
Handbook of Developmental Social Neuroscience

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CHAPTER 25

Socioemotional Development Following Early Abuse and Neglect

Challenges and Insights from Translational Research

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Childhood maltreatment is a significant public health problem. In addition to risk of physical injury or death, children who experience various forms of abuse and neglect are likely to develop a variety of health problems over the course of their lives. These problems appear to result from the stress and emotional distress associated with the behavioral inconsistencies of the children's caregivers. The goal of this chapter is to synthesize what is currently known about how complex sets of neural circuitry are shaped and refined over development by children's social experience. We address questions about the role of social experience in the development of brain-behavior relations by focusing on research with populations of abused and neglected children, as well as research with rodents and nonhuman primates that can be translated or applied to humans. Despite the fact that child maltreatment is notoriously difficult to investigate empirically, it provides an important forum for understanding the role of environmental stress, individual differences, and developmental factors in the ontogenesis of social behavior.

A challenge faced by the field of affective developmental neuroscience concerns the difficulty of precisely measuring the amount of exposure any individual has had to particular emotions. However, it is possible to estimate gross differences across groups. Therefore, studying populations of children who have had extreme social experiences such as abuse and neglect can not only help inform effective prevention and intervention strategies to help

promote these children's optimal development; these studies can also shed light on the ways in which social experiences influence the developing brain. There are many examples of the ways in which maltreating parents provide emotionally expressive environments for their children that deviate in important ways from normal social experience (Camras, Sachs-Alter, & Ribordy, 1996). For example, abusive parents engage in fewer positive emotional interactions with their children than nonabusive parents do (Burgess & Conger, 1978), and direct more negative affect toward their children than nonmaltreating mothers do (Trickett, Aber, Carlson, & Cicchetti, 1991). Indeed, some of our own recent work reveals that abusive parents, not surprisingly, are generally angry people, and that their overall levels of trait anger predict their children's performance on emotion recognition tasks (Pollak, Messner, Kistler, & Cohn, 2009). Later in this chapter, we review current evidence supporting the view that the experience of child maltreatment plays a causal, rather than corollary, role in children's behavioral problems.

Various techniques have increased our understanding of the ways in which children's experiences of maltreatment can lead to emotional disorders. By carefully observing and modeling aspects of child abuse in nonhuman primates, we are also able to examine the neuroanatomical and neurophysiological substrates of emotional processes in ways that are not feasible with human subjects. As humans do, primate species exhibit complex socioemotional and neural development over a protracted developmental period during which the infant is dependent on parental care (Maestripieri & Carroll, 1998b). Indeed, studies of the effects of early experience in nonhuman animals have highlighted candidate processes through which adverse parental care affects the development of the neural systems believed to underlie heightened risk for mental health problems. As it does in humans, maltreatment occurs spontaneously in nonhuman primates, both in captivity and in the wild. In particular, physical abuse has been reported in different species, with rates similar to those seen in human populations (e.g., Brent, Koban, & Ramirez, 2002; Johnson, Kamilaris, Calogero, Gold, & Chrousos, 1996; Maestripieri, 1999). In the case of macaques, infant abuse involves violent behaviors that a mother directs toward her infant, such as crushing, throwing, dragging, and stepping or sitting on the infant (Troisi & D'Amato, 1984). These maternal behaviors are clearly distinguishable from species-typical aggressive behaviors, and they cause intense infant distress and sometimes serious injury or even death. In sum, nonhuman primate models of infant maltreatment constitute unique and naturalistic models of human childhood maltreatment that can help us understand the developmental trajectory of the impact of these early adverse experiences.

Conceptual Issues in the Study of Child Abuse

Many conceptual, practical, and ethical factors complicate the study of child abuse and are important in considering how to evaluate neuroscientific approaches to the phenomenon (for a full discussion, see Pollak, 2005).

One issue is that the identification of child abuse co-occurs with a host of complex risk factors that affect child, parent, and family functioning. Therefore, it is conceptually difficult to evaluate where to place the occurrence of child maltreatment, molecular genetic components, and other latent variables in the causal chain leading to mental health problems. This issue of causality is described very nicely by Caspi and Moffitt (2006).

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A second issue is that, in contrast to most studies of adult (and many child) psychiatric disorders, it is extremely complicated or impossible to obtain and verify data on the specifics of children's maltreatment experiences. Moreover, even when such data are obtained, there is no scientific agreement about how the data should be categorized. Therefore, although contemporary neuroscience-based techniques can now be applied to understanding outcomes associated with maltreatment, basic issues about operational definitions of maltreatment and details about the constitution of the samples being studied require close scrutiny. As a result, it is often impossible to determine how comparable one "maltreated" sample is to another. Studies of maltreatment among nonhuman primates help address part of this problem, in that parent-child interactions can be reliably measured and quantified in a more controlled environment—though there is still uncertainty about which operational criteria constitute different forms of maltreatment in monkeys. These definitional problems are described by Dubowitz et al. (2005).

A simple, albeit valid, response to these criticisms of research on child maltreatment is that most human research on the developmental effects of stress exposure requires us to be opportunistic. We need to address the real events that naturally occur in children's lives, even if those events are terribly messy, inconvenient, or even inconsistent with the ideals of experimental design. As described above, studies of nonhuman animals are extraordinarily useful in addressing some of these issues. But animal models cannot substitute for human studies. Animal models do not always mimic human emotional disorders; brain development, structure, and function are not identical across species; there are chromosomal differences between species; and the actual behaviors exhibited by parents and the way they are received and experienced by offspring are not identical across species. At the same time, the common denominators that do apply across species, such as poor/inadequate parental nurturance, provide critical clues and allow for human models of the effects of child abuse to be biologically sound. These important commonalities allow us to translate knowledge from experimental animal models of brain-behavior relationships to human situations.

