tyrka et al., 2010). However, one study failed to replicate the association between telomere length and retrospective assessment of physical and sexual abuse in childhood in a large cohort of adult twins (Glass, Parts, Knowles, Aviv, & Spector, 2010). In the first study of children, institutional care was significantly associated with shorter telomere length in middle childhood (Drury et al., 2011). In addition, the E-Risk Study reported that children who experienced two or more kinds of violence exposure showed significantly more telomere erosion between age 5 baseline and age 10 follow-up measurements (Shalev et al., 2012). This finding provided the first evidence that stress-related accelerated telomere erosion between two repeated measures (as opposed to telomere length at one time point) can be observed at a young age while children are experiencing stress and well before they develop poor health as adults.

Telomere length measurement is now offered as a diagnostic tool to monitor health and predict disease risk (Wolinsky, 2011). However, recent findings from studies with repeated telomere measurements indicate caution, because the temporal process of telomere erosion is more complex than initially assumed. For example, telomere length is highly variable across different age groups, there is significant intraindividual variability, telomere erosion is inversely correlated with baseline telomere length, and also, in some individuals, telomeres lengthen over time (Aviv et al., 2009; Epel et al., 2009). In addition, there are controversies regarding the best ways to measure telomere length. Finally, another methodological question concerns the measurement of telomere length in different tissues (Shalev et al., 2012). Because of ethical difficulties obtaining blood from children in the community, most studies in children have used buccal cells instead of the peripheral blood cells more commonly used in studies of adults. This difference must raise the question of whether findings will generalize across age and tissue type. Extreme caution should be taken as more research is needed to clarify the mechanisms that govern telomere length dynamics.

Childhood violence exposure and epigenetic outcomes

Sitting above the DNA sequence is a second layer of information (the *epigenome*) that regulates several genomic functions, including when and where genes are actively expressed. Epigenetics refers to the reversible regulation of various genomic functions, occurring independently of the DNA sequence, mediated principally through biochemical changes in DNA methylation and chromatin structure. Epigenetic processes are essential for normal cellular development and regulation of gene function (Feinberg, 2010). DNA methylation is perhaps the best understood among several kinds of epigenetic modifications. Unlike the DNA sequence, which is stable and robust, epigenetic processes are often tissue-specific, developmentally regulated and highly dynamic. A growing body of evidence shows that the epigenome changes over the life course and is correlated with age, an important observation given that the prevalence of many chronic diseases increases with advancing age (Bjornsson et al., 2008; Bocklandt et al., 2011; Christensen et al., 2009; Flanagan et al., 2006; Fraga et al., 2005). There is also mounting evidence that epigenetic processes are influenced by factors in the environment. DNA methylation, for example, has been shown to vary as a function of nutritional, chemical, physical, and psychosocial factors. Epigenetic mechanisms therefore represent a potential link between genes and the environment, and this hypothesis is supported by observations that monozygotic twins can differ in DNA methylation (Fraga et al., 2005; Wong et al., 2010). It was recently proposed that epigenetic mechanisms play a pivotal role in human health and disease, with increasing evidence for their involvement across the broad spectrum of chronic complex illnesses, including physical, physiological, and mental disorders (Feinberg, 2010; Petronis, 2010).

Changes in DNA methylation following early life stress have been associated with long-term changes in gene expression and behavior and there is initial evidence that they contribute to both psychiatric disorders and physiological disturbances later in life (Champagne & Curley, 2009; Gluckman, Hanson, & Beedle, 2007; Rutten & Mill, 2009).

Research using rodent models provides direct evidence for the role of early life stress on the epigenome; a number of detailed reviews have been recently published on this subject (Champagne & Curley, 2005, 2009). Perhaps the best known example is a report that variation in maternal care in rats alters DNA methylation and histone acetylation near the glucocorticoid receptor gene (nuclear receptor subfamily 3, group C, member 1) in the hippocampus of the offspring, directly affecting transcription and subsequent stress responses in adulthood (Weaver et al., 2004). A cross-fostering design was used to infer a causal relationship between maternal care and epigenetic differences, and it was also discovered that the changes in DNA methylation could be reversed using epigenetic drug

treatments. Despite stimulating research into the epigenetic consequences of early-life adversity, these seminal findings await convincing accumulation of positive replication results.

Research on epigenomic changes in humans occurring in response to early-life adversity is considerably more limited, and the results are often difficult to interpret given the biological, technical and methodological issues inherent in how the studies have been implemented (Beach, Brody, Todorov, Gunter, & Philibert, 2010; Heijmans & Mill, 2012; McGowan et al., 2009; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). The few human studies are all characterized by relatively small changes in DNA methylation, and the biological significance of these changes is yet to be established. Of particular interest are reports of differential DNA methylation in genes related to immune function and inflammation in posttraumatic stress disorder (PTSD patients; Smith et al., 2011; Uddin et al., 2010).

