Development and Psychopathology **22** (2010), 1–22
Copyright © Cambridge University Press, 2010
doi:10.1017/S0954579409990228

Neurobiological adaptations to violence across development

HILARY K. MEAD, THEODORE P. BEAUCHAINE, AND KATHERINE E. SHANNON
University of Washington

Abstract

Developmental adaptations to violent environments involve a multitude of cascading effects spanning many levels of analysis from genes to behavior. In this review, we (a) examine the potentiating effects of violence on genetic vulnerabilities and the functioning of neurotransmitter systems in producing both internalizing and externalizing psychopathology; (b) describe implications of violence exposure for brain development, particularly within the hippocampus and prefrontal cortex; and (c) consider the effects of violence on developing human stress and startle responses. This review integrates literatures on the developmental effects of violence among rodents, nonhuman primates, and humans. Many neurobiological changes that are adaptive for survival in violent contexts become maladaptive in other environments, conferring life-long risk for psychopathology.

Adaptation to environmental contexts is often defined quite differently across scientific disciplines depending on the level of analysis being studied. Broadly speaking, individual adaptations to environmental events and challenges have been described most often in terms of either (a) behavioral changes that affect one's psychological adjustment or (b) structural and functional changes in biological systems subserving behavior.

Behavioral adaptation has been described extensively by others (e.g., Sroufe, 1997; Sroufe & Rutter, 1984). At this level of analysis, adaptation can be defined as behavioral adjustment to the familial, cultural, and community contexts within which a person is reared. Following from this definition, habits that are adaptive in one social context are not necessarily adaptive in another. For example, children who are reared in violent homes may develop self-protective behaviors such as vigilance and/or aggression. Although potentially useful in their environment of adaptation, such behaviors can become liabilities in mainstream settings including school (Sroufe, 1997; Sroufe & Rutter, 1984). From this perspective, many behaviors, including some that are perceived as psychopathological, may be better understood as adaptations to adverse familial, social, and cultural contexts.

This leads to a fundamental question. Are the behavioral changes elicited by high-risk environments such as violent families and communities truly *adaptive*? For example, literature on community violence shows consistent relations between youth exposure to violence and the development of aggression, and weaker although significant associations between exposure to violence and the emergence of depression, anxiety, and posttraumatic stress disorder (PTSD; e.g., Ng-Mak, Salzinger, Feldman, & Stueve, 2004). Based on such evidence alone, one might conclude that behavioral changes that follow violence exposure are usually maladaptive. However, for some adolescents who are exposed to violence, aggressive behavior is associated with *less* psychological distress (Ng-Mak et al., 2004).

Although behavioral adaptations to violence have been described in several previous reviews (e.g., Sroufe, 1997; Sroufe & Rutter, 1984), the literature on biological adaptations, although extensive, has not been well synthesized to date. Accordingly, in this paper we examine adaptation from a primarily biological perspective. Biological adaptation refers to structural and functional changes in neurobiological systems that increase an organism's likelihood of survival within a particular environment of adaptation. Such adaptations likely subserve the behavior changes associated with violence exposure noted above.

At least two fundamental features of biology provide flexibility in adaptive development. First, many genetic influences have probabilistic effects on behavior that are context dependent. For example, exposure to maltreatment moderates the link between genetic predispositions for violence and aggressive outcomes (Caspi et al., 2002; Foley et al., 2004; Kim-Cohen et al., 2006). However, many genetic predispositions do not exert such effects in nonviolent contexts.

Second, neural plasticity and pruning, which produce changes in structural and functional connections within the brain in response to environmental circumstances and experiences, permit individual adjustment to environments of adaptation (for a review, see Cicchetti & Curtis, 2006). For example, among rat pups, differing lengths of postnatal maternal separation contribute to individual differences in developing neuronal systems involved with stress responding (for a re-

Work on this article was supported by Grant MH63699 from the National Institute of Mental Health (to T.P.B.). We express thanks to Sharon Brenner, Sheila Crowell, Lisa Kopp, and Emily Neuhaus.

Address correspondence and reprint requests to: Theodore P. Beauchaine, University of Washington, Box 351525, Seattle, WA 98195-1525; E-mail: tbeaucha@u.washington.edu.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

view, see Sánchez, Ladd, & Plotsky, 2001). Neurobiological and behavioral variations associated with differing postnatal environments prepare the developing rat for similar levels of stress in later life (Teicher et al., 2003).

Human brains and human behavior also exhibit adaptive qualities that facilitate functional adjustment to high-risk environments (Ayoub & Rappolt-Schlichtmann, 2007). Such is often the case in violent contexts, where developing children adjust to chronic stressors, including emotional and physical threats. However, individual differences are observed in the forms and functions of adaptation (Margolin, 2005). Those exposed to the same set of circumstances may develop different adaptive mechanisms and strategies (Cichetti & Rogosch, 2002). Such unique behavioral trajectories following similar environmental stressors reflect what developmental psychopathologists refer to as *multifinality*.

In this paper we selectively review what is currently known about neurobiological adaptations to violence across development. In the first two sections, we focus on mechanisms underlying two broad behavioral predispositions that often follow prolonged exposure to violence: aggression and vigilance/withdrawal. We examine how genetic vulnerabilities affect which behavioral pathway is expressed, and discuss how three neurotransmitter systems are implicated and affected. Next, we consider adaptations in (a) the human stress response, (b) the startle response, and (c) hippocampal and prefrontal cortical development. In doing so, we draw from available literature on violence exposure and stress responding among rodents, nonhuman primates, and humans. We address the effects of several forms of violence exposure, ranging from early physical abuse to witnessing violence perpetrated on others. In the final sections we provide conclusions based on extant research, and recommendations for future research. First, however, we consider genetic effects on the development of behavioral adaptations to violence exposure.

Genetics of Maltreatment and Antisocial Behavior

Behavioral genetics

Given similar exposure to violence, not all children are affected equally. This is exemplified in recent research on the role of maltreatment in potentiating heritable vulnerabilities for child antisociality. Some children perpetuate violence, some become depressed, and others emerge functioning very well (Cicchetti & Toth, 1995, 2005). In part, these different behavioral responses to similar high-risk environments result from variations in genetic vulnerability. Indeed, the studies reviewed below demonstrate a complex interplay of genetic vulnerability and maltreatment risk exposure on antisocial outcomes among children.

Among 5-year-old twin pairs, Jaffee and colleagues (Jaffee et al., 2005; Jaffee, Caspi, Moffitt, & Taylor, 2004; Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004) demonstrated that risk for conduct disorder (CD) following maltreatment was strongest for those at high genetic risk. Exposure to maltreatment increased the likelihood of CD by 2% among children at lowest genetic risk (monozygotic twin did not have CD), but by 24% among children at higher genetic risk (monozygotic twin had CD). Parental antisocial behavior accounted for 56% of the effect of maltreatment on antisocial outcomes at age 7 (Jaffee, Caspi, Moffitt, Polo-Tomas, et al., 2004). It is important to note, however, that research with monozygotic and dizygotic twins reared together versus apart are the only studies that can factor out shared environmental effects.

One possible explanation for this finding is an evocative gene–environment correlation (*r*GE). In this case, children's behavior, which is affected by genes, may elicit hostile parenting practices that in turn potentiate antisocial behavior (see Patterson, DeGarmo, & Knutson, 2000). It has long been known that children with CD elicit negative and aversive behaviors from adults (Anderson, Lytton, & Romney, 1986; Patterson, 1982; Patterson, Capaldi, & Bank, 1991; Snyder, Edwards, McGraw, Kilgore, & Holton, 1994; Snyder, Schrepferman, & St. Peter, 1997). Furthermore, longitudinal studies of adoptees demonstrate that adoptive parents are more likely to engage in negative parenting with genetically vulnerable children than with children without such vulnerability (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). Behavioral genetics studies also indicate that about 50% of the association between parental criticism and adolescent antisociality is attributable to heritable effects (Narusyte, Andershed, Neiderhiser, & Lichtenstein, 2007). Consistent with this finding, Jaffee et al. (2004) found that parents were more likely to use physical discipline strategies with children at high genetic vulnerability for CD compared to children at low genetic vulnerability. However, genetic vulnerability did not predict parental abuse.