Of course, there are more detailed ways to consider the problems of experimental methods and definitional issues. We briefly review these issues before summarizing research findings.

Defining Child Maltreatment

Problems in defining maltreatment complicate attempts to study biological mechanisms. In human studies, the term "maltreatment" is often used inclusively, so that samples of maltreated children include individuals who have experienced multiple types of adverse experiences (i.e., physical abuse, sexual abuse, emotional abuse, and/or neglect). The proportions of different types of maltreatment vary in these samples; moreover, issues such as the definition of "emotional abuse," which is nearly impossible to measure and verify, often go unaddressed. Furthermore, the ways in which different types of maltreatment are determined across studies include methods as diverse as social service agency designations, clinical interviews, self-report of parents and/or children, behavioral observations, and retrospective reports. Although all extant approaches are subject to criticism, and researchers using them must deal with significant sensitivity-specificity tradeoffs, each approach also confers some advantage. For example, the use of legal and social services records and classifications has the advantage of being objective, but the disadvantage of being based on information that is

collected and classified for administrative rather than scientific purposes. Furthermore, the legal threshold for what constitutes maltreatment is very broad: Children can be designated as "neglected" for reasons ranging from leaving a young child unsupervised to failing to follow societal rules (e.g., not sending a child to school). Thus the classification a child receives in the legal or social services system may provide little theoretically driven and scientifically useful information about maltreatment. Furthermore, developmentally informed research requires knowing the severity and duration, not merely the type, of experience. Although it is challenging to derive from legal and administrative records, this information matters. For example, Manly, Cicchetti, and Barnett (1994) showed that while infrequent but severe forms of maltreatment had a negative impact on child outcomes, frequent but less severe maltreatment experiences were also detrimental.

Defining maltreatment in nonhuman primates has also been a difficult endeavor, especially for neglect. Like humans, nonhuman primate mothers demonstrate a broad spectrum of caregiving styles toward their infants. Some rhesus macaque (*Macaca mulatta*) mothers show poor maternal care; for example, they provide infrequent physical contact and fail to protect infants. But it has been difficult to determine how harmful these behaviors are to the infants over time. Therefore, research in this area has taken a conservative approach, limiting definitions of "neglect" in nonhuman primates to extreme behaviors, such as complete abandonment of the infant by the mother (Maestripieri & Carroll, 2000). Among macaques, infant abandonment is exhibited almost exclusively by primiparous mothers (between 1.5–15%), and, unlike in studies of human parenting, it rarely coexists with physical abuse (e.g., Maestripieri & Carroll, 1998a).

We have been examining other forms of monkey parenting that more closely approximate the experiences of neglected human children. In rhesus monkeys, maternal rejection of an infant co-occurs with physical abuse in about 70% of cases (McCormack, Sanchez, Bardi, & Maestripieri, 2006; Sanchez, 2006). Physically abusive rhesus mothers are also anxious and rejecting towards their offspring, and show poor "nurturing/protective" care. These rejecting maternal behaviors occur very early in the infants' lives, when rhesus mothers are typically providing infants with high levels of nurturance (Suomi, 2005). Further understanding of the impact of different kinds of parental care is likely to be a promising approach, and recent data suggest that high maternal rejection is in fact a stronger predictor than physical abuse for poor developmental outcomes in maltreated rhesus infants (McCormack et al., 2006; Sanchez et al., 2007). These studies are described further below.

Co-Occurring Risk Factors

Because child maltreatment cannot be experimentally manipulated, most human studies on the topic lack meaningful experimental controls. Therefore, it is often difficult to discern the extent to which observed effects can be associated specifically with maltreatment or are the concomitant effects of other negative factors, such as poverty, in the lives of maltreated children. A threat to validity in most studies with maltreated humans is the possibility that observed associations between various forms of maltreatment and psychopathology are not due to causal relationships between the two, but either reflect latent variables causing both maltreatment and psychopathology, or are the results of accumulated life stressors (beyond maltreatment) that co-occur in families where abuse has been identified. Historically, an alternative to the view that maltreatment causes behavioral problems was the idea that poor outcomes result from heritable factors that cause the maltreatment, or risk factors in the envi-

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ronment that co-occur with maltreatment. However, recent behavioral and molecular genetic data support the view that the experience of abuse plays a causal role in children's behavioral problems. These data suggest that genetic risk, in combination with early traumatic experiences, dramatically increases the likelihood that children will develop mental health problems (Kim-Cohen et al., 2006). Similar studies (Jaffee et al., 2005; Kendler et al., 2000), using large samples of humans, consistently support a causal relationship between child maltreatment and the development of psychopathology. As in the data from humans, physical abuse in rhesus monkeys has a high prevalence in some maternal lineages, suggesting an intergenerational transmission of vulnerability to maltreatment. Whether this transmission along the maternal line is due to experience or to genetic heritabilities is not yet definitive. However, evidence from cross-fostering studies (e.g., Maestripieri, 2005) suggests that early experience plays an important role in the sequelae and the perpetuation of maltreatment.

Still, the potential role of co-occurring environmental risk factors (as causes, mediators, or moderators) continues to complicate research in this area. Many factors in the lives of humans are extremely difficult to quantify in any single study. For example, a child's risk of exposure to community violence is influenced by family socioeconomic status and the child's gender, ethnicity, and age (Couch, Hanson, Saunders, Kilpatrick, & Resnick, 2000). In addition, various family characteristics have been associated with an increased likelihood of exposure to violence (Osofsky, Wewers, Hann, & Fick, 1993). Our intent in raising these issues early in this chapter is not to be discouraging. Indeed, these areas of scholarly inquiry have progressed in very exciting and productive ways. However, to bridge different lines of research—involving different populations, methods, and species—it is important to be mindful of the conceptual challenges in the work. The ways that these studies inform one another is powerful, but the realities and limitations of this work (especially with human populations of at-risk children) must also be considered. And although similarities between species are exciting, there is much to be learned from the ways in which findings across species or research programs do not align.

