Multilevel developmental approaches to understanding the effects of child maltreatment: Recent advances and future challenges

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Abstract

Recent research in the field of child maltreatment has begun to shed new light on the emergence of health problems in children by emphasizing the responsiveness of developmental processes to children's environmental and biological contexts. Here, I highlight recent trends in the field with an emphasis on the effects of early life stress across multiple levels of developmental domains.

Developmental approaches to understanding the effects of child maltreatment have enhanced our understanding of this serious public health problem. Research on child abuse has also served as a model for exploring the ways in which the social environment can influence the course of an individual's development. Over the past decade, researchers in the field have ushered in a sophisticated emphasis on developmental process that has emphasized more precise predictors of certain behavioral problems and helped clinicians focus on the various forms of symptomatology that may be expressed at different stages of the life course. Perhaps most important, recent research in the field has begun to forge connections between sequelae of child abuse for which linkages were not well understood: these most recent advances highlight the importance of combining multiple levels of analysis to advance knowledge of the interplay between biology and social experience.

In the past, studies on the effects of child abuse largely comprised correlational methods and behavioral observations. This formative research played an important role not only in demonstrating the degree to which maltreatment had a lasting impact on child development but also in beginning to map the wide range of domains affected by child abuse. More recent emphases in developmental psychopathology now focus on elucidating the specific developmental processes affected by child abuse that may lead to maladaptive behavior. This approach mirrors significant changes in the way many developmentalists now conceptualize psychopathology. For example, cutting-edge researchers in the field of child maltreatment now tend to de-emphasize distinctions between what would have previously been construed as mental versus physical disorders. There is also a renewed emphasis among researchers on the interactions between persons and their environments. Below, I illustrate how these types of developmentally informed approaches are testing novel hypotheses about the biological

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conduits across levels of analysis, such as the biology of the individual and that individual's social environment.

The Importance of Developmental Processes in Understanding Child Maltreatment

Researchers in the field are now attempting to understand the associations between brain–behavior relationships and how perturbations in these links leads to maladaptive behaviors. However, although researchers continue to study issues such as dysregulation of mood, they increasingly construe their topics more broadly than diagnostic categories such as "anxiety" or "depression." This emphasis on broader processes, such as emotion regulatory behaviors or emotion–cognition interactions, reflects a major trend in the field to focus on maladaptive processes of change. One reason for this change in emphasis is that it is now apparent that development is best characterized by probabilistic pathways rather than by linear causality. There has been no evidence that early adversity leads ineluctably to any one form of pathology. Rather, social and biological challenges initiate processes that may be more likely to lead to pathology if that maladaptive pathway continues to be supported. In this regard, developmental psychopathologists are attempting to frame questions differently. In the past, researchers in the field may have posed questions such as "what psychiatric diagnoses are maltreated children likely to develop?" However, current research questions may be framed more about what is it about a child's early experience places that child on one developmental pathway versus another. We might ask, "what constrains the individual's ability to alter these pathways," or "during which developmental time periods or circumstances might opportunities for change be greatest?"

Another recent trend has been for researchers to consider "biomarkers" associated with various forms of pathology. The use of biomarkers in psychopathology research has been an attempt to reconcile the extant diagnostic taxonomies of mental health problems with knowledge about underlying biological systems. These biomarker approaches harness technological advances that allow scientists to assay aspects of brain function, genetic and epigenetic markers, and neuropeptide actions on physiology and social behavior (as a few examples). In many ways, these biomarker approaches are beginning to bridge levels of analysis by linking, for example, behavioral regulation with a specific biological substrate such as a hormonal marker. The laudable goal of such approaches is to highlight either key pathogenic features or index responsiveness to treatment.

At present, however, no individual biomarker has yet emerged as a discrete, causal entity that has been shown to account for a sufficient proportion of variance in normative behavior or psychopathology. Nor has any single biomarker been shown to be sensitive or specific to a behavioral disorder. It is in this regard that the developmental psychopathology approach holds promise. Developmental approaches challenge researchers and clinicians to move beyond identifying isolated biomarkers. Instead, the goal has become one of articulating a mechanistic account of behavioral change over time. In isolation, markers (whether of functional brain activities, hormonal assays, interpersonal behaviors, genetic markers, or even detailed interpersonal observations or cognitive test scores) are merely *correlates* of

behavior problems. In contrast, developmental approaches seek to understand the *processes* by which these components have emerged and become integrated across biological, psychological, and social contexts over the individual's life course.