Although there is mounting interest in epigenetic epidemiology, the field is still in its infancy. Specific research into the epigenetic consequences of childhood violence victimization in humans is lacking, although research using rodent models suggests potential links between early-life adversity and epigenomic plasticity. To date, virtually all research into the epigenetic consequences of early-life adversity has focused on DNA methylation changes near a priori candidate genes thought to be involved in mental disorders, stress-response pathways, or neural plasticity. It is therefore unclear how applicable the results are for understanding physical health. However, recent advances in genomic technology make it feasible to undertake unbiased whole genome-scale studies of DNA methylation in response to early-life stressors such as violence victimization. As research starts to identify epigenetic changes relating to early-life adversity and physical health, it will be important to question cause and effect; disease-associated differentially methylated regions may arise prior to illness and contribute to the disease or could be a secondary effect of the disease process, or of the medications used in treatment (Heijmans, Tobi, Lumey, & Slagboom, 2009). It may be difficult (perhaps impossible) to obtain causal evidence linking childhood trauma to altered DNA methylation and subsequent disease, given the ethical issues involved in implementing causal study designs. Large longitudinal epidemiological cohorts are an ideal resource for epigenetic research, but in such studies whole blood or buccal cells are usually the only biological materials archived, which is problematic because DNA methylation differences could be confounded by differences in the cellular composition of samples from different tissue sources. Another key question concerns the extent to which easily accessible tissues (such as blood) can be used to ask questions about inaccessible tissues such as the brain and other internal organs (Davies et al., 2012). Finally, because there is a considerable interest in epigenetic research in both the scientific and popular press, it is important that epigenetics should avoid hype and unrealistic promises and keep in mind that optimal research methods are still very much under construction.

Childhood violence exposure and gene expression outcomes

Peripheral blood gene expression is an interesting recent development in stress biomarker research, with opportunities for both hypothesis-driven research and for hypothesis-free discovery (Sunde, 2010). Blood cell mRNA expression can be measured either through the candidate-gene approach, that is, in one gene at a time, through the whole genome transcriptomic approach using array systems, or through the simultaneous analysis of 30 to 100 related genes selected to represent a biological system (Sunde, 2010). Two main biological systems involved in the stress response, the hypothalamic–pituitary–adrenocortical (HPA) axis and the inflammatory system, have been the focus of a small number of studies in humans that have examined peripheral blood gene expression following exposure to severe stressors. These studies have tended to examine adult patients with PTSD or other stress-related forms of psychopathology who had experienced recent traumatic stressors, such as the events of 9/11, military combat, or assault (Mondelli et al., 2011; Sarapas et al., 2011; Segman et al., 2005; Yehuda et al., 2009). Other studies have identified gene expression differences associated with more chronic adverse experiences, such as maternal separation in rhesus monkeys (Cole et al., 2012) or poverty, long-term caregiving, and loneliness in humans (Chen, Miller, Kobor, & Cole, 2011; Miller et al., 2008; Miller, Rohleder, & Cole, 2009; O'Donovan, Sun, et al., 2011). The emerging literature indicates a role for gene expression in mediating the effects of stress exposure on the immune system and the sympathetic nervous system. However, studies of children linking gene expression to violence exposure are few (Labonté et al., 2012). This research area is yet to be developed.

Childhood violence exposure and mental health outcomes

Although mental health is not a direct stress–physiology measure, we include it here because it is one indicator of the health status of the brain (Lupien et al., 2009), and evidence is mounting that mental disorders involve physiological changes, such as elevated inflammation (Soczynska, Zang, Kennedy, & McIntyre, 2012). Moreover, some research suggests that violence exposure has its greatest effects on future health among the subset of violence-exposed individuals who develop mental disorders following violence exposure (Danese et al., 2008, 2011; Heim et al., 2000; Vythilingam et al., 2002). The disability caused by psychiatric disorders is growing, particularly in developed Western nations, where the burden of communicable diseases is now reduced and psychiatric conditions account for over 40% of all years lived with disability according to the World Health Report (World Health Organization, 2001). Associations between childhood victimization and adult mental disorders have been reported in relation to exposure to domestic violence, physical abuse, sexual abuse, emotional abuse, and neglect (Kessler et al., 2010). Research has also challenged the

view that bullying victimization is harmless by showing that it increases the risk of psychiatric problems (Arseneault, Bowes, & Shakoor, 2010; Fisher et al., 2012, 2013; Winsper, Lereya, Zanarini, & Wolke, 2012).