Child Abuse and Mental Health

Over 3 million children were reported to be victims of maltreatment in the United States in 2003 (Hussey, Chang, & Kotch, 2005). After neglect, physical abuse is the most common form of childhood maltreatment. Furthermore, in addition to those who are directly victims of violence, approximately 3.3 to 10 million children witness violence at home (Straus & Gelles, 1990). Abused children are at extremely high risk for mental health challenges that include conduct/aggression problems, depression, anxiety, and substance abuse; they also lag behind their peers in social skills (Chapman, Wall, & Barth, 2004; Toth, Manly, & Cicchetti, 1992) and experience high rates of physical health problems (Mulvihill, 2005).

Many maltreated children display socioemotional behavioral difficulties even before the onset of clear symptoms of psychopathology. For example, maltreated infants as young as 12 months of age show poor affect regulation (Gaensbauer, 1982). Children who have been maltreated experience problems involving recognition (Camras et al., 1996) and regulation (Main & George, 1985) of emotional states. Physically abused children exhibit elevated aggressive behaviors and social withdrawal during peer interactions (Rogosch & Cicchetti, 1994). Physically abused children display both interpersonal withdrawal and aggression (Rogosch, Cicchetti, & Aber, 1995), attribute hostility to others (Weiss, Dodge, Bates, & Pettit, 1992), and

display contextually inappropriate affect and behavior (Klimes-Dougan & Kistner, 1990). Physically abused children also tend to readily assimilate and remember pictures of angry facial expressions and cues related to aggression, even when those cues are task-irrelevant (Pollak & Tolley-Schell, 2003; Rieder & Cicchetti, 1989). Moreover, there is a positive association among frequency and severity of physical abuse, hostile attribution tendencies toward others, and attentional biases in emotion perception (Price & Glad, 2003; Shackman, Shackman, & Pollak, 2007).

The developmental outcomes of maltreatment in nonhuman primates are comparable to those reported in maltreated children. Maltreated rhesus monkey infants exhibit delayed social development, behavioral signs of distress, heightened anxiety and fearfulness, and impulsive aggression (e.g., McCormack et al., 2006; Sanchez, 2006). Similar alterations have also been observed in other primate species, such as marmosets and vervet monkeys (Fairbanks & McGuire, 1998; Johnson et al., 1996).

One approach to understanding the nature of the risk posed by child maltreatment is to note the kinds of disorders that are likely to emerge in these children. However, the diversity of developmental trajectories taken by maltreated children suggests a complex story. Some reports indicate that child abuse is linked to increased levels of depression in childhood (Kaufman, 1991; Toth et al., 1992), while other reports note increased levels of other disturbances such as conduct disorder, attention-deficit/hyperactivity disorder, and oppositional defiant disorder. Still other studies have found high levels of anxiety and social withdrawal (Famularo, Kinscherff, & Fenton, 1992). Childhood maltreatment has also been linked to substance use disorders, dissociative disorders, and posttraumatic stress disorder (PTSD) (Aarons, Brown, Hough, Garland, & Wood, 2001; Cicchetti & Toth, 1995). Yet much remains to be learned beyond these associations, such as the nature of the etiological mechanisms, the processes that serve to maintain problems in these children, and the reasons why maltreated children may develop so many different kinds of disorders.

To address questions about individual differences in children's developmental outcomes, Manly, Kim, Rogosch, and Cicchetti (2001) examined how the timing of maltreatment affected children's adjustment. Severity of emotional maltreatment in the infancy-toddler period predicted externalizing behavior and aggression during the school-age years, as did victimization by physical abuse during the preschool period. Maltreatment that occurred during the school-age period contributed significant variance even after earlier maltreatment was controlled for. Chronic maltreatment was linked with more maladaptive outcomes, especially with onset during the infancy-toddler or preschool periods. A recent report revealed that individuals who were abused earlier in life demonstrated higher levels of anxiety and depression in adulthood, whereas individuals who were older at the time of the maltreatment were more likely to evince symptoms associated with aggression and substance abuse (Kaplow & Widom, 2007). Replication and further exploration of these findings will be helpful in linking models of developmental neurobiology to the development of psychopathology. These findings underscore the importance of adopting a multifaceted approach to examining child maltreatment, and they emphasize the importance of utilizing a developmental approach and assessing multiple dimensions of such environmental threats as maltreatment to understand patterns of adaptation and maladaptation among children exposed to adversity. Because it is clear that child maltreatment is associated with elevated risk for many different kinds of mental health problems, we highlight the kinds of difficulties that have been most frequently reported, in an effort to focus on candidate developmental mechanisms affected by early experience.

Anxiety and Depression

One area of concern involves the high prevalence of anxiety and depression among formerly abused children. Of course, depression is a heavily studied phenomenon, and many different developmental factors ranging from problems with peers to stressful lives are related to depression (see, e.g., Raver, 2003). Traumatic experiences such as maltreatment may leave children hyperresponsive to emotional stimuli, particularly those that signal threat or danger, with marked shifts in arousal levels (Cummings, Vogel, Cummings, & El-Sheikh, 1989; Eisenberg et al., 1997). Early harsh caregiving experiences also undermine a child's capacity to reflect upon the affective state of both self and others (Fonagy, Target, & Gergely, 2000).