In the same study, Jaffee, Caspi, Moffitt, and Taylor (2004) showed that physical maltreatment predicted antisocial outcomes across 2 years in a dose–response fashion. This effect remained significant after controlling for parental history of antisociality, and for genetic transmission of antisocial behavior. The authors suggested that these results evidenced a passive *r*GE. However, a twin-parent design, rather than a twin-child design, is required to identify a *r*GE with certainty (see, e.g., Rutter, Moffitt, & Caspi, 2006). This is because passive *r*GEs occur when a parent's genes influence his or her behaviors, thereby affecting the rearing environment. Parents may therefore pass on "antisocial genes" that influence both their engagement in maltreatment and their child's CD. Neiderhiser et al. (2004) found that evocative rather than passive *r*GEs influenced negative parenting using both twin mother and twin child designs. Passive and evocative *r*GEs are not mutually exclusive, yet to date there is only evidence that evocative *r*GEs contribute to negative parenting and later child antisociality. These studies suggest that some children are more vulnerable (and that some are more resilient) in the face of physical maltreatment than others. Researchers conducting molecular genetics research have attempted to specify genetic vulnerability polymorphisms.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

Molecular genetics

A polymorphism in the promoter region of the monoamine oxidase A (*MAOA*) gene has gained considerable attention as a potential moderator of individual responses to violence exposure. The *MAOA* gene is located on the X chromosome and encodes for functional variation in the MAOA enzyme. MAOA metabolizes all monoamine neurotransmitters, including norepinephrine (NE), serotonin (5-HT), and dopamine (DA), deactivating each.

Caspi and colleagues (2002) conducted a prospective 26-year longitudinal follow-up study of maltreatment and antisocial outcomes, linking both to polymorphisms in the *MAOA* gene. A main effect of maltreatment exposure on later antisociality and several Gene × Environment (G × E) interactions emerged. MAOA activity alone did not affect antisocial outcomes, yet maltreatment moderated the effect of the functional polymorphism on later antisocial behaviors. Male participants with high MAOA activity who were maltreated as children were less likely than those with low MAOA activity and a history of maltreatment to engage in antisocial behavior. Results converged across a composite index and several of the individual measures.

Foley et al. (2004) replicated these results among white male twins ages 8–17. Environmental risk was indexed broadly by parent and child reports of parental neglect, exposure to interparental violence, and inconsistent discipline. The authors found a main effect for adversity on CD and a moderational (interaction) effect for childhood adversity and the *MAOA* genotype. Other researchers have failed to find moderating effects of maltreatment on MAOA in predicting CD (Haberstick et al., 2005; Huizinga et al., 2006; Young et al., 2006). However, in two of these studies maltreatment was reported retrospectively, and outcomes were assessed during childhood and adolescence rather than adulthood. Nonetheless, Kim-Cohen et al. (2006) replicated findings among a younger sample. This research group also conducted a meta-analysis of MAOA moderation of maltreatment and later antisocial outcomes among white males. Across studies, children with low MAOA activity were more likely to develop conduct problems than children with high MAOA activity.

Despite several positive findings, MAOA × Maltreatment interactions on antisociality require further study. In theory, such findings should hold for males in particular because MAO is X linked. Accordingly, females who inherit a low MAOA activity allele on one of their two X chromosomes have less vulnerability compared with males who inherit a copy on their single X chromosome. Consistent with this conjecture, Beaver, DeLisi, Vaughn, and Barnes (in press) recently reported that males with a the high risk MAOA allele were (a) more likely to join gangs and (b) more likely to use weapons than those without the high risk allele. Despite a large sample of both sexes, no such effects were found for females. Furthermore, emerging literature suggests that MAOA activity may confer risk for aggression among males but depression among females. Although this sex effect is poorly understood (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009), it may be rooted in differences in neurotransmitter expression, which we consider in later sections.

Several null findings of MAOA interactions have also been reported among non-White samples. One potential explanation for these negative findings is low statistical power (see Beauchaine, Hinshaw, & Gatzke-Kopp, 2008). For example, Widom and Brzustowicz (2006) failed to find a moderational effect of the *MAOA* gene among non-White abused individuals, yet the high *MAOA* activity gene buffered abused and neglected Whites from becoming violent and antisocial in adulthood. However, only one-third of the sample was non-White, and included African Americans, Latinos, Native Americans, and Pacific Islanders, among other racial minorities. Thus, the minority sample was much smaller than the White sample. It is also problematic that all non-White participants were combined into a single minority group for analyses. This is because the promoter gene polymorphism is stratified by ethnicity (e.g., Balciuniene, Syvänen, McLeod, Pettersson, & Jazin, 2001). Thus, replication among other racial groups is important, and future research should include adequate sample sizes to conduct within racial groups analyses.

Adaptiveness of antisocial behavior

In general, aggression and impulsivity are adaptive for immediate self-protection, and for long-term establishment of dominance in social hierarchies. Indeed, at the behavior level aggression is likely to be negatively reinforced by offenders when met with retaliation. Subsequently, children who have used aggression successfully for self-protection may develop an aggressive response style in anticipation of future violence.

However, the adaptiveness of aggression and associated impulsivity for any particular individual depends on context and developmental level. For example, an aggressive response style is likely maladaptive for young children within abusive homes. In such cases, parent- and/or caretaker-directed aggression would likely provoke abusive responses from adults. However, for adolescents aggression may serve more of a protective role because it may deter adults from further physical confrontation.

Aggression is also maladaptive in nonviolent contexts. Children who are raised within violent homes and neighborhoods form aggressive interpersonal schemas and anticipate that interactions with others will involve violence (see, e.g., Dodge, 1993). Given this social–cognitive framework, unprovoked aggression may be expected, yet is nevertheless a hindrance to positive adjustment in mainstream culture.

Our review of Gene × Maltreatment interactions may lead the reader to question the adaptive value of particular genes. Yet genes themselves are not adaptive or maladaptive. Rather, genes relate to behavioral traits that are adaptive in

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

particular contexts. Low MAOA activity is better construed as a vulnerability in high-risk environments. That is, low MAOA activity appears to confer vulnerability for the development of antisocial behavior following maltreatment. In contrast, high MAOA activity confers protection.

It is important to note that maltreatment in the home represents an extreme form of violence. Very little research has addressed the interaction of MAOA and other forms of violence (e.g., peer victimization, witnessing community violence). Firm inferences about whether MAOA moderates antisocial outcomes for other types of violence exposure will require targeted research. However, what is clear from Caspi et al. (2002) and the other studies is that antisocial behavior is more likely among individuals who have incurred severe forms of maltreatment. Yet it is also possible that less severe violence exposure moderates the effects of MAOA on antisocial outcomes (see, e.g., Beaver et al., in press). Yet, as demonstrated in the following literature concerning maltreatment and depression, protective factors such as social support may mitigate such effects. Furthermore, some children who are exposed to violence outside their homes may receive appropriate nurturance within their homes.

Maltreatment and Depression

Behavioral genetics

The relation between exposure to maltreatment and later depression is well established (Cicchetti & Toth, 1995, 2005). However, genetic and otherwise heritable effects have not been investigated as thoroughly as in the antisociality and maltreatment literatures. Nevertheless, research conducted with depressed and abused children (Kaufman, Birmaher, Brent, et al., 1998), and depressed adults who are exposed to stressful life events (Kendler et al., 1995; Kendler & Karkowski-Shuman, 1997) suggests that the likelihood of developing mood disorders following maltreatment may be partly heritable.

Research from the Virginia Twin Study provides evidence for an interaction between heritability for mood disorders and stressful life events in the emergence of depression among adult women (Kendler et al., 1995). For those at lowest genetic risk (monozygotic twins, co-twin unaffected), the probabilities of developing depression were 0.5% and 6.2% in the absence and presence of stressful life events, respectively. For those at high genetic risk (monozygotic twins, co-twin affected), the probabilities of developing depression were 1.1% and 14.6% in the absence and presence of life events, respectively. Furthermore, discrete time survival analysis showed that genetic risk for depression increased the likelihood of exposure to stressful life events (Kendler & Karkowski-Shuman, 1997), suggesting an evocative *r*GE. These studies provide evidence that heritable vulnerabilities influence the development of depression following maltreatment, leading to interest in identifying probable candidate genes.