Taken together, the evidence shows that childhood violence victimization is associated with risk for (a) many different kinds of psychiatric disorders, (b) comorbidity, (c) unfavorable course of illness, and (c) poor treatment response. It is difficult to identify a disorder to which childhood victimization is not linked. It is significantly associated with mood disorders, anxiety disorders, behavior disorders, and substance-use disorders and with an individual having more than one of these disorders simultaneously (Green et al., 2010; Kessler et al., 2010; Scott, McLaughlin, Smith, & Ellis, 2012). A recent discovery is that childhood violence victimization is also linked to schizophrenia, psychosis, and psychotic-like symptoms (Arseneault et al., 2011; Toth, Pickreign Stronach, Rogosch, Caplan, & Cicchetti, 2011; Varese et al., 2012). In relation to course of illness, a meta-analysis revealed that childhood maltreatment predicts an unfavorable course of depression, as defined by both recurrence and persistence (Nanni, Uher, & Danese, 2012). Less evidence is available about the course of other disorders, but in analyses undertaken for this article in the Dunedin study, childhood maltreatment significantly predicted a more recurrent course of major depressive disorders, anxiety disorders, alcohol-dependence disorders, and drug-dependence disorders. In relation to treatment response, a meta-analysis of clinical trials treating depression showed that childhood maltreatment was associated with elevated risk of nonresponse or relapse during treatment (Nanni et al., 2012).

How good is the evidence and how strong is the connection? As usual, it depends on study methodology. Today, childhood violence exposure is a widely accepted cause of psychiatric disorder. However, this is a recent historical development. Thirty years ago, childhood maltreatment was not included in most etiological theories of mental disorder, in part because many forms of maltreatment were considered to be too rare to account for population prevalence rates of psychiatric conditions. For this reason longitudinal–epidemiological studies launched as late as the 1970s did not systematically inquire about violence exposure. As a result, much of our information linking childhood violence victimization to adult psychiatric disorder relies on unwell adults' retrospective reports of their victimization years in the past, a method known to introduce bias (Susser & Widom, 2012). The dangers of retrospective data are known: normal forgetting, revisionist recall, bias by respondents' knowledge of subsequent disease outcome, bias from respondents' cognitive dysfunction or altered mood, and telescoping of recalled events. Despite this reason for caution, persuasive studies with prospective measures of violence exposure, and studies of siblings discordant for violence, have tended to confirm that childhood violence exposure leads to poor mental health in adolescence and adulthood (Arseneault et al., 2010; Gilbert, Widom, et al., 2009; Kendler et al., 2000; Nelson et al., 2002). However, in general, retrospective victimization is more strongly associated with disorder than prospective victimization, a difference that is evident in within-study comparisons as well as in between-study comparisons (Gilbert, Widom, et al., 2009; Susser & Widom, 2012; but see Scott et al., 2012). As such, it is wise to be cautious when estimating how much of the psychiatric disease burden in the population could be reduced if all violence-exposed children were successfully treated. Finally, although violence victimization is a potent risk factor for developing psychiatric disorders, there are marked individual differences in response and many children who are victimized remain healthy (Cicchetti, 2013; Cicchetti & Rogosch, 2009).

Childhood violence exposure and neuropsychological health outcomes

Neuropsychological tests are sensitive indicators of integrity of the brain and its mental functions. An aggregate of an individual's neuropsychological abilities (the IQ) is a proven reliable predictor of life-long health, all-cause morbidity, late-life frailty, and early mortality (Deary, Whiteman, Starr, Whalley, & Fox, 2004; Gottfredson, 2004). Moreover, the IQ is the best predictor of life success outcomes that enhance midlife health: education, occupational attainment, and job performance (Schmidt & Hunter, 2004). A bird's-eye view of theory linking childhood stress to brain health includes a sequential chain in which early-life chronic stress disrupts the homeostasis of stress-biology systems (including inflammation and HPA-axis hormones), which in turn disrupts normal development of brain structures, which in turn produces observable deficits in stress-exposed individuals' tested learning, memory, and attention capacities (Danese & McEwen, 2012; McEwen, 2012; Sapolsky, 1996). All of these theoretical steps in the causal chain have been well worked out in animal stress research, particularly in rodent models (Millan et al., 2012; Shors, 2006; Teicher, Tomoda, & Andersen, 2006).