Central findings in this area concern the interactions of early adverse environments with genetic risk factors. A very consistent body of evidence for these early environment \times gene interactions involves a neurotransmitter transporter gene called 5-HTT that fine-tunes transmission of serotonin (5-HT) by reuptaking it from the synaptic cleft. The gene comes in two common allelic variants: the long allele and the short allele, which confer higher and lower 5-HT reuptake efficiency on 5-HTT, respectively. Animal studies have shown that in stressful conditions, those with two long alleles cope better. Mice with one or two copies of the short allele show more fearful reactions to stresses such as loud sounds. In addition, monkeys with the short allele that are raised in stressful conditions have impaired 5-HT transmission. Caspi et al. (2003) studied 847 individuals who had undergone a variety of assessments over more than two decades, starting at the age of 3. The negative effects of maltreating experiences were stronger among people with one short allele, and stronger still for those with two short alleles. For people with two short alleles, the probability of a major depressive episode rose to more than double the risk for the subjects with two long alleles who had similar levels of life stress. More specifically, childhood abuse predicted depression after the age of 18 only in people carrying at least one short allele. Among the 11% who had experienced severe maltreatment, the subjects with two short alleles ran a 63% risk of a major depressive episode. The participants with two long alleles averaged a 30% risk, regardless of whether they had been abused as children or not. In this study, the possibility that a short allele could somehow predispose a person to experiencing maltreatment was essentially ruled out; there was no significant difference among the three genotype groups in the number of adverse experiences reported.

Aggression and Antisocial Behavior

A second area of mental health concern involves to high levels of antisocial and aggressive symptoms observed among abused children (Parker, Rubin, Price, & DeRosier, 1995). On average, children who have been abused are more aggressive toward peers than are their nonmaltreated counterparts (Dodge, Bates, & Pettit, 1990; Kaufman & Cicchetti, 1989). Many youth with child maltreatment histories develop serious conduct problems, including arrests for violent offenses (Widom & Brzustowicz, 2006). Type of abuse experience may play a role in the development of delinquency (Jonson-Reid & Barth, 2000).

Recent findings suggest that one explanation for variability in outcomes among maltreated males relates to a gene-environment interaction involving a functional polymorphism in the promoter region of the monoamine oxidase A (MAOA) gene. Specifically, maltreated boys with the MAOA genotype conferring low levels of the MAOA enzyme developed conduct disorder, antisocial personality, and violent criminality in adulthood more often than

maltreated boys with a high-activity MAOA genotype did. MAOA selectively degrades 5-HT, norepinephrine, and dopamine following reuptake from the synaptic cleft, and therefore plays a key role in regulating behavior (Caspi et al., 2002; Sabol, Hu, & Hamer, 1998; Shih, Chen, & Ridd, 1999).

Stress Disorders

Child abuse also appears to increase the comorbidity of PTSD with both depression and substance abuse (Kilpatrick et al., 2003). PTSD may not be a normative response to traumatic violence. Instead, it may represent a disordered stress response related to preexisting biological and psychological vulnerabilities (Yehuda & McFarlane, 1995). Characteristics of the social environment, such as social support and family cohesion, seem to play a role in how children respond to violence (Kliewer, Lepore, Oskin, & Johnson, 1998). Genetic mechanisms may make some individuals more susceptible to stressful environments. No specific genes have been linked conclusively to PTSD. The one study that did identify a particular gene, the gene for the dopamine D2 receptor (Comings, Muhleman, & Gysin, 1996), was not replicated (Gelenter et al., 1999).

Neural Mechanisms of Risk

Emotion and Attentional Processing

The overarching model guiding the work of Pollak and colleagues has been to focus on the interactions between the plasticity of general perceptual and attentional systems, threat and stress regulatory processes, and learning mechanisms (Pollak, 2003, 2005). The work of Sanchez and her colleagues (see Maestriperi, 1999; Sanchez, 2006) with nonhuman primates has provided a rough guide for this research on abused children. Although one must always be cautious in translating basic findings across species, basic neuroscience research converges with the human studies in suggesting that higher-order functions such as selective control of attention to threat, combined with alterations in stress reactivity, may account for maltreated children's reactions to social stimuli (Pollak, 2008). Rather than using their attentional resources to attenuate emotional reactivity, physically abused children appear to overly attend to threatening cues, perhaps at the expense of other contextually relevant information (Dodge, Pettit, Bates, & Valente, 1995; Pollak & Tolley-Schell, 2003). Converging empirical support also comes from the laboratories of De Bellis (2005) and Heim (Heim, Ehler, & Hellhammer, 2000; Heim, Plotsky, & Nemeroff, 2004).

To examine the effects of different kinds of experiences, Pollak, Cicchetti, Hornung, and Reed (2000) contrasted the emotion recognition skills of abused and neglected children. Maltreatment subtypes were classified hierarchically, such that none of the children had documented sexual abuse; neglected children did not have records indicating physical abuse; but physically abused children might also have experienced neglect. Physically abused children had experienced abuse by commission (they were injured by a parent). Neglected children experienced abuse by omission (lack of care and responsiveness from parents). The neglected children had difficulty differentiating facial expressions of emotion, whereas the physically abused children performed well, especially when differentiating angry facial expressions. These data suggest that specific kinds of experiences, rather than simply the presence of stress or heterogeneous forms of maltreatment, have differential effects. Two psychophysi-

ological studies of children's ability to allocate attention to emotional cues revealed that while nonmaltreated children and adults responded uniformly when attending to happy, fearful, and angry faces, physically abused children displayed relative increases in brain electrical activity only when actively searching for angry faces. Abused children performed identically to controls when attending to other emotional expressions, suggesting that attentional processes directed toward anger distinguish abused children's emotion processing (Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak, Klorman, Brumaghim, & Cicchetti, 2001).