Understanding Child Maltreatment From a Multilevel Perspective

It has been well documented that child maltreatment predicts unfavorable mental health outcomes as well as poor responsiveness to mental health treatment (Nanni, Uher, & Danese, 2012). Developmental cognitive neuroscience approaches have been a promising area of research. Studies of attention, executive functioning, and the neuroscience underlying emotion regulation serve to highlight connections between biological systems of domains of behavioral development relevant to the problems experienced by maltreated children. There is developmental evidence that an important facet of risk for maltreated children involves altered neural processing of social stimuli, which broadly impairs their regulatory processes. This research both informs our understanding of the emergence of health problems in children and adults and sheds light on understanding principles of normative development. In this manner, we increase understanding of how it is that children's social experiences subsequently shape their thoughts, feelings, biology, and behavior. This approach has been applied to understanding both internalizing and externalizing types of problem behaviors.

Maltreated children are at risk for developing externalizing behavioral problems that are characterized by reactive aggression. A recent study sought to understand how processes across a range of levels of analysis might underlie such as association by linking parent's interactions with their children, child behavior, and physiology (Shackman & Pollak, 2014). Maltreated children in this study exhibited greater negative emotions when confronted by an interpersonal stressor. This higher level of negative affect was subsequently associated with more aggressive behavior toward their peers during the same laboratory session. This relationship between emotion and behavior was mediated by children's allocation of attention to angry faces as measured by brain event-related potentials (Shackman & Pollak, 2014). These data are consistent with the view that physical maltreatment leads to patterns of attention to emotional cues that serve to undermine children's regulation of both negative affect and aggression. Such processes likely place maltreated children at increased risk for the development and maintenance of externalizing behavior disorders as well as issues with social competence.

However, as noted earlier, child maltreatment is not solely associated with any one kind of behavioral problem. Besides externalizing disorders, some children who experienced early maltreatment are at heightened risk for mood disorders (though not all individuals who experience maltreatment develop depression or anxiety). One clue about the ways in which the early experience of maltreatment may lead to depression may also be found in observations of these children's attention bias for emotional cues (Pollak, Cicchetti, Hornung, & Reed, 2000). A recent study reported that maltreated children showed attentional biases to depression-relevant cues in certain conditions: first, after they had experienced a sad emotional state, and second, if they tended to have high levels of trait (or stable) cognitive patterns of rumination (Romens & Pollak, 2012). These cognitive patterns may identify which maltreated children are most likely to exhibit biased attention for sad

cues and be at heightened risk for depression. The phenomenon of rumination (passively and repetitively dwelling on and questioning negative feelings in response to distress) is a known risk factor for the development of psychopathology, especially depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Recent research in a community sample of 9- to 14-year-olds showed it was common for youth to focus on an interpersonal stressor for a brief period of time after experiencing it; thus, some rumination appears to be normal, even useful, after an interpersonal challenge. Yet about 10% of the youth continued to ruminate for a long period of time after the stressor ended (Hilt & Pollak, 2013). Although most participants were able to disengage from their ruminative thinking, those individuals who continued to ruminate showed attentional biases away from positive stimuli (Hilt & Pollak, 2013). Thus, these children actively avoided environmental cues that might have helped them regain a positive mood state and recover from the stressful event. Similarly, rumination in adolescents is associated with difficulty inhibiting negative information when switching from processing of negative to positive information (Hilt, Leitzke, & Pollak, 2014). The ruminative process is difficult to stop once it has begun. However, relatively straightforward interventions, such as brief periods of distraction or mindfulness, appear to be helpful in getting children out of ruminative states (Hilt & Pollak, 2012) and thus may be useful components of interventions for maltreated children.

Concerns for maltreated children are not only internalizing and externalizing psychopathology but also subclinical problems that decrease children's quality of life, such as emotion regulatory difficulties, problems with social competence, factors that interfere with optimal scholastic/school performance, as well as components that affect physical health. A focus on these broader issues reflects the increasingly broad focus on the whole child, rather than psychiatric diagnoses in particular, within developmental psychopathology. Children with healthy social information processing abilities tend to be more skilled in initiating and maintaining positive relationships, rely on behaviors that are more prosocial, are more socially accepted by peers, and have more satisfactory friendships (Burgess, Wojslawowicz, Rubin, Rose Krasnor, & Booth LaForce, 2006; Fraser et al., 2005; Lemerise & Arsenio, 2000; Quiggle, Garber, Panak, & Dodge, 1992).

An unintended effect of focusing on processes versus discrete disorders has been a blurring of traditional disciplinary boundaries. Methods and concepts from fields such as psychiatry, psychology, and pediatrics have come into greater contact with those from internal medicine, immunology, endocrinology, epidemiology/population health, and genetics. For example, research on children's responses to trauma and stress still includes issues such as anxious and aggressive symptoms, but also now includes foci such as sleep, physical growth and bone density, allergy/asthma, infectious disease, and cancer vulnerability (Danese, 2014; Kiecolt-Glaser et al., 2011; Miller, Chen, & Parker, 2011; Shirtcliff, Coe, & Pollak, 2009; Shonkoff, Garner, & the Committee on Psychosocial, Developmental, and Behavioral Pediatrics, 2012; Taylor, Way, & Seeman, 2011). Several large cross-sectional studies have reported relations between child maltreatment and adult health outcomes such as heart disease, cancer, and chronic diseases of the lungs and liver (Gilbert et al., 2009). In other words, mental health problems are being understood and linked with indicators of physical health, eroding the distinction between mental and physical ailments.