A handful of studies have compared maltreated children to comparison children and detected deficits in the omnibus IQ, as well as tests of memory, executive functions, attention, and concentration (reviewed in Wilson, Hansen, & Li, 2011). The hallmark longitudinal follow-up of 413 officially substantiated child maltreatment victims showed that as adults they scored on average 10 IQ points below matched controls (Perez & Widom, 1994). Chronicity of exposure is important; a study of 1,777 children registered with Child Protective Services reported that children victimized chronically across multiple years had lower IQs than children who were situationally maltreated (Jaffee & Maikovich-Fong, 2011). In the E-Risk Longitudinal Study of a nationally representative UK birth cohort of 2,232 children, physical maltreatment, frequent bullying victimization, and domestic violence exposure were each independently associated with a general neuropsychological deficit of 4 to 8 IQ points (Jaffee, Caspi, Moffitt, Polo-Tomás, & Taylor, 2007; Koenen, Moffitt, Caspi, Taylor, & Purcel, 2003). In analyses undertaken for this article

in the Dunedin longitudinal study, maltreated children scored on average 5 IQ points lower than cohort peers as adolescents, but when the same children were retested 25 years later the deficit had worsened to 8 points, and neuropsychological testing revealed that formerly maltreated children had deficits in working memory, visual–spatial perceptual reasoning, and verbal comprehension as late as age 38. Disrupted homeostasis of stress hormone and inflammatory systems is thought to alter the brain development necessary for healthy neuropsychological functions, suggesting the hypothesis that treatments able to reestablish homeostasis in these systems may enhance mental abilities.

Childhood violence exposure and neuroimaging outcomes

Neuroimaging measures allow inferences about the structural and/or functional integrity of the brain. Structural measures such as the size of specific brain regions and volume of grey and white matter are assessed with structural magnetic resonance imaging (MRI). In contrast, functional MRI (fMRI) relies on changes in the blood oxygenation level as a consequence of neuronal activation and thus measures neuronal activity indirectly and with a delay of several seconds but with a high spatial resolution. Participants in fMRI studies are typically administered tasks to measure brain activation. Positron emission tomography measures changes in the blood flow to reveal active brain regions. Diffusion tensor imaging ascertains integrity of white matter tracts connecting brain regions. A considerable number of neuroimaging studies using these technologies have investigated associations with child maltreatment. Because of challenges in undertaking neuroimaging of young children, most studies have examined adult patients with trauma-related psychiatric conditions (e.g., Andersen & Tomada, 2008; Weniger & Lange, 2008), or adults who retrospectively reported maltreatment (e.g., Cohen & Grieve., 2006; Dannlowski & Stuhrmann, 2012). Because of the difficulty of testing children with functional activation paradigms, most studies of children have reported only structural MRI measures. Two recent, excellent and comprehensive reviews have summarized and critiqued the neuroimaging literature on child violence exposure (Hart & Rubia 2012; McCrory, De Brito, & Viding, 2010), concluding that structural and functional findings have consistently appeared in the circuitry of the frontal and limbic regions of the brain, which include structures such as the hippocampus, amygdala, striatum, prefrontal cortex, orbitofrontal cortex, and anterior cingulate gyrus.

Certain notable patterns have emerged from the many imaging studies reported. The hippocampus has been a structure of special focus because animal models have shown that stress-induced high levels of glucocorticoids over prolonged periods of time can impede hippocampal development and impair memory. A meta-analysis of structural imaging studies concluded that hippocampal volume is smaller in adults reporting a childhood maltreatment history but not in maltreated children, prompting the hypothesis that childhood stress may cause abnormal hippocampal development that only becomes detectable in the mature brain (Woon & Hedges, 2008). A cautionary note has been raised by the finding that hippocampi were small in nontrauma-exposed monozygotic twins of PTSD patients, suggesting the possibility that inherited small hippocampal volume antedates trauma exposure and poses risk for PTSD (Gilbertson et al., 2006). The amygdala has also been a frequent subject of study, because it is involved in fear conditioning and negative emotionality, and research suggests stress can enlarge it (Davidson & McEwen, 2012). Although there are a few functional findings, a meta-analysis did not yield consistent structural differences in amygdala volume (Woon & Hedges, 2008). Another brain structure that has received much attention in studies of maltreatment is the prefrontal cortex, of interest because it matures late and may thus be especially vulnerable to early stress and because it is involved in emotion regulation. Structural abnormalities in this region have been reported for maltreated juveniles (Andersen & Tomada, 2008; De Bellis & Keshavan, 2002; Edmiston et al., 2011; Hanson et al., 2010), as have a few functional findings. This literature also contains scattered findings involving the cerebellum (De Bellis & Kuchibhatla 2006), white matter tracts (e.g., De Bellis & Keshavan, 2002), and other brain areas in relation to child maltreatment.