Most of the neuroscience-oriented research to date has not involved samples of children with relatively distinct types of maltreatment. In these cases, we refer to these samples as "maltreated" if the type of experiences represented in the sample is broad. Otherwise, we refer to samples as "abused" (for physically abused), "neglected," or "isolate-reared." We do not include studies of sexual abuse in this chapter. Consistent with observations of socially deprived rhesus monkeys, neglected children have difficulties in differentiating between and responding to expressions of emotion and formulating selective attachments to caregivers (Wisner Fries & Pollak, 2004; Wisner Fries, Zigler, Kurian, Jacoris, & Pollak, 2005). (Note, however, that socially deprived monkeys, in addition to lack of maternal caregiving, also experience sensorimotor deprivation; this is not usually the case in human abuse and neglect.)

These social and emotional difficulties may reflect neuropsychological difficulties in maltreated children that reflect alterations in brain maturation (Prasad, Kramer, & Ewing-Cobbs, 2005). Indeed, impaired cognitive functioning in socially deprived monkeys is associated with decreased white matter volume in parietal and prefrontal cortices, as well as alterations in the development of neuropeptide receptors that underlie fearful and anxious behaviors (Sanchez, Hearn, Do, Rilling, & Herndon, 1998; Sanchez, Smith, & Winslow, 2003). A recent brain imaging study of children with maltreatment and PTSD revealed decreases in regions such as the prefrontal cortex and right temporal lobe volumes, and increases in hippocampal white matter volume, in comparison to sociodemographically matched controls; these effects were particularly strong among abused boys (Tupler & De Bellis, 2006). It is not yet clear whether these brain differences reflect vulnerability to, or effects of, maltreatment.

Pollak and Kistler (2002) also sought to examine whether maltreatment experience alters children's sensory thresholds in ways that might undermine effective regulation of emotion. Categorical perception occurs when perceptual mechanisms enhance differences between categories at the expense of perception of incremental changes within a category. Perceiving via categories is adaptive, because it allows an observer to efficiently assess changes between categories that are environmentally important, while ignoring subtle changes that are not important. Children performed a task that required them to distinguish faces that had been morphed to produce a continuum on which each face differed in signal intensity. Abused children had atypical perceptual preferences that influenced how they categorized angry, but not other, facial expressions. These findings are consistent with the view that infants need to adjust or tune their preexisting perceptual mechanisms to process salient aspects of their environments. To further examine whether children exposed to high levels of threat are perceptually sensitive to threat cues, Pollak and Sinha (2002) examined whether these children could readily relate visual cues to representations of emotions. To do so, they developed a technique that could capture the sequential and content-based dynamics of emotion recognition. As predicted, physically abused children accurately identified facial displays of anger on the basis of less sensory input than did controls.

Pollak and Tolley-Schell (2003) also explored a second hypothesis: that the acquired salience of anger or threat-related signals undermines abused children's attentional control. Using a selective attention paradigm, they found that abused children demonstrated relative increases in brain electrical activity when they were required to disengage their attention from angry, but not happy, faces. Physically abused children also oriented rapidly to spatial locations primed by anger. Because abused children did not differ from controls on other types of trials, these findings provided additional support for the hypothesis that physically abused children have a specific problem involving flexible processing of anger, rather than general information-processing deficits. More recently, Shackman et al. (2007) found that abused children allocated more automatic resources when attempting to inhibit attention to their mothers' angry voices (Shackman et al., 2007). Importantly, these differences were correlated with both the magnitude of abuse endured by these children and their degree of anxiety symptoms (Shackman et al., 2007).

A critical question concerns how these perceptual differences in abused children might influence affective processes further along the path of information processing. In a recent study, Perlman, Kalish, and Pollak (2008) focused on children's abstract knowledge about emotions. They found that abused children differed from controls in their appraisals of the links between events and emotions. Abused preschool-age children, unlike controls, saw anger and sadness as possible emotional outcomes following from positive situations. These findings suggest that among the consequences of learning about emotions within a physically abusive context are non-normative intuitions about the causes of emotions. Such a cognitive difference would affect the thinking that guides children's social behavior. Another recent study, also with preschool-age children, examined children's control and regulation of attention when confronted with emotional stimuli (Pollak, Vardi, Bechner, & Curtin, 2005). In this study, multiple physiological measures were obtained while children overheard two adults engaged in a hostile argument. Once the angry exchange began, abused children maintained a state of anticipatory monitoring of the environment which continued even after the angry exchange ended. In contrast, control children were initially more aroused by the introduction of anger (suggesting some habituation to anger on the part of abused children); controls showed better regulation once they had assessed the background anger. These data suggest that physically abused children develop greater sensitivity to expressions of anger as a form of adaptation to an environment where threat signals may predict the occurrence of abuse. Although adaptive in an abusive context, such processes lead to complex information-processing atypicalities that compromise children's regulatory capacities.

The Hypothalamic-Pituitary-Adrenal Axis

One biological system implicated in children's regulation is the hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine system particularly vulnerable to the effects of mother-infant disruption (Gunnar, 2000; Sanchez, Ladd, & Plotsky, 2001). The mammalian stress neuroendocrine response involves the HPA and sympathetic-adrenomedullary (SAM) systems. These systems, interrelated at many levels, are coordinated in the central nervous system in part by the action of corticotrophin-releasing factor (CRF [or CRH]) in the hypothalamus and in extrahypothalamic nuclei, such as the central nucleus of the amygdala and the bed nucleus of the stria terminalis (Rosen & Schulkin, 1998). The HPA and SAM systems are functional prior to birth, but undergo maturational processes in the transition to extra-uterine life and postnatally.