Learning Processes as a Bridge Between Levels of Analysis

Learning theory provides an account of the emergence of behavior that has a deep history in psychological science (Thorndike, 1911). Such a perspective helps explain how individuals optimize their control of, or adjustment to, an environment. The history of psychology is rich with examples of the immediacy and power of basic learning processes. For example, we need only become ill once to create a strong food aversion, and changes in the frequency of reward schedules can quickly change behavior (Gallistel & Gibbon, 2000).

To use learning successfully in complex social situations, individuals are confronted with a difficult task: they must derive efficient representations of the environment from sensory inputs, and use these to generalize past experience to new situations. Humans and other animals seem to solve these types of problems efficiently through a combination of reinforcement learning and hierarchical sensory processing systems (Schultz, Dayan, & Montague, 1997). Therefore it is possible that the social information processing difficulties that have been observed in maltreated children could reflect developmental variations in basic associative learning.

Associative learning is when one event or stimulus becomes linked to another event or stimulus through an individual's experience. Such processes can be adaptive when they facilitate the child's accurate prediction of future events on the basis of relevant cues (Gottfried, O'Doherty, & Dolan, 2003; Wasserman & Miller, 1997). When learning proceeds adaptively, it facilitates useful behavioral responses and coping strategies for children. As learning becomes more elaborated, children are able to learn both simple associations and also relationships between stimuli, enabling the formation of general rules or categories that can help guide children through a variety of social experiences (Call, 2001). One component of associative learning, reward processing, provides a useful window into understanding the multiple levels of impact that child abuse can have on social development.

Rodent studies provide compelling evidence that learning theories can uncover rich information about the neurobiology of socioemotional behavior. For example, experimental disruption of reward circuitry in the brain prevents mice pups from emitting vocalizations when removed from their mothers; such a disturbance interferes with brain reward systems and also prevents mice from showing a preference for their own mothers (Moles, Kieffer, & D'Amato, 2004). This association also works in the opposite direction: when attachment to the parent is disrupted, other aspects of the animals' reward systems are also affected. To illustrate this point, animals with disrupted attachments to their parents also have abnormal responses to novelty, altered appetitive conditioning, and unusually high sensitivity to dopamine antagonists and reactivity to other drug administrations (for a review, see Bakermans-Kranenburg & van IJzendoorn, 2011; Matthews & Robbins, 2003).

A rich body of evidence, across a variety of methods and levels of analyses, indicates that aspects of associative learning can be compromised or promoted by environmental experiences. These include studies that manipulated the rearing environments of monkeys (Capitanio, 1985; Mason & Capitanio, 1988; Mason & Kenney, 1974). Seminal experiments by Papoušek and Papoušek (1975) found that exposing infants to response-contingent

stimulation (as signaled by multicolored lights) affected their learning and the infant's emotional behavior. Conversely, noncontingent stimulation impaired infant learning (Bigelow & DeCoste, 2003). All of these results suggest that environmental experiences can powerfully shape these learning systems, which would have major implications for behavior.

There are many ways in which an abusive family environment might influence a child's associative learning processes. Although studies of abusive parents have lacked a high level of precision, findings have been surprisingly consistent. Physically abusive parents tend to be some combination of impulsive, emotionally volatile, and inconsistent in their parenting, and less verbal in discussing/explaining emotional states with their children (Bousha & Twentyman, 1984; Lyons-Ruth & Block, 1996; Oldershaw, Walters, & Hall, 1986; Pianta, Egeland, & Erickson, 1989; Rohrbeck & Twentyman, 1986; Shackman et al., 2010; Shipman et al., 2007; Timmons & Margolin, 2015). In these ways, children who have suffered from physical abuse are exposed to inconsistent or poorly conveyed emotional signals in their environments.

The adults who ought to be responsible for these children's care tend to convey nonnormative emotional displays. Yet these social interactions with primary caregivers are the primary basis upon which these children begin to learn about their social environment. All of these experiences may create a challenging learning environment, making it especially difficult for children to understand the associations between their behavior and later outcomes. Such conditions likely also direct children to learn and base their behavior based upon aberrant outcomes, such as physical violence, that are not typical of most parent–child relationships. For this reason, greater understanding of the brain regions associated with learning reward or punishment is likely to help account for the effects of the environment on these children's interpersonal behavior.