Molecular genetics

As noted above, it is well established that exposure to maltreatment increases the probability of emerging depression (e.g., Kaufman et al., 2004, 2006; Taylor et al., 2006). A genetic polymorphism in the promoter region of the 5-HT transporter (*5-HTT*) gene appears to moderate this relation. *5-HTT* affects reuptake of 5-HT within brain synapses. The short (s) allele produces lower transcriptional efficiency of the promoter and lower 5-HT reuptake compared with the long (l) allele (Nakamura, Ueno, Sano, & Tanabe, 2000).

Using prospectively collected maltreatment and genotype data, Caspi et al. (2003) explored depressive outcomes among 26-year-old Caucasian New Zealanders. Although the *5-HTT* gene did not have a direct effect on depression, men and women with childhood maltreatment histories were more likely to endorse depressive symptoms as adults if they were either homozygous (s/s) or heterozygous (s/l) for the s allele than if they were homozygous for the l allele (l/l). These effects were independent of MAOA status. This implicates maltreatment as a moderator of the long-term effects of 5-HTT on depression.

Others have replicated this result using cross sectional data. For example, among an ethnically diverse group of 5- to 15-year-old maltreated children, Kaufman and colleagues (2004) reported that s/s individuals were more likely to experience current depressive symptoms than s/l and l/l children. However, the presence of social supports lowered the associated risk of the *5-HTT* s/s genotype for depression. Social supports were independent of maltreatment status. In another report, Kaufman et al. (2006) investigated maltreatment, *5-HTT*, and genotypes of brain-derived neurotrophic factor (BDNF). BDNF, a protein that supports growth and differentiation of neurons (including 5-HT), has been associated with childhood-onset depression (Strauss et al., 2004). At least one methionine allele in the val^{66}met polymorphism of the *BDNF* gene is associated with lower secretion of BDNF, reduced neocortical volume (Pezawas et al., 2004), and abnormal hippocampal structure and function (Egan et al., 2003). A three-way interaction between maltreatment, *5-HTT* gene expression, and the val^{66}met polymorphism of the *BDNF* genotype predicted symptoms of depression in children. Children who were (a) homozygous for the short allele of the *5-HTT* gene and (b) positive for the met allele of the *BDNF* genotype had the highest depression scores. Again, social support attenuated the associated risk between maltreatment and genetic vulnerability. Wichers et al. (2008) replicated this three-way interaction among an adult female twin sample. Individuals with the *BDNF* met allele and the *5-HTT* s allele, who experience greater childhood adversity, were most likely to report current depression. However, it is important to note that three-way interactions are notoriously difficult to replicate (see Beauchaine, 2009). Thus, further study of such interactions is particularly important.

Research with adult males and both adolescent and adult females (Caspi et al., 2003; Eley et al., 2004; Kendler et al., 2005; Taylor et al., 2006) has also documented moderating

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

effects of general stressful life events on relations between *5-HTT* and depression. Such stressors include childhood physical punishment, emotional abuse, exposure to domestic violence, and parental discord. As expected, the s/s and s/l genotypes increased the likelihood of depression under stressful life circumstances. Importantly, Caspi et al. (2003) ruled out the possibility of an evocative *r*GE effect in which the genotype is linked with experiencing more stressful life events. Together, these results suggest that broad rather than specific forms of stress exposure, including witnessing violence, may confer risk for depression among those with at least one copy of the *5-HTT* s allele. Despite several replications, however, the moderating effect of the *5-HTT* s allele on depression following stress exposure has recently been called into question (Risch et al., 2009). Thus, further research may be needed to disentangle circumstances that have led to both positive and negative findings.

One important consideration is that s alleles of the *5-HTT* gene are not distributed equally across ethnic groups. About 50% of Caucasians carry at least one s allele (Caspi et al., 2003), whereas African Americans are more likely to be homozygous for the l allele than both Caucasians and Latinos (Kaufman et al., 2004, 2006). Moreover, Japanese individuals are more likely to carry one or more s alleles than Caucasians (Kunugi et al., 1997). Thus, the *5-HTT* gene is stratified by race, suggesting that rates of depression following exposure to maltreatment (and other stressors) should vary across ethnic groups.

Cicchetti, Rogosch, and Sturge-Apple (2007) recently reported on depressive outcomes related to childhood maltreatment and polymorphisms of both 5-HTT and MAOA among adolescents. Results indicated that adolescents with low MAOA activity, who experienced at least three types of maltreatment in terms of neglect, physical abuse, sexual abuse, and emotional abuse, were likely to report elevated depression scores. Adolescents who were homozygous for the s allele of the *5-HTT* polymorphism and had histories of sexual abuse showed elevated depression, anxiety, and somatic symptoms. Among adolescents with sexual abuse histories, only those who had at least one short *5-HTT* allele *and* low MAOA activity had elevated depression, anxiety, and somatic symptoms. This research may clarify our understanding of the effect of 5-HTT on depression, with both stressful life events and MAOA activity acting as moderators. As noted above, however, it is especially important to replicate higher order interactions.

Adaptiveness of depression

Depression may be considered adaptive if it protects children from imminent danger, bodily injury, and/or wasted effort (Nesse, 2000). For example, low motivation and learned helplessness may prevent ineffective resistance to violent and dominant adults. Furthermore, withdrawal and vigilance are useful behaviors because they facilitate early detection of future violence. Children who anticipate violence by reading warning signs among caregivers may escape abuse. More generally, anxiety and inhibition decrease the likelihood of approaching threatening situations. Nevertheless, like aggression, anxiety and mood disorders may become maladaptive when applied outside of violent contexts. For instance, depression is associated with poor social skills among children (Segrin, 2000). Furthermore, heightened vigilance may present difficulties in more benign environments such as school.

Again, behaviors themselves rather than genetic vulnerabilities are adaptive. The research reviewed above suggests that the l allele of the *5-HTT* polymorphism, and the high activity *MAOA* gene are protective against the development of depression among youth exposed to maltreatment. In contrast, the s allele of the *5-HTT* polymorphism and the low *MAOA* activity genotype appear to be vulnerability factors for depression in violent contexts.

Effects of Violence Exposure on Neurotransmitter Function

Because MAOA is responsible for degrading all monoamine neurotransmitters, the low activity genotype affects synaptic DA, NE, and 5-HT levels. The short allele of the *5-HTT* gene leads to less efficiency in 5-HT reuptake, and more synaptic 5-HT. Although it is tempting to conclude that more of these neurotransmitters lead to psychological difficulties in the developmental context of violence, evidence suggests that neurotransmitter–behavior relations are far more complicated. Individual differences in these neurotransmitters and their interactions influence temperament and stress responsivity. In turn, these individual differences affect how individuals cope with and/or react to exposure to violence.

Accordingly, in this section we addresses environmentally elicited changes in monoamine neurotransmitter system functioning. These neurotransmitters have been the focus of considerable theoretical and empirical work on behavior regulation, personality, and psychopathology (e.g., Beauchaine, 2001; Cloninger, 1987; Fowles, 1988; Gray, 1982, 1987; Gray & McNaughton, 2000; Quay, 1993, 1997; Rogeness, Javors, & Pliszka, 1992; Rogeness & McClure, 1996). For example, Gray (1982, 1987) proposed that two neurobiological systems, the behavioral inhibition system (BIS) and the behavioral activation system (BAS), subserve aversive and appetitive motivation, respectively. Based on literatures addressing animal learning and anxiolytic drugs, Gray suggested that specific DA networks comprising the BAS subserve both approach behaviors in response to reward and active avoidance behaviors in response to punishment, whereas noradrenergic and serotonergic networks subserve passive avoidance of punishment. Gray also suggested that the relative strength of the BIS and BAS interact to affect individual differences in behavior (Gray, 1987). These three neurotransmitters innervate many common brain regions (Rogeness & McClure, 1996). Thus, although we examine each neurotransmitter system separately, one should keep in mind that these systems interact to affect behavior. For example, 5-HT neurotransmission gates activity within mesolimbic DA

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

networks (e.g., Gershon, Vishne, & Grunhaus, 2007). In the sections below, we review each neurotransmitter with respect to behavior and sensitivity to violent contexts.