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Challenges to social relationships can be potent stimuli of the HPA axis and sources of stress (Sapolsky, 1998; Selye, 1976). These factors frequently characterize situations of child abuse. Of particular concern is that the HPA axis is still maturing when children are subjected to maltreatment, raising questions about the biological consequences of maltreatment for the developmental organization of a child's stress response system (Bremner & Vermetten, 2001). The HPA axis is a major system that mediates neuroendocrine responses to stress, resulting in the release of glucocorticoids (GCs; cortisol in humans and nonhuman primates) from the adrenal cortex (see Herman et al., 2003). Superimposed upon its circadian pattern of activity, stress activates stressor-specific pathways that converge in the hypothalamus, where this information is integrated in the paraventricular nucleus by parvocellular neurons expressing CRF. CRF is released from nerve endings in the median eminence in response to metabolic, psychological, or physical threats and stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. ACTH in turn stimulates the release of GCs (cortisol in primates) from the adrenal cortex.

GCs are highly catabolic steroid hormones that affect multiple bodily functions associated with the kinds of problems observed in abused children, including energy mobilization, immune and reproductive functions, and cognition. Alterations in the normal pattern of cortisol secretion (either higher or lower than normal) have been associated with both psychiatric and somatic illnesses (McEwen, 1998; Yehuda, Halligan, & Bierer, 2002).

In rodents, there is compelling evidence that the quality of maternal care (high vs. low) has a dramatic impact on the development of neuroendocrine and neurobiological systems regulating stress physiology and adaptive behavior in the offspring. For example, the HPA axis is immature in young rodents. This is also true of other afferent and efferent pathways of threat detection and response systems that connect with the prefrontal cortex. There is substantial evidence that the development of these systems is particularly plastic and open to modification by experience during early life (e.g., Levine, 1994; Suomi, 1997; Wismer Fries, Shirtcliff, & Pollak, 2008). In particular, we know that low-quality parental care or repeated maternal separations result in offspring that become more anxious and stress-reactive adults (e.g., Meaney & Szyf, 2005; Sanchez et al., 2001). We even know very sophisticated details of the molecular mechanisms mediating some of these effects, including how maternal care affects methylation of the glucocorticoid receptor gene, and therefore its expression levels and HPA axis function (Meaney & Szyf, 2005). Recent rodent studies also indicate that interventions in the postinfancy period may help ameliorate some, but not all, of the impacts of early inadequate parental care (Francis, Diorio, Plotsky, & Meaney, 2002). Yet the validity of rodent studies for modeling the effects of early adverse experiences on stress physiology in primates is questionable. The problems include the critical differences between rodent and primate HPA axis development, and the possibility that different developmental consequences in each species are mediated by different biological mechanisms. These differences would explain the inconsistent evidence of alterations reported in studies of rat and primate HPA axis functioning (Gunnar & Vazquez, 2006).

Some primate researchers have argued that variation in parental care results in long-term changes in the neuroendocrine and neurobiological development of the offspring (e.g., Hinde, 1974). Yet little is known about the underlying mechanisms and time course of these purported effects. One clue about potential mechanisms comes from similarities between studies of nonhuman primates and rodents that pertain to effects of early adverse caregiving on the development of the frontal system and other neocortical regions involved in emotion and attention regulation. For example, Sanchez et al. (1998) studied rhesus monkeys that

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DHEA could play a major role in moderating the genesis of new brain cells (Suzuki, Wright, Marwah, Lardy, & Svendsen, 2004). Furthermore, it is possible that a combination of hyperarousal of cortisol and a blunted rhythm of DHEA may amplify the impact of adverse care on the developing brain and place adolescents at risk for anxiety and depression (Goodyer, Park, Netherton, & Herbert, 2001; Michael, Jenaway, Paykel, & Herbert, 2000).

The hypothalamic-pituitary-gonadal axis, indexed through testosterone in males, interacts with the HPA in relation to chronic stress (Dallman et al., 2002; Viau, 2002) and has been linked to individual differences in children's problem behaviors (Granger et al., 2003). Testosterone is an anabolic steroid that exaggerates aggression, competition, dominance, and risk-taking behavior in males (Monaghan & Glickman, 1992), and is suppressed by social stress or high cortisol levels (Dallman et al., 2002), particularly during puberty (Almeida, Anselmo-Franci, Rosa e Silva, & Carvalho, 1998).

Testosterone and DHEA may be particularly important during the pubertal transition, when these androgens change dramatically and behavior problems are likely to emerge (Angold & Worthman, 1993). DHEA and testosterone activity may be affected due to their sensitivity to stress (Angold, 2003; Granger et al., 2003; Mazur & Booth, 1998). Therefore, Pollak et al. (Wismar Fries et al., 2008) have recently begun examining these hormone systems in abused children. Although they are not normally viewed as stress-reactive hormones like cortisol, we believe that the evidence indicating the stress sensitivity of these hormones and their regulatory role on behaviors of interest supports the inclusion of testosterone and DHEA in studies of maltreated children.