Development of Attentional Systems Underlying Learning That May Be Affected by Stress

Children who have been physically abused become adept at recognizing cues of anger and hostility (Cicchetti & Curtis, 2005; Curtis & Cicchetti, 2011; Pollak, Vardi, Putzer Behner, & Curtin, 2005; Shackman, Shackman, & Pollak, 2007; Shackman et al., 2014). These patterns reflect ways in which children learn to direct their attention to salient and meaningful information in the environment. This type of attention to threat cues in the environment subsequently affects the way children come to construe their social worlds. As an illustration, one study found that 5-year-old abused children tended to believe that almost any kind of interpersonal situation could result in an adult becoming angry; in contrast, most nonabused children see anger as likely only in particular interpersonal circumstances (Perlman, Kalish, & Pollak, 2008).

These types of data have raised new questions about how probabilistic information about other people's behaviors becomes instantiated in children's thinking. Given that children have a limited processing capacity and that there are limitless aspects of the world that can be attended to at any given moment, it may be the case that abused children prioritize negative social cues at the expense of positive cues. Consistent with this view, on a

probabilistic reward task, most children respond quickly as their chances of winning a reward increase. In contrast, maltreated children fail to show sensitivity to important environmental cues, such as changing rewards (Guyer et al., 2006; Mueller et al., 2012; Weller & Fisher, 2012). Reports of primate behavior also suggest that maltreated monkeys display less interest in rewards relative to control monkeys (Pryce, Dettling, Spengler, Schnell, & Feldon, 2004). A few candidate brain systems have emerged as potentially underlying these phenomena and provide clues about the development of psychopathology.

Development of Neural Systems Underlying Learning That May Be Affected by Stress

Potential brain circuits that might be affected by child maltreatment include the prefrontal cortex (PFC, a likely candidate because of its protracted period of postnatal development, as well as ties to behavioral regulation abilities such as impulse control and executive functions), the amygdala (because of ties to emotional regulation), and the basal ganglia (BG) and orbitofrontal cortex (OFC), which together seem to represent the outcomes of situations that the organism has experienced (for a review, see McCrory, De Brito, & Viding, 2012).

Much current research activity has been focused on the role of maltreatment on children's cognitive abilities, specifically executive functioning dependent on the PFC. Children reared in deprived environments, such as institutions for the care of orphaned or abandoned children, are at increased risk for attention and behavior regulation difficulties often associated with development of the PFC. Behavioral measures of sustained attention indicate that these children have difficulty with attentional functioning, and event-related potentials findings have revealed differences in inhibitory control and error monitoring, as postinstitutionalized children had smaller N2 amplitudes on a go/nogo task as well as smaller error-related negativity on a flanker task (Loman et al., 2013). This pattern of results raises questions regarding the nature of attention difficulties for these children. The behavioral errors likely reflect difficulties in overall sustained attention, whereas the event-related potential results are consistent with deficits in inhibitory control and error monitoring. Therefore, further research is needed to clarify the nature of these effects.

The anterior cingulate cortex (ACC) is an area of the frontal cortex implicated in associative learning. Lower neuronal integrity and smaller volumes in the ACC have been reported in children who have suffered physical abuse compared to nonmaltreated children (Carrion, Weems, Richert, Hoffman, & Reiss, 2010; De Bellis, Keshavan, Spencer, & Hall, 2000; Thomaes et al., 2010). Hanson et al. (2012) found that children who experienced high levels of early life stress had smaller volumes in the ACC and also more errors during an executive functioning task. In that study, individual differences in ACC volumes accounted for the association between levels of early life stress and the number of errors children made during the task. Research in nonhuman animals has also noted structural differences in the ACC, with lower dendritic branching in this area in rodents exposed to early stress (Gos, Bock, Poeggel, & Braun, 2008; Murmu et al., 2006). Functional brain imaging has also revealed lower brain activity in the ACC during a cognitive control task in adolescents who suffered

abuse (Mueller et al., 2010). Similarly, resting-state functional connectivity points to effects of child maltreatment in the circuit level dynamics of the ACC related to abuse (Herringa et al., 2013). Computational models, single-unit recording in nonhuman animals, studies of human patients with brain damage, and basic cognitive neuroscience studies in typically developing humans all cohere in suggesting that the ACC plays a central role in how organisms make predictions and improve those predictions by processing prediction errors (Botvinick, Cohen, & Carter, 2004; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Schultz & Dickinson, 2000). Prediction errors are engines of learning because detecting differences in outcomes guides subsequent actions. Taken together, these findings are consistent with the possibility that children who have suffered physical abuse experience problems related to associative learning processes. Such processes may lead to a cascade of developmental challenges because they are a major component of adaptive social learning. In this manner, learning difficulties may undermine children's attempts to develop effective strategies to cope with changing environmental contingencies.