DA

Nonhuman primate studies demonstrate that DA receptors, particularly within mesolimbic brain regions including many structures within the striatum, develop early in gestation. In contrast, peak dopaminergic axonal growth in mesocortical structures, including the neocortex, is not reached until the onset of puberty (Lewis, 2000). After puberty, axon densities decline rapidly and ultimately reach stable levels. DA receptors appear throughout the brain, but two areas are responsible for initiation of DA neurotransmission: the ventral tegmental area and the substantia nigra. These structures project to the three major DA pathways, each of which has distinct yet interrelated functions. DA cells that originate in the ventral tegmental area project through the mesolimbic pathway to the nucleus accumbens. DA signals then project forward through the mesocortical pathway to the anterior cingulate and medial prefrontal cortices (PFCs; Gatzke-Kopp & Beauchaine, 2007; McArthur, McHale, & Gillies, 2007; Sagvolden, Johansen, Aase, & Russell, 2005). Broadly speaking, the mesolimbic pathway subserves reward and punishment responding, approach motivation, and emotion, whereas the mesocortical pathway subserves cognition, working memory, self regulation, and planning (McArthur et al., 2007). DA neurotransmission originating in the substantia nigra projects along the nigrastriatal pathway, which subserves sensorimotor integration and fight/flight responding.

The mesolimbic pathway comprises the BAS described by Gray (1987; Gray & McNaughtan, 2000) and others. Cloninger (1987) proposed that DA neurotransmission within this network is linked with individual differences in novelty seeking, including impulsive responding and exploratory behaviors. Extending this work, Beauchaine (2001), Fowles (1988), Quay (1993), and Rogeness et al. (1992) proposed that DA dysfunction underlies unrestrained approach behaviors characteristic of attention-deficit/hyperactivity behavior (ADHD) and CD.

More recently, theories of ADHD and CD have been refined based on advances in neuroimaging technologies. Hypodopaminergic functioning within the mesolimbic system has been proposed as a core neural substrate of ADHD, and of disinhibition more generally (Beauchaine & Neuhaus, 2008; Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005). Data from positron emission tomography studies show that low levels of subcortical DA are linked with irritability and novelty seeking among healthy adults (Laasko et al., 2003; Suhara et al., 2001). Similarly, functional magnetic resonance imaging (MRI) data show decreased ventral striatal activation during anticipation of reward among children with ADHD (Scheres, Milham, Knutson, & Castellanos, 2007). The hypodopaminergic functioning hypothesis of impulsivity is also supported by studies that show attenuated sympathetic-linked cardiac reactivity to reward among children and adolescents with ADHD and CD (e.g., Beauchaine, Hong, & Marsh, 2008; Beauchaine, Katkin, Strassberg, & Snarr, 2001; Crowell et al., 2006). Such effects appear to be downstream consequences of mesolimbic DA dysfunction (Brenner, Beauchaine, & Sylvers, 2005).

Several lines of research suggest that exposure to adverse environments, including those characterized by violence, can induce long-term downregulation of central DA activity. These studies show compensatory decreases in DA transporter (DAT) expression, increased responses to stress, and behavioral sensitivity among exposed rats (Meaney, Brake, & Gratton, 2002). In addition, recent research indicates a relation between low levels of homovanillic acid, a DA metabolite, and maternal rejection among cross-fostered infant rhesus macaques (Maestripieri, Higley, et al., 2006).

DA functioning may also be altered in both deprived and violent contexts. For example, experience-dependent changes in DAT densities within mesolimbic brain regions of male rats are observed following repeated exposure to dominant males (Lucas et al., 2004). Moreover, repeated episodes of maternal separation early in the lives of rat pups produce long-term decreases in DAT expression (Meaney et al., 2002). Of particular significance, these effects result in greater sensitivity to the behavioral effects of cocaine and amphetamines later in life. In contrast, literature on neonatal handling shows that early maternal care mitigates DA responses to stress in adulthood. In this paradigm, human handling of neonatal rats engenders *enhanced* maternal care, including increased arched-back nursing, licking, and grooming. Through these mechanisms, rat mothers mitigate repeated stressful handling events. For example, Panagiotaropoulos and colleagues (2004) found a higher DA turnover rate, particularly in the hypothalamus, among rats that had been handled as neonates.

Studies of adult rats have also been used to examine the effect of stress on DA functioning, and may inform our understanding of neural plasticity within dopaminergic structures. For example, in a restraint paradigm, rats initially showed an increase in mesolimbic DA release during the first 40 min of a 120-min restraint (Imperato, Cabib, & Puglisi-Allegra, 1993). However, after repeated exposure to stress, DA release decreased. Thus, exposure to the same stressor over time eventually reduced DA levels. Lowered DA in these brain regions is consistent with other investigations of the effects of chronic stress (e.g., Sheikh et al., 2007).

Chronic exposure to stress hormones may also inhibit DA metabolism (Lindley, Bengoechea, Wong, & Schatzberg, 2002). Single and controllable stressors appear to induce an influx of DA in the nucleus accumbens, whereas repeated and uncontrollable stressors deplete DA in the nucleus accumbens (for a review, see Cabib & Publisi-Allegra, 1996). This appears to occur through compensatory changes in DAT expression. The DAT regulates synaptic DA concentrations through reuptake into presynaptic terminals. Isovich, Mijnster, Flügge, and Fuchs (2000) examined the effect of chronic social stress on the DAT in shrews. Subordinate male shrews evidenced elevated stress hormones and enlarged adrenal glands after repeated exposure to a dominant male. DA

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

transporter binding sites were reduced in the caudate and the putamen, two structures located within the mesolimbic reward pathway, but not the nucleus accumbens, ventral tegmental area, or substantia nigra. Lucas et al. (2004) also reported decreased DAT densities in the caudate and putamen after a single social stressor, and reduced DAT densities in the nucleus accumbens of male rats in a similar chronic social stress paradigm. In turn, this shift in DAT densities reduced DA reuptake, and increased DA availability in the synapse.

Altered DA functioning appears to be moderated, at least in part, by social factors during recovery. Lucas, Wang, McCall, and McEwen (2007) demonstrated decreased DAT binding in the striatum among rats that were exposed to repeated restraint stress and then housed individually. In comparison to a group of rats that were housed in pairs, individually housed rats experienced persistently high stress hormone levels. The rats housed in pairs did not demonstrate the expected reduction of DAT binding. Rather, these rats showed an increase in DAT binding. Thus, stress responding appears to be implicated in altered DA functioning.

Finally, social defeat, which might be considered analogous to violence exposure, appears to sensitize the mesolimbic DA system to drugs of abuse later in life (Miczek, Covington, Nikulina, & Hammer, 2004). For example, Covington and Miczek (2005) showed that subordinate male rats that lost in an aggressive interaction self-administered more cocaine than those in control social conditions. These rats also demonstrated enhanced motoric behavior after amphetamine challenge compared to both rats that had won the aggressive interaction and controls. Thus, social defeat also appears to sensitize the mesolimbic DA system.

In summary, evidence from rat studies shows that central DA systems are altered by chronic stress, which downregulates central DA functioning. Furthermore, neuroimaging research with humans suggests that hypoactive DA levels in mesolimbic structures are linked with hyperactivity and impulsivity. One possible implication is that stressful environments potentiate impulsive behavior due to environmentally induced alterations in central DA systems.

How genetic vulnerability, including lower MAOA activity, interacts with the effects of stress on DA has yet to be elucidated. The authors of one study failed to establish *MAO* gene expression as a mediator of glucocorticoid induced DA alterations (Lindley, She, & Schatzberg, 2005). The search for the specific mechanism of action of MAOA within violent contexts will likely guide future research in this area. For now, it is clear that (a) DA, particularly in the mesolimbic reward pathway, is downregulated by stress, including acute and chronic exposure to diverse forms of aggression; and (b) early adverse experiences moderate the effects of MAOA polymorphisms on future antisocial behavior.

NE

NE is released both centrally from the locus coeruleus (LC), which is situated within the pons of the brain stem, and peripherally from the adrenal medulla. NE is synthesized from DA, which exemplifies the interdependence of these neural systems. Two notable enzymes in the conversion of DA to NE are tyrosine hydroxylase, which limits the rate of synthesis (Lewis, 2001), and DA-β-hydroxylase (DBH), which catalyzes the oxidation of DA into NE. Developmentally, NE plays a primary role in the self-organization of the brain (Flügge, van Kampen, & Mijnster, 2004). The LC projects to the neocortex, limbic brain regions, the thalamus, and the cerebellum, which are activated during wakeful states.