As a caution, the neuroimaging literature is far from addressing the question of causality, as it lacks equivalent measures in experimental animal models, lacks differential imaging findings among siblings discordant for childhood violence exposure, and also lacks prospective studies showing within-individual change in imaging measures from before to after violence exposure. In particular, sample sizes are generally far too small to attempt including statistical controls for the host of correlated factors known to be associated with childhood violence exposure and its consequent psychiatric conditions.

Interventions for Childhood Violence Exposure

If we presume that childhood violence exposure is common and that it can alter victims' stress biology, to eventually increase adult disease morbidity and mortality, the question arises, what might be done about this? Prominent questions concern prevention and reversibility. Can physical harm to body and brain be reduced by family programs that prevent childhood violence exposure? Can harm be reversed by individual psychosocial treatments that reverse the psychological sequelae of maltreatment? In this section we briefly note interventions that have been scientifically tested and declared promising for preventing or reversing outcomes of psychological harm. Our suggestion is that stress-biology measures ought to be added to trials of interventions like these, to test whether they might also prevent or reverse physical harm to body and brain.

Interventions for children who have experienced violence-related trauma

Several reviews have evaluated psychological interventions for posttraumatic reactions in children, including but not lim-

ited to violence-induced trauma (Cohen, Berliner, & Mannarino, 2010; MacMillan et al., 2009; Perrin, Smith, & Yule, 2000; Robjant & Fazel, 2010; Rodenburg, Benjamin, de Roos, Meijer, & Stams, 2009; Rolfsnes & Idsoe, 2011; Stallard, 2006). These posttrauma reactions are not constrained to PTSD symptoms but include a host of emotional and behavioral sequelae (Carrion & Kletter, 2012). The evidence base has been criticized for the usual methodological shortcomings known to bedevil treatment research (Mikton & Butchart, 2009). Nevertheless, meta-analyses and systematic reviews of randomized clinical trials identify cognitive behavior therapy (CBT) approaches as effective, specifically trauma-focused CBT (TF-CBT; Kowalik, Weller, Venter, & Drachman, 2011; Rolfsnes & Idsoe, 2011; Stallard, 2006; Wethington et al., 2008). TF-CBT combines parent and child skills-based components within a framework of a trauma model. These components include psychoeducation (information about trauma and trauma reactions), parenting skills (i.e., behavior management skills), relaxation skills (to manage physiological reactions to trauma), affective modulation skills (to manage affective responses to trauma), cognitive coping skills (to explore and discuss connections between thoughts, feelings, and behaviors), trauma narrative and processing (to correct cognitive distortions related to trauma, to reorganize memories), in vivo mastery of trauma reminders (to overcome generalized fear related to trauma), and safety planning for the future. These components are taught in parallel parent and child sessions as well as in conjoint child–parent sessions. The number of sessions varies between 12 and 16. TF-CBT appears to reduce PTSD-related symptoms and general problem behaviors. Recent studies on TF-CBT not yet included in meta-analyses or reviews support the previous conclusions but also add new insights: a trauma narrative is not necessarily needed (Deblinger, Mannarino, Cohen, Runyon, & Steer, 2011; Salloum & Overstreet, 2012), and TF-CBT also works with children of different ages from preschool to high school (Nixon, Sterk, & Pearce, 2012; Scheeringa, Zeanah, Drell, & Larrieu, 2011). Other treatments for violence-exposed children are under initial evaluation, for example, Eye Movement Desensitization and Reprocessing (Rodenburg et al., 2009) and Narrative Exposure Therapy for Children and Adolescents (Robjant & Fazel, 2010).

Interventions for families to reduce children's violence exposure

In addition to interventions that directly treat child victims, there are a number of other psychosocial interventions available to enhance children's psychosocial adjustment in the context of violence exposure, by working with parents, or with parents and children together. These include intervention programs intended to reduce violence exposure and prevent child maltreatment by providing education and supervision to parents of very young children. Nurse-Family Partnership and Early Start are examples of two home-visiting programs with this aim that have been evaluated as effective (MacMillan et al., 2009). Also among the leaders are interventions to reduce risk of child maltreatment by improving parenting, such as Project Support (Jouriles et al., 2010) and Pathways Triple P (Prinz, Sanders, Shapiro, Whitaker, & Lutzker, 2009; Wiggins, Sofronoff, & Sanders, 2009), and treatments aiming to strengthen infant–parent attachment in families at risk for maltreatment (Cicchetti, Rogosch, & Toth, 2006). For example, Project Support is a family intervention to provide instrumental and emotional support to mothers and teach them child-management skills. It was originally developed to reduce conduct problems in children from families using domestic violence shelters. As another example, parent–child interaction therapy (Chaffin et al., 2004; Chaffin, Funderburk, Bard, Valle, & Gurwitch, 2011) works with both the violence-exposed child and the (nonoffending) parent, aiming to improve parental skills and motivation and enhance parent–child interactions. This is accomplished by direct coaching of parents and direct practice of skills in dyadic parent–child sessions. Preliminary evidence points to the significance of an additional module (six motivational sessions) when working with families in child welfare for child maltreatment.