The BG is a diverse network of subcortical structures that work in concert to orchestrate and execute planned, motivated behaviors that require integration of movement, thinking, and feeling (Haber, 2003). The OFC is a rapidly flexible associative-learning area that is crucial for signaling outcome expectancies such as reward/punishment and the regulation of flexible behavior (Kringelbach & Rolls, 2004). Current thinking is that the BG guides learning based on assessments of the probability of a positive outcome, while the OFC represents gain–loss information, and together, these systems provide a robust way for the organism to learn from and adapt to the environment (Frank & Claus, 2006). As expected, impairments in these systems are associated with poor learning from environmental cues. It is especially interesting that OFC neurons do not stop firing in response to the reward after learning, suggesting that these neurons support predictions on the basis of afferent input and anticipation prior to other emotion-processing regions such as the amygdala (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009). Consistent with this view, damage to the OFC causes deficits in reversal learning, reduces the speed of reward learning, and is activated in humans during processes such as regret and counterfactual reasoning (Honey, Kotter, Breakspear, & Sporns, 2007; Murray, Wise, & Rhodes, 2011; Passingham, Stephan, & Kotter, 2002). Common to these examples is the need to signal, in real time, information about outcomes predicted by circumstances in the environment. Some emerging evidence suggests functional changes in the OFC and BG during reward processing in adolescents. This further suggests that these systems are a source of developmental changes in social behavior (Galvan, 2006).

There is also some evidence that functioning of these systems may account, in part, for how child maltreatment confers pervasive lifetime risks for children. Many kinds of early life stressors (maternal separation, social defeat, chronic stress exposure, and abuse) appear to alter neurotransmitters and receptors in the BG that are subsequently associated with impairments in learning (Desteno & Schmauss, 2009). In this regard, child maltreatment has been associated with lower BG recruitment during a reward task (Mehta et al., 2010), and children who experienced early life stress have smaller brain volumes in the OFC (Hanson et al., 2010).

There is less consistency in the literature regarding the effects of physical abuse on the structure and function of the OFC. The OFC plays a central role in flexibly adapting behavior in response to changing contingencies (Murray, O'Doherty, & Schoenbaum, 2007). There have been reports of both smaller volumes (Hanson et al., 2010; McCrory et al., 2012) and larger volumes (Carrion et al., 2009) in the OFC for children and adolescents who have suffered physical abuse. No clear explanation exists to date regarding these opposing findings, because researchers have examined similar-age participants and with similar types of early life stress. Inconsistencies have also been found in nonhuman animals, with both dendritic expansion (Liston et al., 2006) and retraction (Helmeke et al., 2009) reported in the OFC after chronic stress exposure. Functional brain imaging may help in clarifying the role of frontal lobe circuitry in developmental problems associated with maltreatment. However, a major limitation of structural imaging is that brain structure and a region's function may not always be in concordance. For example, brain areas may be smaller in volume but exhibit greater activity for specific tasks; brain regions may be larger in volume but no differences in brain activity may actually be present after controlling for these factors.

There has also been much research attention, but just as much inconsistency in findings, regarding the amygdala and its role in emotional dysregulation. The divergence in findings may stem from methodological factors, heterogeneous samples of at-risk children, nonlinear effects of life stress, or a combination of all three. To address some of these issues, Hanson et al. (2014) completed rigorous hand tracing of the amygdala in samples of children who experienced different forms of early stress including physical abuse, early neglect, or extreme family poverty. They found smaller amygdala volumes for children exposed to these different forms of stress, with brain development associated with both greater cumulative stress exposure and the emergence of child behavioral problems (Hanson et al., 2014). These data suggest that early and severe life stress may be associated with increased excitation and cell death, reflected in reductions in brain volume. However, caution must be used when inferring developmental patterns from cross-sectional studies; only longitudinal research can truly validate such a model of amygdala development after early stress exposure. Structural and functional alterations in the amygdala may help us understand individual differences in risk and resilience to behavioral problems as related to toxic stress.

What developmental processes might link these components of neural circuitry? One well-understood system is the hypothalamic–pituitary–adrenal axis, which is central for understanding the negative effects of stress and trauma on children. When an individual encounters a stressor, corticotropin releasing hormone is secreted from the hypothalamus. This hormone acts on the pituitary gland, causing it to release adrenocorticotropic hormone. Adrenocorticotropic hormone then acts upon the adrenal gland, resulting in the production of cortisol. Cortisol binds with glucocorticoid (GR) receptors in the hippocampus to regulate the hypothalamic–pituitary–adrenal axis and inhibit further release of corticotropin releasing hormone. Similarly, cortisol released in response to stress binds with GR receptors at the cellular level to regulate the immune system (Lupien, McEwen, Gunnar, & Heim, 2009). This system promotes adaptation in response to normative stressors. In this manner, toxic or extreme levels of early life stress exposure may impair this system (Koss, Hostinar, Donzella, & Gunnar, 2014). Other hormone systems also hold potential for understanding how early life adversity affects subsequent social behavior. For example, a recent study