Cloninger (1987) proposed that NE is related to resistance to extinction of previously rewarded behaviors and to enhanced responses to conditioned signals of relief from punishment. According to Cloninger, those with sensitive NE systems have reward-dependent personality styles, including sensitivity to social cues, eagerness to please and help others, productivity, and the propensity to delay gratification for later rewards. In contrast, those with insensitive NE systems are likely to prefer less social contact. In support of this claim, lower cerebrospinal fluid levels of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) have been linked with solitary play and avoidance of others among cross-fostered juvenile nonhuman primates (Maestripieri, McCormack, Lindell, Higley, & Sánchez, 2006).

The LC serves as a general arousal system. Acute stress activates the LC via corticotrophin releasing factor, a major hormone of the hypothalamic–pituitary–adrenal (HPA) axis (Charney, 2004; Tsigos & Chrousos, 2002). This process stimulates the sympathetic nervous system, resulting in immediate increases in heart rate and downstream HPA axis reactivity. Concurrently, NE release suppresses parasympathetic and neurovegetative functions such as eating and sleeping (Charney, 2004; Porges, 1995; Tsigos & Chrousos, 2002). High levels of activation of the LC inhibit activation of the PFC, which can lead to dominance of instinctual over executive cognition (Charney, 2004). The LC also stimulates the amygdala during acute stress, and enhances memories via activation of the hippocampus (Tsigos & Chrousos, 2002). NE production is regulated through a negative feedback loop (Tsigos & Chrousos, 2002).

NE has a faster turnover rate during periods of stress (Carrasco & Van de Kar, 2003; Flügge et al., 2004). Production of NE is facilitated during stress through increased production of tyrosine hydroxylase (Stone & McCarty, 1983). Animal studies show that physical stress increases (a) conversion of NE into adrenaline in the brain stem (Flügge et al., 2004), (b) levels of the NE metabolite MHPG in the brain, (c) the release of NE in the hippocampus, and (d) sensitization to future stressors (for a review, see Carrasco & Van de Kar, 2003). NE released in response to acute stress enhances classical conditioning, and is partly responsible for the expression of anxiety (Tanaka, Yoshida, Emoto, & Ishii, 2000).

Mechanisms through which stress affects central NE pathways in developing organisms have not been investigated thoroughly. However, data from maternally separated versus handled neonatal rats show that early stress events affect NE

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

responses to stress in adulthood (Liu, Caldji, Sharma, Plotsky, & Meaney, 2000). As mentioned previously, brief human handling of neonatal rats leads to enhanced maternal care. Liu et al. (2000) found that maternally separated neonates exhibit elevated NE as adults during prestress conditions. In response to restraint stress, maternally deprived neonates displayed elevated NE, whereas those handled exhibited suppressed NE in the hypothalamus as adults compared with a control group. In vitro audioradiographic analyses showed that handled neonates had the greatest number of α_2 noradrenergic receptors in the LC, followed by control rats. Maternally separated rats had the fewest α_2 noradrenergic receptors. Thus, early stress events may contribute to dysregulation of the LC negative feedback loop via a down regulation of α_2 noradrenergic receptors. In turn, this likely contributes to elevations in HPA axis reactivity.

Research indicates elevated cisternal cerebral spinal fluid (CSF) corticotropin releasing factor (CRF) among adult bonnet macaques raised under variable foraging conditions as infants (Coplan et al., 1996, 1998). Variable foraging conditions lead to alterations in maternal behavior including increased dominance and decreased maternal grooming, and to stable anxiety traits among infants (e.g., Rosenblum & Paully, 1984). However, this rearing condition has not produced changes in CSF MHPG (Coplan et al., 1998). In contrast, intermittent mild stress during early development lowers baseline MHPG among adolescent squirrel monkeys (Parker et al., 2007). However, exposure to mild stress has not been related to MHPG measured later in adulthood, nor to measures of any specific behaviors (Parker et al., 2007).

Among humans, children with PTSD following diverse maltreatment histories show elevated 24-hr urinary NE compared to (a) children without maltreatment histories, (b) children without psychiatric problems, and (c) children with anxiety disorders (De Bellis, Baum, et al., 1999). Levels of urinary NE correlate with the duration of both trauma and PTSD (De Bellis, Baum, et al., 1999), and predict PTSD symptoms 6 weeks posttrauma (Delahanty, Nugent, Christopher, & Walsh, 2005). Moreover, girls with sexual abuse histories exhibit elevated urinary concentrations of the NE metabolite vanillyl mandelic acid in the absence of elevated NE (De Bellis, Lefter, Trickett, & Putnam, 1994). These children also display increased rates of dysthymia, suicidal ideation, and suicide attempts. Notably, participants in the De Bellis et al. study had a mean age of 11 years, experienced sexual abuse for several months beginning at around age 6, but had been in safe homes for at least 1 year. Among adults, women with childhood abuse histories and current PTSD also show elevated urinary NE (Lemieux & Coe, 1995).

Elevated catecholamines have also been observed among children with less direct exposure to violence. For example, Gottman and Katz (1989) observed a positive relation between parental discord and child urinary catecholamines. Among adolescents, elevated daily NE is also associated with experiencing, seeing, and even hearing about violence (Wilson, Kliewer, Teasley, Plybon, & Sica, 2002). Elevated epinephrine following violence exposure is found consistently in research with both depressed children and adults (see Heim & Nemeroff, 2001).

Interrelations among stress, DBH, and behavior have also been investigated. DBH is detectable in plasma and CSF, and is associated with fluctuations in DA and NE levels (Cubells & Zabetian, 2004). Low DBH is associated with elevated DA to NE ratios (Kim et al., 2002). Furthermore, studies have associated peripheral levels of DBH with aggressive behaviors, particularly among males (Bowden, Deutsch, & Swanson, 1988; Gabel, Stadler, Bjorn, Shindledecker, & Bowden, 1993; Rogeness, Hernandez, Macedo, Amrung, & Hoppe, 1988). Consistent with such findings, Bowden et al. (1988) found that their sample also had relatively low levels of platelet MAO.

Violence exposure during certain developmental periods appears to dampen DBH activity. Galvin et al. (1995) noted that stress initially stimulates DBH production, yet similar to findings outlined above regarding DA, chronic stress appears to suppress enzymatic activity. Rogeness, Amrung, and Harris (1984) provided the first clinical evidence of this effect, demonstrating low serum levels of DBH among boys who were neglected and/or abused physically. However, Rogeness et al. (1986) did not find an association between abuse and serum enzyme activity in a larger sample. Galvin et al. (1995) proposed that this null finding may have been due to failure to account for the timing of abuse.

Studies with two samples of maltreated children support this supposition. Galvin and colleagues (1991) found an inverse relation between DBH and children's history of abuse or neglect, but only when maltreatment occurred before age 36 months. Further analyses of this sample revealed that boys with low DBH also had problems with authorities and peers, which were more frequent when abuse occurred before age 36 months (Galvin, Stilwell, Shekhar, Kopta, & Goldfarb, 1997). Examination of serum DBH activity in another sample of psychiatrically hospitalized boys showed that those who experienced maltreatment before age 6 had lower enzyme levels than both controls and boys who first experienced maltreatment after age 6. Thus, maltreatment early in development is related to lower levels of serum DBH among boys. It is unclear why this relation does not extend to girls.

Rogeness et al. (1992) indicated that low DBH is more reflective of low NE than altered DA. Quay (1993) also suggested that the relation between low DBH and problems of disinhibition reflects an inefficient NE system. In turn, data suggest that lowered NE is associated with aggression among boys, and may be related to early abuse.

Although interesting, these findings do not inform us directly about neurotransmitter levels, as relationships between the enzyme activity and neurotransmitter levels are rarely 1:1. Furthermore, without conducting true experiments in which children are randomized into high and low risk environments, a morally indefensible practice, directions of causality cannot be determined. Indeed, recent molecular genetics research

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

suggests that plasma DBH is determined in large part by heritability, and is stable across time (Cubells & Zabetian, 2004).