The Triple P system was evaluated using a cluster design to randomize eighteen counties in South Carolina to either Triple P's social learning-based program or to a care-as-usual control condition. Following intervention, the Triple P counties observed lower rates of found cases of child maltreatment, hospitalizations and injuries due to maltreatment, and out-of-home placements due to maltreatment (Prinz et al., 2009). This was the first time a public health parenting intervention has shown positive population-level effects on child maltreatment in a randomized design with county as the unit of random assignment. Both experimental and clinical research have demonstrated that structured parenting programs are among the most efficacious interventions available to promote the mental health and well-being of children, particularly in families who are at risk of maltreatment (Mihalopoulos et al., 2011; National Research Council and Institute of Medicine, 2009).

Interventions for couples to reduce children's violence exposure

Children are psychologically harmed by exposure to intimate partner violence between adults in their lives, as well as by conflict between their parents (Buehler et al., 1997; Cummings & Davies, 2010). Moreover, research has further shown that intimate partner violence among adults coincides with physical maltreatment of children in the home at rates far beyond chance (Osofsky, 2003; Øverlien, 2010; Taylor, Guterman, Lee, & Rathouz, 2009). Given these two findings, interventions effective at strengthening couple relationships and reducing couple conflict may also have the unexpected benefit of reducing childhood violence exposure and psychological harm. Treating parents makes sense, because the younger a child is, the more likely that victimization is perpetrated by parents (Finkelhor, 1997).

Over the last 30 years, approximately 100 clinical trials have demonstrated the efficacy and effectiveness of cognitive behavioral couple interventions to reduce conflict and prevent relationship distress and divorce (Hahlweg, Baucom, Grawe-Gerber, & Snyder, 2010). Although couple programs seem to be effective in reducing conflict, evidence is lacking that they are effective after a couple has become physically violent, and thus most programs aim at prevention early in relationships. For example, skills-based couples' programs, such as Premarital Relationship Enhancement Program (Markman, Floyd, Stanley, & Stoorasli, 1988; Markman, Renick, Floyd, Stanley & Clements, 1993), Premarital Preparation—A Couples' Learning Program (Hahlweg, Markman, Thurmaier, Engl, & Eckert, 1998; Thurmaier, Engl, & Hahlweg, 1999), or Freiburger Stress Preventions Program (Bodenmann, 2004) have demonstrated effectiveness. Moreover, the Premarital Relationship Enhancement Program and the Premarital Preparation—A Couples' Learning Program couples have shown significant, improved outcomes after 5-year follow-up. Given divorce rates of about 50% across countries, and knowledge that couple conflict and separation/divorce are associated with increased risk for children's violence victimization, early interventions to enhance couples' relationship satisfaction may be an important strategy to reduce child harm (Hahlweg et al., 2010).

Bringing Stress-Biology Research and Clinical Intervention Science Together

As implied by the title, this article invites intervention scientists and stress-biology researchers to collaborate in adding stress-biology measures to randomized clinical trials of interventions intended to reduce effects of violence exposure on children. Doing so would fill two scientific gaps.

The first gap concerns a potential benefit for treatment trials: objective measures of important treatment outcome. Most psychosocial intervention trials collect only a narrow set of outcome data, limiting themselves to such targets as children's PTSD symptoms, aggression, emotional problems, school achievement, or related psychosocial measures. Such assessments entail methodological challenges, such as the need for objective raters who are blind to treatment. In addition, behavior ratings can be insensitive as change indicators, and agreement between adult reporters is often weak. In contrast, before- and after-treatment measures, such as fMRI, inflammation, cortisol reactivity, or neuropsychological tests of attentional vigilance, are inherently objective and might prove sensitive to treatment effects. In any case, it is fundamentally important to find out if psychosocial interventions actually can shift stress-biology indicators.

The second scientific gap concerns a potential benefit for stress-biology research: new answers to the thorny question of causation. Our review above revealed that, although there is much excitement about stress biomarker research, evidence of simple association in human children is very sparse, and therefore, testing for stress-biomarker abnormalities in samples recruited for violence-exposure treatment trials would add badly needed basic descriptive data. We further noted that ethical and logistical challenges have made it difficult to test whether psychosocial stressors truly cause alterations in body and brain measures in human children; therefore, the evidence base for causation remains mostly observational. By themselves, intervention studies that generate pre- versus posttreatment or treatment versus control differences in children's inflammation, telomere erosion, or executive function by treating violence exposure would not uncontrovertibly prove that violence exposure damages health (just as reducing fever with aspirin does not prove that aspirin deficiency causes fever). However, intervention trials with random assignment could add now-missing experimental evidence to augment causal inference. Some challenges to, and the considerable benefits of, integrating biological measurements into intervention studies have been discussed previously (Cicchetti & Gunnar, 2008). A very small number of violence-related treatment trials have already incorporated stress-biology measures, and we introduce examples of them below. The next section also makes recommendations for research designs.