examined functioning of the neuropeptide oxytocin (OT) in children aged 8–11 years following a social stressor. Girls with histories of physical abuse showed higher levels of urinary OT and lower levels of salivary cortisol following the stressor when compared to controls (Seltzer, Ziegler, Connolly, Prososki, & Pollak, 2014). Abused and control boys, however, did not differ in their hormonal responses. These data suggest that early adversity may disrupt the development of the stress regulation system in girls by middle childhood, and disruptions of this system has implications not only for children's successful regulation of emotion but also for aspects of comforting behaviors such as the establishment of stable and secure interpersonal relationships. A related study examined the role of the oxytocin receptor gene as a moderator between social support and psychological symptoms among abused children. The polymorphism of the oxytocin receptor gene (*rs53576*) differentiated outcomes between children with low social support in terms of internalizing symptoms. This is striking in that these groups of children did not differ on objective measures of maltreatment such as type, duration, or severity of abuse (Hostinar, Cicchetti, & Rogosch, 2014). The authors speculated that, unlike maltreated A-allele carriers, individuals who were G/G homozygotes might be more attuned to negative social experiences.

From a developmental perspective, it is important to emphasize that enhanced threat detection (as well as the myriad systems that children use to promote self-regulation and comforting) are critical for children living in contexts that do not provide adequate protection. Thus, neuropeptide systems such as glucocorticoids and OT that play a role in coordinating these responses (Hostnar & Gunnar, 2013) may be important targets for interventions aimed at improving children's adjustment.

Epigenetics as a Model for Rethinking the Relationship Between Biology and Experience

The use of epigenetic approaches to understand emotion regulatory processes holds tremendous progress for advancing new treatments for children who have experienced maltreatment. Epigenetics may well provide new traction in understanding etiological processes in a range of psychological disorders. While in the past, inheritance was conceptualized in terms of the letters of the DNA code passed from parents' egg and sperm, we now know that there is another path. Parental behavior can write information onto DNA completely bypassing egg and sperm, adding a level of flexibility that extends the DNA code. This biological flexibility seems quite logical: through experience, individuals use information about the world they are growing up in, changing DNA to cope with the environment.

Of particular importance for understanding developmental processes affected by child maltreatment, there appear to be many ways to trigger epigenetic changes. One avenue is the actual characteristics of the environment that might affect gene functioning, such as violence, threat, or instability. However, it is also possible that children's interpretations and subjective perceptions of their experience may be enough to trigger epigenetic changes (Slavich & Cole, 2013). As reviewed above, there have been many studies indicating that maltreated children overly attend to threat/hostility in their environments. For example,

children who suffered physical abuse are more likely to view others as hostile and the world as generally unsafe (Gibb, 2002; Keil & Price, 2009). These biases influence information processing, with previous research finding physically abused children incorrectly encode social cues and exhibit hostile attributional biases (Teisl & Cicchetti, 2008). Such attentional processes may reflect short-term adaptation to hostile environments, but carry long-term risk for health and behavior, especially given that the behavioral problems of maltreated children are largely accounted for by experiential rather than genetic risk factors (Jaffee, Caspi, Moffitt, & Taylor, 2004).

Although the mechanisms of these effects likely involves diverse cellular and molecular pathways, there is emerging evidence supporting the hypothesis that epigenetic changes, such as DNA methylation and histone modifications, mediate the effects of early life variations on the social interactions. Moreover, there may be plasticity within these epigenetic pathways at later developmental time points, such that the social experiences of juveniles and adults may also induce epigenetic change (for a review, see Champagne & Curly, 2011). These findings have implications for understanding the emergence of behavior problems, in early childhood (such as emotion regulation problems) as well as distal problems in adulthood (such as cancer and cardiovascular disease). These data also highlight the dynamic interactions occurring between genes and environments during the course of development.

Recently, epigenetic changes in the GR gene were examined in whole blood from children aged 11–14 years (Romens, MacDonald, Svaren, & Pollak, 2014). The promoter region of the gene is the sequence needed to turn the gene on and off. It is usually found near the beginning of a gene, and has binding sites for enzymes that make RNA. In the Romens et al. study, abused children had more methylation on several sites within exon 1F of the promotor region of the nuclear receptor subfamily 3, group C, member 1 (*NR3C1*) gene, especially cytosine nucleotide–phosphate–guanine nucleotide (CpG) site 3, which may have important implications for brain development given that it is the binding site for nerve growth factor (Weaver, Hellstrom, & Brown, 2014). These results highlight molecular mechanisms linking childhood stress with biological changes that may lead to mental and physical disorders. Consistent findings across both rodent and human studies suggest that better parental care decreases methylation of the GR promoter, increasing GR expression. Increased GR expression in the hippocampus reduces stress responsiveness. Although this is an oversimplified explanation (other factors are involved, such as chromatin and histones), the general idea is that methyl inhibits gene transcription and can be thought of as a useful framework for understanding the complexities of gene expression.