Nevertheless, it is clear from animal research that NE functioning is altered following a wide range of stressors, including chronic though indirect violence exposure (e.g., Wilson et al., 2002). Consistent with inferences about DA, we expect that specific genetic polymorphisms contribute to individual variability. Future research exploring the correlates of NE expression will likely elucidate specific mechanisms. One likely candidate mechanism is the MAOA polymorphism, given its effect on both NE and DA, and given that NE is synthesized from DA.

5-HT

Serotonergic neural circuits originate in the raphe nuclei of the brain stem and project throughout the central nervous system (Rogeness et al., 1992). 5-HT is synthesized from the precursor amino acid tryptophan. In turn, tryptophan hydroxylase is a rate-limiting converting enzyme. As a neurotransmitter with widespread projections throughout the brain, 5-HT plays a role in modulating and gating the responses of other neurotransmitters, including DA. In addition, 5-HT contributes to the regulation of arousal, mood, and impulse control. There are at least seven groups of 5-HT receptors. Among these, 5-HT_{1a} contributes to modulation of anxiety, whereas 5-HT_{1b} is implicated in impulsive behaviors including aggression and both alcohol and drug use (Cravchik & Goldman, 2000). 5-HT_{1a} receptors are found in the superficial cortical layers, the hippocampus, the amygdala, and the raphe nucleus.

Aversive stimuli, whether real or perceived, activate the septohippocampal system and inhibit exploratory behavior. In contrast to traditional theories of the hippocampal role in memory and spatial learning, Gray (1982, 1987; Gray & McNaughton, 2000) proposed that the septohippocampal system is also involved in inhibition and anxiety. The septohippocampal system includes the septum, hippocampus, dentate gyrus, entorhinal cortex, subicular area, and the posterior cingulated cortex. Gray suggested that this system detects conflict in goals, monitoring punishment and nonrewarding stimuli. This detection leads to increased attention and passive avoidance of threat, an evolutionarily adaptive response to uncertainty.

Like Gray, Cloninger (1987) linked 5-HT functioning to harm avoidance, or trait anxiety. Consistent with this supposition, anxiolytic drugs inhibit basal hippocampal activity (Gray & McNaughton, 2000). Moreover, anxiety disorders and depression have been linked consistently with 5-HT dysfunction. Accordingly, most pharmacological treatments for depression target the central 5-HT system (Hidalgo & Davidson, 2000), and many selective 5-HT reuptake inhibitors (SSRIs) also have anxiolytic effects (Carrasco & Van de Kar, 2003). In addition, 5-HT_{1a} receptor densities are reduced among depressed patients during both depressive episodes and remission, and among patients with panic disorder (Drevets et al., 1999, 2007; Neumeister et al., 2004).

As noted by Gray (1982, 1987; Gray & McNaughton, 2000), benzodiazepines and other anxiolytics block the expression of both previously acquired avoidance behaviors and electrodermal reactivity in anticipation of conditioned aversive stimuli. Benzodiazepines inhibit serotonergic neurons originating in the dorsal raphe nuclei. Because 5-HT facilitates the acquisition of avoidance in the face of punishment, suppression of 5-HT inhibits conditioned anxiety to aversive stimuli (Lucki, 1998).

5-HT has also been implicated consistently in the expression of aggression. Research with rodents and nonhuman primates shows that depletion of 5-HT leads to aggressive behavior (for review, see Lucki, 1998). Among children, both cross-sectional and longitudinal research have linked lower peripheral 5-HT to aggression (Kruesi et al., 1990, 1992). More recent research has linked reduced 5-HT reactivity to fenfluramine among children with antisocial personality traits 9 years later (Flory, Newcorn, Miller, Harty, & Halperin, 2007). An inverse relation between whole-blood 5-HT and problem behaviors has also been found among children of alcoholic fathers (Twitchell et al., 1998). Among adults, impulsive aggression, including suicide attempts, predicts blunted prolactin responses to the fenfluramine challenge (Coccaro et al., 1989). Fenfluramine activates 5-HT release and inhibits 5-HT reuptake. Prolactin is released by 5-HT stimulation, so prolactin responding indexes 5-HT reactivity (Pine et al., 1997). However, there are inconsistencies regarding this effect in the literature (Castellanos et al., 1994; Halperin et al., 1997; Pine et al., 1997; Schulz et al., 2001).

5-HT synthesis is affected by the typical stress response. For instance, various physical stressors produce increases in tryptophan availability, 5-HT synthesis, and 5-HT metabolism. These increases may be an adaptation to initial 5-HT depletion (see Carrasco & Van de Kar, 2003), as CRF released in the raphe nuclei is associated with decreased release of 5-HT (Heim & Nemeroff, 2001). 5-HT expression is also affected by early life stress. 5-HT_{1A} receptors are downregulated under conditions of elevated stress hormones (Charney, 2004). This functions to lower the threshold for anxious reactions to events.

Among rodents, the effects of neonatal handling on both basal 5-HT and 5-HT turnover in response to stress have been investigated. Prepubertal rats that are handled as neonates show increased basal 5-HT levels and lowered 5-HT turnover in the hypothalamus, striatum, and hippocampus (Papaioannou, Dafni, Alikaridis, Bolaris, & Stylianopoulou, 2002). In response to short-term stress, rats show increased levels of 5-HT in the hypothalamus. Among neonatally handled rats exposed to single and repeated stressors in adulthood, increased 5-HT levels are also observed in the hypothalamus and striatum, as are increased 5-HT turnover in the striatum, hippocampus, and hypothalamus (Panagiotaropoulos et al., 2004).

Separation stress appears to exert opposite effects on the developing brain. Arborelius, Hawks, Owens, Plotsky, and Nemeroff (2004) demonstrated that prolonged separation

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

stress during neonatal development can lead to decreased 5-HT release in the raphe nuclei of rats in response to increasing doses of citalopram, an SSRI. Adult rats that are separated from their mothers also show passive coping styles to stressful events (Veenema, Blume, Niederle, Buwalda, & Neumann, 2006). In addition, they exhibit a reduction in 5-HT immunoreactivity and correlated intermale aggression (Veenema et al., 2006). Maternal rejection early in life has been linked with lower CSF levels of 5-HIAA, and higher anxiety in cross-fostered female rhesus macaques (Maestripieri, Higley, et al., 2006). Furthermore, variable maternal foraging conditions produce decreased behavioral responsiveness to the 5-HT agonist *meta*-chlorophenylpiperazine (*m*CPP) among bonnet macaques (Rosenblum et al., 1994). Such rearing conditions also result in decreased social interaction, and decreased behavioral responses to fear stimuli among adolescent bonnet macaques compared with controls (Rosenblum, Forger, Noland, Trost, & Coplan, 2001). Bonnet macaques reared in variable foraging demand conditions also show elevated CSF concentrations of the 5-HT metabolite, 5-HIAA (Coplan et al., 1998; Mathew et al., 2002). However, others have failed to find differences in 5-HIAA among adolescent squirrel monkeys exposed to mild intermittent stress in early development (Parker et al., 2007). Although the direction of the results is not uniform, 5-HT dysregulation, particularly hyporesponsivity, appears to be related to early adversity (Mathew et al., 2002).

Among humans, there is also evidence of 5-HT dysfunction following maltreatment. Abused children with depression show increased prolactin responses after the injection of L-5-HTP, a precursor to 5-HT, compared to a control group and nonabused depressed group of children (Kaufman, Birmaher, Perel, et al., 1998). Boys with adverse rearing histories also show elevated prolactin responses, and dampened cortisol responses to fenfluramine challenge (Pine et al., 1997). Prolactin responses are mediated by 5-HT_{1a} receptors, whereas cortisol release is not. This suggests that early life stress may sensitize these receptors (Heim & Nemeroff, 2001). Note that these findings conflict with the animal literature reviewed above, showing a positive correlation between prolactin and 5-HT stimulation. Interestingly, a group of adult women with borderline personality disorder demonstrated blunted responses to the 5-HT agonist *m*CPP (Rinne, Westenberg, den Boer, & van den Brink, 2000). Women with a history of repeated physical abuse had the most extreme prolactin blunting compared to both women with borderline personality disorder but no trauma history, and healthy controls. These results are consistent with animal research on adult 5-HT functioning and early adversity. Heim and Nemeroff suggested that the effect of early life stress may include a "developmental switch." Initial 5-HT hyperactivity may lead to a downregulation and 5-HT hypoactivity in adulthood. Prospective research is needed to clarify this possibility.