Arginine Vasopressin and Oxytocin

In addition to CRF, other neuroactive peptides, such as arginine vasopressin (AVP) and oxytocin (OT), participate in the neuroendocrine, emotional, and autonomic responses to stress (e.g., Nemeroff & Vale, 2005; Sanchez et al., 2001). AVP and OT are neuropeptides that, in addition to their classical roles as neurohypophysial hormones (AVP as an antidiuretic hormone and OT in parturition, lactation, and reproductive behaviors), have emerged as important regulators of stress responses and critical mediators of affiliative behaviors and social recognition/memory (Whitaker-Azmitia, 2005). In the case of OT, animal and human studies have shown that this neuropeptide plays a critical role in mediating affiliative behaviors (maternal behavior, attachment, and social bonding), and reduces anxiety and HPA axis responses to stress. Early adverse experiences cause persistent decreases in OT neural circuits of animals (Winslow, Noble, Lyons, Sterk, & Insel, 2003). These findings have been recently confirmed in humans as well, as demonstrated by evidence that women with histories of childhood maltreatment had lower cerebrospinal fluid (CSF) levels of OT than controls had (Heim et al., 2006). In addition, CSF OT levels in those women were negatively correlated with severity of maltreatment. This reduced OT activity could have a detrimental effect on affiliative behaviors and stress vulnerability of women with early adverse experiences.

The effects of maltreatment experiences on OT neural circuits have been further confirmed in human studies in Pollak's lab, as demonstrated by evidence that children who experienced severe early neglect showed lower levels of salivary OT reactivity as compared with controls (Wismar Fries et al., 2005). Such findings are especially relevant, given that severely neglected children tend to have difficulties forming discriminating attachments. For example, a recent meta-analysis suggests that even many months after adoption, internationally adopted children and their parents have not caught up with typically reared children

and their parents in attachment security (van IJzendoorn & Juffer, 2006). These children may treat strangers with visible displays of affection, while they are unable to establish a sense of security with or to feel protected by their own parents (O'Connor & Zeanah, 2003).

Serotonin

One neural system of relevance to abused children is the amygdala circuitry, implicated in the evaluation of stimulus salience and, therefore, in threat responses. Hariri et al. (2002) used functional MRI (fMRI) to directly explore the neural basis of the apparent relationship between a common allelic variant in the human 5-HTT gene and emotional behavior in adults. Subjects performed a simple perceptual processing task involving the matching of fearful and angry human facial expressions. This task has been effective at consistently engaging the amygdala (Meyer-Lindenberg et al., 2005; Tessitore et al., 2005; Wang, Vijayraghavan, & Goldman-Rakic, 2004). Consistent with their hypothesis, subjects carrying the less functional 5-HTT short allele exhibited increased amygdala activity in comparison to subjects homozygous for the long allele. This finding suggests that the increased anxiety and fearfulness may reflect the hyperresponsiveness of the amygdala to relevant environmental stimuli (Bertolino et al., 2005; Heinz et al., 2005). Studies (in human and nonhuman animals) suggest that amygdala activation due to chronic stress is associated with changes in HPA axis function (Lopez, Vazquez, & Olson, 2004). A critical question in the early experience and stress literature is whether infancy experiences have organizing effects on the limbic HPA and threat systems, or whether adverse outcomes associated with early maltreatment reflect adversity that continues throughout childhood.

Brain 5-HT systems are involved in the control of mood, sleep, aggression, and locomotor activity—core functions showing dysregulation in children and adolescents with histories of childhood maltreatment. In fact, reduced serotonergic function has been reported in maltreated children (Kaufman et al., 1998). Alterations in brain 5-HT neurotransmission also contribute to different forms of psychopathology, including anxiety and mood disorders (Manji, Drevets, & Charney, 2001), and their related pathophysiological states, such as HPA axis dysregulation.

The brain 5-HT systems play an important role in the regulation of emotionality and stress physiology, and their development is sensitive to alterations in the early environment. In fact, previous studies have demonstrated that early adverse experiences (maternal deprivation and peer rearing) have a negative impact on brain 5-HT function, as reflected by lower CSF levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) than in controls (e.g., Higley, Suomi, & Linnoila, 1996). Consistent with those reports, studies by Sanchez and colleagues have demonstrated that infant maltreatment also affects the development of brain 5-HT systems in rhesus monkeys. This was reflected by reduced levels of 5-HT and 5-HIAA in CSF of maltreated monkeys, which were in turn correlated with increased anxiety in the maltreated animals (Maestripieri et al., 2006b; Sanchez et al., 2007). Based on the high comorbidity of physical abuse and high maternal rejection in animals included in the "maltreatment group," Sanchez and colleagues looked more closely at the data to determine what best predicted this finding. It was actually the high levels of maternal rejection received by the animals, and not levels of physical abuse, that were strongly associated with the observed reduction in brain 5-HT function.

The reduced CSF levels of 5-HIAA were highly stable across the first 3 years of life and were also associated in females with differences in maternal behavior with the first offspring

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try, implicated in parental rejection (Furman et al., 2002). Parental rejection is associated with abnormal relational behavior, including the matching of behavior to the environment at consistently low levels (Wang, Vijayakumar, & Wang, 2005). Effects carrying the same genotype in comparison to nonabused anxiety and depression at environmental levels in human animals suggest changes in HPA axis function with experience and that the limbic HPA system and maltreatment reflect

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emotionality and early environment. (maternal deprivation) reflected by lower levels than in controls as shown by Sanchez and development of brain 5-HT and 5-HIAA increased anxiety in animals based on the high levels found in the "maltreated" animals. To determine what factors determine what level of rejection received by the animals with the observed

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(Maestri et al., 2006a). Thus females that were physically abused by their mothers as infants and became abusive mothers themselves had lower 5-HIAA CSF levels than abused females that did not perpetuate abuse with their own offspring had. Altogether, these findings indicate the important role of early maternal care in both proper behavioral and neurobiological development of primates. They also open new questions to deepen our understanding of the biological mechanisms underlying developmental psychopathology. Consistent findings are emerging in studies of abused children. For example, maltreated children with the 5-HTT short allele and little social support had high levels of depression; however, maltreated children with the same genotype and similar levels of maltreatment, but with access to social support from other adults, showed minimal depressive symptoms (Kaufman et al., 2004). These findings not only are consistent with research in adults showing that 5-HTT allelic variation moderates the development of depression after stress, but suggest that negative outcomes may be modified by environmental factors that confer risk for psychological disorders.