However, translation across species is difficult. The current GR epigenetic data are consistent with the view that genes can be turned on and off, yet such studies in humans cannot infer causality and are limited in terms of specificity of the cellular processes occurring in the brains of living children. They also do not reflect gene expression. What the animal studies can do is to control for confounding variables that are not possible to account for in studies of humans, where we need to be opportunistic in our research. One clear link between the controlled animal studies and peripheral measurement of epigenetic changes in humans concerns effects of early stress on immune system competence. Consistent with

peripheral changes in methylation of the GR gene, children with early stress exposure show deficits in immune functions (Danese, 2014; Shirtcliff et al., 2009).

Conclusion

In this paper, I have attempted to illustrate ways in which contemporary multilevel developmental scientific approaches hold promise for elucidating a deeper understanding of the effects child maltreatment. Inherent in multilevel approaches is the challenge of situating biological development within an environmental context. Epigenetic processes, changes in the neuroendocrine system (Hostnar & Gunnar, 2013), and altered neural processing of social cues (Briggs-Gowan et al., in press; Hankin, Gibb, Abela, & Flory, 2010; Pollak, 2012; Reeb-Sutherland et al., 2015) all have provided new windows into understanding developmental processes of risk, and all hold promise for helping us to better facilitate recovery from the effects of early life stress.

Integrating research about the neurobiology of learning may prove to be a powerful way to test novel hypotheses about how the environment comes to regulate behavior. This is because successful social adaptation reflects children's ability to learn from complex and varied interpersonal experiences. Children need to discern factors including cues for approach versus withdrawal, actions that lead to punishments versus rewards, and behaviors that lead to success in having needs and desires met. These processes become increasingly intricate and fine-tuned as relevant neuroanatomical systems develop, and as the range, complexity, and amount of social information increases for the developing child. A focus on developmental processes across levels of analysis allows us to formulate questions about which neural mechanisms humans use to process socioemotional information, how these mechanisms are themselves shaped by social context, why adverse social environments confer risk for children, and perhaps, what sorts of neutrally informed interventions might remediate deficits in self-regulation.

Issues for future directions

Years ago, my colleagues and I argued that from a developmental perspective, the specific types of adverse experiences that children encounter matter. At the time, many studies included heterogeneous samples of maltreated children, including those who had experienced neglect or sexual abuse, witnessed domestic violence, and a host of other adverse conditions. We reasoned that each of these circumstances likely resulted in different kinds of effects on a variety of neurodevelopmental systems. For example, the experience of severe threat exposure among physically abused children could have different developmental sequelae as contrasted with the outcomes that might result from the isolation and lack of care afforded to neglected children. We found that children who experienced primarily physical abuse had patterns of emotion recognition that were quite distinct from those of children who suffered primarily from caregiving neglect (Pollak et al., 2000). Children in the former group were more likely to develop hypervigilance to threat cues, whereas children in the latter group were more likely to have difficulty differentiating various emotional signals. Yet, there are also ways in which different kinds of early adversity appear to have similar developmental effects. For example, we (and others) have found that children in other risk

groups have problems that appear very similar. As an example, neurocognitive delays tied to behavioral problems have been observed among physically abused children, children who experienced early neglect, children reared in institutionalized settings (Hanson, Adiuru, et al., 2013; Pollak et al., 2010; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012), and children raised in very low-income families (Hanson, Hair, et al., 2013). These patterns of similarities and differences illustrates that multilevel approaches are needed to better conceptualize and understand the effects of child maltreatment. To do so, researchers will need to specify the "active" aspects of experience that disrupt development as well as the processes or mechanisms affected by the experience.

Sometimes what was old becomes new again, and this is very much the case in research on early adversity in children. As far back as the 1930s, Hans Selye addressed a growing problem in studies of stress. He argued that the word "stress" had been used in so many different ways that it lacked precision and clarity, and it would therefore become too difficult to associate the concept of stress with specific biological processes. To address this issue, he attempted to introduce the notion of "general adaptation syndrome," which never gained traction with other scientists (Selye, 1946). Ultimately, he too would write about "the stress response" when describing a host of heterogeneous behavioral, hormonal, gut, and immunological sequelae of environmental challenges encountered by organisms. Part of the semantic difficulty with the notion of stress is reflected in how the term is used in disciplines other than the biobehavioral sciences. For example, when engineers refer to "stress" on a structure such as a bridge, they mean the excessive weight of the cars and trucks on the bridge. For engineers, stress is the "external force" on the system; it is not the response of the bridge structure to that external force. When describing what happens to metal girders of the bridge in response to external forces, engineers use the term *strain*. This is just the opposite of how the term *stress* is used in the biomedical fields, where it refers to the organisms' internal adjustments to an external challenge.