It is clear is that 5-HT regulation is sensitive to early rearing environments, particularly abuse. This pattern of findings is likely related to problems with anxiety, depression, and impulsive aggression observed among children exposed to violence. Whether these findings extend to more general violence exposure should be investigated empirically. What is certain is that genetic variability in the *5-HTT* gene interacts with stress exposure in general rather than violence specifically. Therefore, it is probable that the mere witnessing of violence could alter 5-HT functioning, as suggested above. This literature suggests that lower efficiency of the *5-HTT* gene leads to greater vulnerability in developmental contexts of violence. Furthermore, environmentally elicited changes in all three neurotransmitter systems are correlated with, if not the result of, stress-induced changes in biological functioning. With this in mind, we now turn to neuroendocrine effects of violence exposure by reviewing literature on the HPA axis.

Effects of Violence Exposure on the Neuroendocrine System

Acutely, physical threat leads to a cascade of neuroendocrine responses that prepare an organism to either escape the situation or stay and defend itself. In such a moment, the primary objective is immediate survival. Accordingly, the body prepares for action via attentional allocation and behavioral arousal. This results in increased heart rate, blood pressure, and breathing in order to supply energy and oxygen to the musculature (Sapolsky, 2000). In turn, the body suppresses other functions, such as digestion, growth, and reproduction, that are not necessary for immediate situational demands (Sapolsky, 1998, 2000). Collectively, these and other reactions comprise the stress response.

The sympathetic nervous system and the HPA axis form two interrelated effectors of the mammalian stress response (Adam, Klimes-Dougan, & Gunnar, 2007; Gunnar & Vazquez, 2006). The parasympathetic nervous system also plays an important role (Porges, 1995). Threats of violence lead to the activation of all of these systems. Fear activates the amygdala, which projects other midbrain structures, the brain stem, and cortex (Glaser, 2000). The sympathetic nervous system response is effected through parts of the cortex and brain stem nuclei, which project to the adrenal gland. The medulla of the adrenal gland secretes epinephrine and NE. These neurotransmitters raise heart rate and blood pressure, and increase sweating. The parasympathetic nervous system contributes through withdrawal of inhibitory vagal efference, leading to near instantaneous acceleration of heart rate (Porges, 1995). The sympathetic cardiac response is a bit slower, as it operates through a second messenger system, thereby reacting within a few seconds of detection of danger. In turn, the HPA response may take several minutes, and has longer temporal effects (Glaser, 2000; Sapolsky, 1998).

Physical threats to life activate the HPA axis primarily through NE neurons in the brain stem, including the LC (Adams et al., 2007). CRF and vasopressin are released from the paraventricular nucleus of the hypothalamus into blood vessels that reach the anterior pituitary. At the pituitary gland, CRF stimulates the production and release of adrenocortico-

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

tropin hormone (ACTH). In turn, the ACTH released into the blood reaches the adrenal glands, which release glucocorticoids (cortisol in humans and other primates, corticosterone in rodents).

Cortisol is a catabolic hormone, activating energy mobilization, focused attention, vigilance, and memory formation (Charney, 2004; Sánchez, 2006). Cortisol increases the availability of glucose, helps to avail fats for energy, increases blood flow, and stimulates behavioral responses. Glucocorticoids also suppress the immune, growth, and reproductive systems (Charney, 2004; Sánchez, 2006). Fluctuations are not exclusively stress induced, as cortisol has a diurnal periodicity. Humans experience a daily peak of cortisol about 30 min after waking, and a gradual decrease over the course of the day (Tarullo & Gunnar, 2006). Cortisol contributes to the inhibition of the HPA axis activity through negative feedback. Cortisol binds to glucocorticoid receptors in the hippocampus, hypothalamus, and the pituitary, which suppresses CRH, ACTH, and glucocorticoid production.

Evidence from animal models (e.g., Sánchez, 2006) suggests that the stress response is self-programming, particularly during developmentally critical periods. Individual differences in maternal behaviors during rat infancy affect HPA axis development and reaction to future stress. For example, offspring of mothers high in maternal care show reduced ACTH and corticosterone in response to stress (Liu et al., 1997). As adults their offspring display increased hippocampal glucocorticoid receptor messenger ribonucleic acid mRNA expression (Liu et al., 1997; Weaver et al., 2004), enhanced glucocorticoid negative feedback sensitivity (Liu et al., 1997), and decreased CRH mRNA levels (Francis, Diorio, Liu, & Meaney, 1999). Higher maternal care during infancy has also been tied with less fearfulness in adults (Caldji et al., 1998; Francis et al., 1999). This research suggests that the HPA axis is delicately sensitive to normal variation in maternal behavior among rodents and primates. Such sensitivity may apply to humans, but has yet to be demonstrated empirically.

It follows that exposure to more extreme developmental contexts, including violence, alters HPA axis functioning. These functional changes are observed both at rest and during stress reactivity. Evidence comes from studies of maternal separation and deprivation in rats. For example, adult rats that are deprived of maternal contact as neonates show elevated basal and stress-induced corticosterone (Ladd, Owen, & Nemeroff, 1996) and decreases in cell proliferation in the hippocampus (Mirescu, Peters, & Gould, 2004). There is also evidence of environmentally mediated alterations in HPA axis functioning, albeit more limited, from physical stressor paradigms among rat neonates. For example, Hatalski, Guirguis, and Baram (1998) showed changes in CRF mRNA expression in the hypothalamus and CRF content in the amygdala after neonatal rats were exposed to repeated cold stressors. These changes may be interpreted as adaptive (Teicher et al., 2003) if the individual's stress response system activates in anticipation of comparable levels of future environmental stress.

There is also evidence from rat studies that altered neuroendocrine functioning from early life stress can be buffered by maternal care giving behaviors (for review, see Sánchez et al., 2001). Similarly, research among children in circumstances of extreme deprivation such as Romanian orphanages shows that lack of social stimulation has profound effects on cortisol diurnal rhythms, but placements with trained foster parents ameliorates these irregularities (Adams et al., 2007). Thus, the stress response is regulated in part by both social and early life stress effects. Child maltreatment studies provide evidence of similar effects among humans, and several recent reviews have addressed this topic (e.g., Adams et al., 2007; Gunnar & Vazquez, 2006; Tarullo & Gunnar, 2006).

Children's basal responses

Some investigators have reported elevated cortisol levels among children with abuse histories (e.g., Carrion et al., 2002; Cicchetti & Rogosch, 2001a, 2001b; De Bellis, Baum, et al., 1999). Other reports have failed to find differences in morning cortisol levels (Hart, Gunnar, & Cicchetti, 1995, 1996). Two reports indicate that abused children show a rise from morning to afternoon cortisol levels (Hart et al., 1996; Kaufman, 1991), which is opposite from the typical diurnal pattern. Similarly, children with exposure to marital violence have displayed elevated cortisol in the afternoon, after controlling for direct abuse (Saltzman, Holden, & Holahan, 2005).

The duration and type of violence exposure may contribute to neuroendocrine functioning. Cicchetti and Rogosch (2001a) reported that boys and girls with histories of both physical and sexual abuse displayed elevated basal morning cortisol compared with children without abuse histories, and with those who experienced either single type of abuse. Carrion et al. (2002) also found a main effect for higher basal cortisol in children exposed to diverse sources of trauma (e.g., separation and loss, physical abuse, witnessing violence). De Bellis, Baum, et al. (1999) reported that duration of abuse was a predictor of cortisol responding in prepubescent children who had experienced primarily sexual abuse. In contrast, Cicchetti and Rogosch (2001a) found that a subgroup of abused children with histories of physical abuse without sexual abuse displayed a trend toward lower morning cortisol and significantly less diurnal variation compared to nonmaltreated children. Importantly, children participating in each of these studies were currently living in stable conditions. Another study showed negative relations for both peer victimization and witnessing violence and basal cortisol levels among children living within urban neighborhoods with high rates of violence (Kliewer, 2006).