Treatment trials incorporating stress-biology measures

At least two reports of successful small-scale clinical trials of interventions for maltreated preschool children have reported that, on average, treatment normalized levels of the stress hormone cortisol (Cicchetti, Rogosch Toth, & Sturge-Apple, 2011; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Fisher, Gunnar, Chamberlain, & Reid, 2000). In addition, one neuroimaging study compared psychoeducational and cognitive behavioral group treatment versus usual treatment for maltreated children with PTSD. Treatment induced changes in the activation of the anterior cingulate gyrus and insula that were detected by fMRI during a Stroop interference task. The changes were interpreted as reflecting increased selective attention and lower emotional arousal after treatment (Thomaes & Dorrepaal, 2012). There is also evidence from neuroimaging studies in adults that treatment of PTSD induces changes in brain function on fMRI (e.g., Felmingham et al., 2007). Finally, a 3-month meditation intervention has been reported to be associated with higher telomerase activity, which could lengthen telomeres (Jacobs et al., 2011).

In addition to this small set of treatment studies, there are other intriguing indications that interventions of varying types might be able to reverse the effects of violence exposure on stress biology (Davidson & McEwen, 2012). With respect to telomere erosion, evidence from a genetically modified mouse model showed that pharmacological activation of telomerase reversed indicators of mouse aging (Jaskelioff et al., 2011). In human studies, healthy diet and high social support attenuated the relationship between short telomere length and presence of heart disease (Diaz & Samani, 2010), and reduction of psychological distress was associated with increased

telomerase activity (Daubenmier et al., 2012). With respect to epigenetic changes, epigenetic disruption is potentially reversible and thus is a realistic target for pharmacological and/or behavioral interventions. Numerous agents have been discovered to alter DNA methylation and histone modifications, and several are being tested in ongoing clinical trials. So-called epigenetic drugs are being developed for a range of disorders, most notably cancer (Kaiser, 2010), and many currently used psychiatric medications have effects on the epigenome (Boks et al., 2012). One potential obstacle is that drugs that target the epigenome globally can have unexpected (and potentially pathogenic) effects on the transcription of genes that are not the desired target. With respect to chronic inflammation levels, several effective treatments could reduce them. In an initial study of rats subjected to maternal-separation stress, the expected working-memory deficit was prevented by prophylactic administration of nonsteroidal anti-inflammatory medication (Brenhouse & Andersen, 2011). Several classes of medications have anti-inflammatory effects, including the frequently used nonsteroidal anti-inflammatory drugs. Exogenous glucocorticoid hormones are also potent steroidal anti-inflammatory drugs, and some antidepressant medications also have anti-inflammatory effects (Miller, Maletic, & Raison, 2009). Anti-inflammatory effects have been claimed for dietary omega-3 polyunsaturated fatty acids, physical exercise, acupuncture, and meditation (Handschin & Speigleman, 2008; Kiecolt-Glaser et al., 2010; Oke & Tracey, 2009; Zhang & Spite, 2012). Finally, one study suggested that engagement in cognitively based compassion training is associated with progressive reduction in salivary inflammation biomarkers among adolescents in foster care (Pace et al., 2012). These potential reversibility effects remain speculative until replicated, and long-term follow-up will be required to ascertain whether these changes are maintained and translate into improved health outcomes (Miller & Cohen, 2001).

Recommendations for research designs

Unforeseen methodological challenges must be solved along the way in the course of any new research endeavor. Nevertheless, we offer some starting recommendations for researchers who wish to add stress-biology measures to randomized clinical trials of interventions intended to reduce effects of violence exposure on children.