Immune System

In addition to activation of the HPA axis, stress is associated with activation of innate immune responses, including the release of proinflammatory cytokines and activation of proinflammatory cytokine-signaling cascades (Pace et al., 2006; Raison, Capuron, & Miller, 2006). Relevant to the impact of early life stress on 5-HT metabolism, activation of the p38 mitogen-activated protein kinase (MAPK)-signaling cascade by cytokines including interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) increases the expression and activity of 5-HTT in the brain (Zhu, Carneriro, Dostmann, Hewlett, & Blakely, 2005). This in turn increases 5-HT reuptake, resulting in reduced levels of 5-HT available at the synapse. Based on this effect of proinflammatory cytokines on brain 5-HT systems, a study by Sanchez et al. (2007) recently examined the relationship between activation (phosphorylation) of p38 MAPK in peripheral blood monocytes and central 5-HT function in maltreated juvenile rhesus monkeys. The data showed activation of inflammatory signaling pathways in the maltreated macaques (as reflected by an increased percentage of monocytes staining positive for p38 MAPK). In addition, the activation of inflammatory signaling pathways was associated with levels of maternal rejection received early in life, and with decreased CSF concentrations of 5-HIAA. That is, the higher the maternal rejection, the higher the inflammatory markers; and the higher the inflammatory markers, the lower the CSF 5-HIAA concentrations.

These data provide the first evidence of an *in vivo* relationship between activation of p38 MAPK-signaling pathways in monocytes and reduced brain 5-HT function/metabolism in an animal model of infant maltreatment. By increasing 5-HTT expression/activity, activation of p38 MAPK-signaling pathways would be expected to decrease synaptic availability of 5-HT and to reduce 5-HT metabolites, as was found in this study. Of note, proinflammatory cytokines, including IL-1 and TNF- α , are also capable of influencing the activity of the enzyme indoleamine 2,3-dioxygenase, which metabolizes tryptophan to kynurenine and quinolinic acid, thereby shunting tryptophan from the synthesis of 5-HT (Raison et al., 2006). Thus, in addition to directly influencing the expression of 5-HTT, proinflammatory cytokines may influence 5-HT metabolism by altering the availability of tryptophan, the primary precursor of 5-HT. Taken together, the data suggest that increased activity in p38 MAPK pathways as a function of infant maltreatment may represent a novel mechanism by

which early life stress can be translated into risk for illness. Moreover, p38 MAPK pathways may serve as a unique translational target for reversing the impact of early life stress on relevant pathophysiological endpoints, including anxiety and depression. Similarly, adults who retrospectively recall maltreatment show sustained effects on immunity, such as altered B- and cytotoxic C-cell numbers and inflammatory markers (e.g., C-reactive protein, a pattern consistent with psychological states of physiological arousal and increased autonomic activity) (Danese, Pariante, Caspi, Taylor, & Poulton, 2007). These effects also appear in children (Dorshorst, Shirtcliff, Coe, & Pollak, 2007).

Summary

Research with nonhuman primate models of infant maltreatment is crucial if we are to fully understand the causes, consequences, and underlying biological mechanisms of similar experiences in humans. Longitudinal studies performed under well-controlled experimental conditions will be essential to characterize the developmental time course of biobehavioral and neurobiological alterations. Translational challenges involved in neuroscience-based approaches to understanding the effects of child abuse include the fact that most rodent and nonhuman primate studies have focused on the effects of maternal separation or isolation rearing, which more closely approximate neglect in humans than other forms of maltreatment, such as physical abuse. In addition, most clinical studies of maltreatment involve heterogeneous samples of children with different combinations of experiences. We and our colleagues are trying to address these issues by using the types of paradigms needed to conduct sophisticated and parallel neuroscience studies with children and nonhuman primates, and doing so in ways that can build bridges between the neuroscience and preventive intervention communities of researchers. By conducting preclinical studies of at-risk human children on the one hand, and harnessing the neurophysiological precision available from nonhuman primate studies on the other hand, we hope to clarify issues such as the modulatory role of the prefrontal cortex and infralimbic regions in reactivity to threat, as well as other ways in which experience-dependent fine-tuning of attention, learning, emotion, and memory systems (Black, Jones, Nelson, & Greenough, 1998) affects emotion regulation. The development of this circuitry could certainly be influenced by early maltreatment through overactivity of endocrine systems such as the HPA axis, and may be moderated by heritable characteristics of the child. The study of altered emotion-regulating processes associated with child abuse, together with biological approaches to excavate mechanisms conferring developmental risk, will synthesize key areas in which we desperately need more information to generate new solutions to mental health problems in children and adults. These include, first a focus on the neural circuitry and neurobiology of the brain's regulation of emotion, with an emphasis on understanding adaptations and sequelae of chronic social stress exposure on affective neural circuits. Second, we must focus on the development of these circuits—specifically, the processes underlying periods of rapid neurobiological change in humans during which the brain may be particularly sensitive to contextual or environmental influences. Third, we must focus on defining and specifying ways in which the environment creates long-term effects on brain and behavior, including potential corrective experiences that might foster recovery of competencies and promote health. Each of these foci holds tremendous promise for advancement of knowledge and application to the improvement of public health.

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