Others have tried to address this point, but there has not yet been a multilevel view for which consensus has been reached by child maltreatment researchers. For example, Lazarus (2006) advanced the idea that dealing with stressful events is inherently taxing, suggesting that the coping process itself was the real stressor that generated health consequences. This is essentially the "strain" perspective that is similar to that used in engineering. Over the last decade, this idea has been developed to have greater synchrony with biological processes, as in concepts such as "allostasis" and "allostatic load." That is, stressful events, when repeated or chronic, result in an adjustment. That adjustment in the body's regulatory set points could be thought of as strain (McEwen & Stellar, 1993; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). A limitation of this view, though, is that allostatic load has been morphed into "transactional models" that are often mechanistically vague and overly general. In such cases, the argument is essentially that stress and the response to stress is a bit of every cognitive and biological regulatory system. Thus, the developmental outcome associated with early adversity is viewed as a summation of all of the different facets of stress. The problem with such approaches is that they do not leave us with specific mechanisms to target for prevention/intervention strategies for individuals who have experienced child maltreatment. Lacking in specificity, these accounts also do not help usto formulate

mechanistic models of some of the complex stress-related disorders like posttraumatic stress disorder, chronic fatigue syndrome, or fibromylagia.

My colleague Chris Coe (personal communication, February 2, 2015) simplifies these levels of analysis in a way that is likely to be beneficial for advancing understanding of the effects of child maltreatment. On Coe's view, the external events that occur in children's environments are "stressors." Any biological change internal to the child in response to those external events is the "stress response." These are distinct from any subjective emotional reactions associated with the need to activate the stress response system, such as "distress." In addition, the health consequences of chronic or prolonged engagement of the stress response system or negative emotion are "diseases of adaptation and coping." This represents an extremely useful direction for future research on child maltreatment. Often these issues and processes are confounded; however, we are likely to achieve greater clarity and progress in developing effective interventions for individuals who experienced child maltreatment if we attend to these different levels of associated phenomena.

There are still many unanswered questions about how and why child maltreatment has such a lasting and pernicious affect across the life span. However, accounts that can begin to unpack stress, strain, response systems, and coping are likely to address these issues. For example, we need to better understand what levels of stress can be tolerated by children without developmental consequences versus the levels of stress that are harmful. Biological systems tend to be robust, and children are unlikely to develop long-term problems in response to the slightest permutation or deviation from the ideal environment. Therefore, the next wave of research in the field of developmental psychopathology will need to better explore what kinds of circumstances are necessary for environmental experience to sustain a long-term impact on behavior. Another way to formulate such as questions is to ask: what are the thresholds for when issues such as stress move from tolerable to toxic, or what are the central differences between individuals' responses to adversity that lead some to develop "diseases of adaptation." The critical question concerns understanding when adverse experience crosses a threshold that has long-term implications for a child's developmental trajectory. Such information will be necessary to develop prevention and intervention programs that are effective and appropriate for individuals at different phases of development.

Clinical implications

An understanding of developmental processes includes understanding adaptation as well as maladaptation. Therefore, a key aspect of developmentally appropriate interventions requires contextualizing a child's behavior in terms of how it may have been useful to the child in the past. It appears that some cognitive, affective, and behavioral patterns that emerge in stress-exposed children may have allowed children to cope with aberrant life circumstances. As an example, in a psychiatric context, we construe anxiety as a disadvantage. Anxiety is problematic for individuals living in low-danger, highly consistent environments. However, if danger or uncertainty is high, then keeping a low profile and responding quickly to possible threat may be useful. For this reason, it is important to view symptoms within children's life context rather than solely within their present circumstances. If a child is

continuing to live in a family context that is unstable, where threat is high, it may well be harmful to reduce the child's anxiety or vigilance to threat. Even at high cost, children need support to cope with the realities of their lives.

As clinicians and researchers begin to develop new and effective treatments for children, a challenge will involve learning how to tailor interventions for given individuals given those individuals' specific biological and environmental circumstances. At present, many treatments for children remain somewhat generic, with popular approaches such as cognitive–behavioral, mindfulness, or attachment-oriented therapies being applied similarly across a range of mental health conditions, ages, and individual differences. In addition, intervention studies tend to focus on very broad, nonspecific behavioral outcome measures, such as ratings or interviews of overt symptomatology, school achievement, or observed ratings of behavior. However, our behavioral constructs have not yet evolved to have the same level of mechanistic specificity as newer biological measures. More sensitive and specific behavioral measures will be necessary to truly discern the processes underlying mental health issues.

There is hope for effective interventions. Although data suggest that social experiences can alter human physiology, these changes are not necessarily permanent. For example, there is some evidence for epigenetic reversibility from rodents within the GR system (Weaver et al., 2005). Such advances will require not only that we discover ways to target and change biobehavioral processes but also that we are able to personalize or individualize treatments based on the nature and timing of a child's experience and the individual child's sensitivity/ reactivity to those experiences. This will be the challenge for the next decade of developmental psychopathology.

Acknowledgments

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