First, there are logistic considerations. Allow plenty of time and face-to-face contact for intervention scientists and stress biologists to build an effective collaborative team. These two professions conduct science under markedly different sets of assumptions and can easily misunderstand each other. Anticipate that the usual challenges in relation to ethical review, participant recruitment, retention, and informed consent may be magnified by the addition of biomarker data collection. We have found that families and children enjoy biomarker data collection, even blood phlebotomy, and they generally like the notion that they are engaged in "real science!" (However, it can be difficult to persuade cautious ethical review panels of this in advance.) Plan to provide extra confidentiality protection for biomarker data. Engage the therapeutic staff by insuring they understand the project fully and have a chance to give real input to the design. Learn about the logistics of biomarker data-collection. For example, for "wet" measures, there are three separate stages: initial tissue collection, tissue storage, and later assay. Tissue collection is often enticingly inexpensive, whereas storage space and assays often entail larger, hidden costs. Consider the pros and cons of giving families feedback on biomarker status; they may expect a lab report, as is typical after a doctor visit, but research measures are different from clinical tests in fundamental ways. Establish in advance what, if any, level of biomarker elevation would be sufficiently alarming to warrant a medical referral. For example, neuroimaging has the potential to detect so-called "incidental findings" of neurological disease.

Second, there are design recommendations. Select a treatment protocol that is a good bet, one that already has strong evidence of behavior-change effectiveness, such as TF-CBT. Do not allow the addition of biomarker measurement to alter or disrupt the treatment protocol; for example, do not have the CBT therapists draw blood samples or give neuropsychological tests. Select a stress biomarker outcome measure that is likewise a good bet, one that has strong a priori evidence that it is altered by psychosocial stress, and one that is capable of changing on a time scale that fits the intervention. Common sense recommends starting with biomarkers that are inexpensive, noninvasive, repeatable, and low tech. Learn about the distribution of the selected biomarker across age and sex, and recruit a sample that can mitigate or accommodate any such heterogeneity. Recruit a sample of patients to be randomly assigned to treatment versus control who have well-characterized and documented violence-exposure histories. One element that requires thought (and more informative data) is whether to enroll in intervention research only the subset of violence-exposed young people who exhibit consequent mental health difficulties, as opposed to any violence-exposed young people. Administer psychosocial measurements and biomarker measurements at the same time. Take a baseline biomarker measure before randomization, to avoid contaminating baseline with the patients' knowledge of their group assignment. Repeat biomarker measures frequently, at least at baseline, start, midpoint, and discharge, to allow for ascertainment of trajectories of change across three or more measurement points. Use a care-as-usual control condition instead of wait-list controls who are eventually given the treatment, as care-as-usual controls enable a long-term follow-up comparison. Discuss the potential reputational costs of null findings to both intervention scientists and stress biologists and agree in advance how any null findings will be reported.

The need for guiding theory

Many fundamental questions of a theoretical nature need to be answered to explain how, and how much, childhood

victimization contributes to health problems across the life span. Although a thorough treatment of theory is beyond the scope of this article, we point to two key areas in need of theory development (Miller, Chen, & Cole, 2009). One key theoretical question has to do with the nature of violence exposure itself. Are all forms of victimization (bullying, maltreatment, domestic violence) expected to have the same consequences for health? If so, theory must specify a psychobiological common denominator these exposures share, perhaps a generic cognitive appraisal of threat or enhanced perceptual sensitivity to threat-related cues. If not, then perhaps what is especially damaging for children's biological systems is the profound violation of trust that follows parental maltreatment, the social rejection inherent in chronic bullying, or persistent fears about safety that accompany exposure to adult domestic violence. However, it would be necessary to explain what mechanisms allow different exposures to produce similar (or different) physiological effects. This issue becomes even more important when asking whether or not mechanisms following violence exposure differ from those arising from other adversities, such as poverty or parental loss.

Another key theoretical question has to do with mind–body mechanisms. How does violence get under the skin, at the level of tissues and organs, to push forward the pathogenesis of disease? Thanks to many years of research, it is known, in some detail, how threats that emanate in the social world activate the neural circuitry regulating the autonomic nervous system and the HPA axis and how the outflow of these two systems affects cardiac, vascular, immune, and metabolic systems. A much thornier issue arises when we consider the temporal features of the connection between childhood victimization and adult health. Most mechanistic knowledge of stress pertains to its immediate biological consequences. There is also some understanding, from work on PTSD, of how stress systems look in situations where the precipitating stimulus has dissipated but a subjective sense of threat lingers. However, the period of incubation between child maltreatment and coronary heart disease is approximately 40–70 years. To be successful, research and theory will need to bridge that temporal gap in a manner that is psychologically and biologically plausible. Does childhood violence exposure set young people on pathways in which each adversity begets further adversities, and the cumulative effects of stress exposures sustain risk for later health problems, as proposed in life-course theory (Pollitt, Rose, & Kaufman, 2005)? Is early-life stress programmed into physiology during a sensitive period of child development, in a permanent, irreversible manner, as argued in the "fetal origins hypothesis" (Barker, 1992)? These and other "big" questions need theoretical and empirical attention if we are to argue that the population's burden of disease could be reduced if all violence-exposed children were successfully treated.

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