Current behavioral functioning is also correlated with neuroendocrine functioning among older children. Cicchetti and Rogosch (2001b) found that children with maltreatment histories and internalizing psychopathology had higher morning and afternoon cortisol levels compared with (a) controls, (b) children with maltreatment histories and externalizing psy-

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

chopathology, and (c) children with psychopathology without abuse histories. Similarly, both Carrion et al. (2002) and De Bellis, Baum, et al. (1999) reported higher cortisol levels and primarily internalizing symptoms among participants in their studies, who were recruited for current PTSD. These results are consistent with findings among children with melancholic depression (e.g., Birmaher et al., 1996), and with some studies of children and adolescents with depression without abuse histories (e.g., Goodyer, Herbert, & Altham, 1998; Klimes-Dougan et al., 2001). Thus, internalizing problems appear to be linked to higher cortisol levels in children.

Overall, maltreated children with externalizing problems do not show basal cortisol differences compared to controls. However, Cicchetti and Rogosch (2001b) found that maltreated girls, particularly those with externalizing problems, had lower morning cortisol levels than maltreated girls without such problems. This is consistent with studies that show that nonmaltreated boys with aggressive tendencies have relatively low basal cortisol levels and flatter diurnal variations (Tarullo & Gunnar, 2006). In the same study, maltreated children with both externalizing and internalizing problems showed relatively flat diurnal patterns compared to other maltreated children.

Other research suggests that glucocorticoid levels among children with abuse histories may return to more typical levels following psychosocial interventions. Dozier et al. (2006) showed that infants and toddlers' cortisol levels and diurnal variation resembled a comparison group after receiving the Attachment and Biobehavioral Catch-Up Intervention. In contrast, the group of infants and toddlers who received foster parent treatment as usual had higher cortisol levels across the day than the other two groups. Likewise, a study on the Early Intervention Foster Care program showed that preschool age children with abuse histories can improve cortisol and behavior regulation with targeted intervention (Fisher, Gunnar, Chamberlain, & Reid, 2000). Interestingly, the control and specialized treatment groups among infants and toddlers did not differ in terms of current behavioral functioning. Neuroendocrine functioning may prove to be a useful biomarker of adjustment, particularly among very young children.

Children's reactivity

The stress response can also be examined in response to pharmacological and psychological stressors. In the CRH challenge paradigm, participants' ACTH and cortisol are examined after CRH is injected intravenously. These studies show conflicting results. De Bellis, Chrousos, et al. (1994) found blunted ACTH and normal cortisol levels among girls with sexual abuse histories. This is consistent with findings of blunted ACTH among infant nonhuman primates with abusive mothers (Sánchez, 2006). In contrast, Kaufman et al. (1997) found elevated ACTH in response to CRH among a group of depressed children with histories of abuse compared to both controls and children with depression and no history of abuse. However, this result was driven exclusively by half of the maltreatment group who were currently living under conditions of intense family disruption and emotional abuse. Sánchez (2006) suggested that nonhuman primate models support an initial elevation of basal cortisol during the abusive acts, and subsequent downregulation of CRF receptors in the pituitary. This would explain these seemingly contradictory findings.

Fewer investigations have examined how psychological stressors affect neuroendocrine responses of children with histories of violence exposure. Hart et al. (1995) examined preschoolers who were attending a therapeutic school for abused and neglected children. Children with maltreatment histories showed less cortisol reactivity on days with higher classroom conflict. A subset of these children also showed less cortisol reactivity on days when they were restrained to control aggressive behavior. In contrast, Bugental, Martorell, and Barraza (2003) showed that toddlers who had been exposed to corporal punishment had greater cortisol reactivity upon separation from their mothers during the Strange Situation. Similarly, children who had witnessed more violence showed increased cortisol while watching a movie clip of peer victimization (Kliewer, 2006). Greater cortisol reactivity under such conditions is consistent with nonhuman primate studies among abused and harshly treated youth (Dettling, Pryce, Martin, & Döbelli, 1998), and among young animals exposed to experimentally induced glucocorticoids during gestation (Uno et al., 1994).

Adults' reactivity

Tarullo and Gunnar's (2006) detailed review of the adult literature produced the following conclusions: first, retrospectively reported childhood maltreatment is generally associated with potentiated ACTH responses to psychological stressors in adulthood. Second, cortisol levels appear normal among adults without psychiatric symptoms. This suggests a downregulation and insensitivity of the adrenals. However, adults with current PTSD and depression show corresponding elevated ACTH. This indicates the possibility that adults with psychiatric symptoms lack this compensatory mechanism.

Adaptation of the stress response to violence

Acute release of stress hormones serves a clear adaptive purpose: the diversion of energy from metabolic processes that are nonessential to functions that are critical for immediate survival. Cortisol reactivity among adults with abuse histories suggests a downregulation and insensitivity of the adrenal gland to CRH, which may be adaptive. Among children, there seems to be less consistency in the direction of change. However, timing and duration of violence exposure may influence current stress response status. Importantly, both elevation and depression of cortisol are associated with behavioral difficulties, suggesting change without a clear adaptive function. Furthermore, both hyper- and hyporesponding are harmful (Sa-

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

polsky, 1998). Chronic stress and associated elevations in circulating glucocorticoids have negative effects on the body, including elevated risk for cardiovascular disease, ulcers, amenorrhea, and immune system dysfunction (Sapolsky, 1998, 2000). In contrast, failure of HPA axis to respond appropriately to threat is clearly maladaptive.

Such individual differences are likely influenced by genetic vulnerabilities and protective factors. For example, animal studies implicate the *5-HTT* gene in affecting HPA axis functioning. 5-HT is involved in the activation and feedback of the HPA axis, and 5-HTT knockout mice display elevated corticosterone responses to chronic stress (Lanfumey, Mannoury La Cour, Froger, & Hamon, 2000). Furthermore, homozygosity of the *5-HTT* l allele is associated with smaller ACTH responses during separation stress among macaques reared specifically by peers (Barr et al., 2004). This indicates a Rearing Condition × Gene interaction, which may have implications for links between exposure to violence and depression. Future research among humans could examine associations between genetic vulnerabilities and HPA responding following violence exposure to elucidate relations with psychological functioning (Tarullo & Gunnar, 2006).

In the next section we address two important brain areas involved in self-regulatory behaviors that are particularly vulnerable to changes in HPA reactivity: the hippocampus and PFC. Functional changes in these brain regions are also mediated by environmentally elicited alterations in monoamine neurotransmitter systems. Broadly speaking, these changed appear to be more maladaptive than adaptive.

Brain Development

When considering changes that occur in brain structure and function as a result of exposure to violence, it is important to keep in mind the normal progression of brain development from conception to adulthood. In general, the in utero brain develops from the bottom up, organizing phylogenetically older structures first, including the brain stem and subcortical structures, before evolutionarily newer structures develop, such as the cerebral cortex (Perry, 2008). Thus, the brain develops hierarchically and sequentially, and different areas of the brain mature at different points throughout the life span. Thus, exposure to violence can have dramatically different effects depending on timing and length of exposure. Throughout infancy and childhood, the brain forms new neural connections and prunes synapses in a use- and experience-dependent fashion (Cummins & Livesey, 1979; Perry, 2008). Because early brain development may affect later brain development, stress exposure early in life has the highest potential for long-term dysfunction in neurobehavioral systems that mediate emotional responses, abstract thinking, and social interaction. Furthermore, although more dramatic changes in brain structure cease after childhood, the frontal cortex and the hippocampus continue to develop well into early adulthood. Thus, in contrast with more primitive functions such as sensory inputs, cortically mediated functions are likely to have a relatively longer sensitive period (Perry, 2008).

Hippocampus

The hippocampus is particularly vulnerable to stress exposure because it has a protracted postnatal developmental period, a high density of glucocorticoids receptors, and exhibits postnatal neurogenesis (Teicher et al., 2003). As noted earlier, the hippocampus both regulates and is affected by the stress response. Under conditions of acute stress, hippocampal functions such as memory are enhanced (e.g., Cahill, Prins, Weber, & McGaugh, 1994). Improvements are observed in both anterograde and retrograde memory among animals and humans (for review, see McEwen & Sapolsky, 1995; Sala et al., 2004). However, the enhancements last only for the first 30 min after exposure to a stressor, and prolonged glucocorticoid exposure can damage hippocampal neurons beyond this period (McEwen & Sapolsky, 1995; Sala et al., 2004). Sustained elevation of glucocorticoids leads to the inhibition of available glucose for hippocampal cells. In turn, learning and memory are impaired, particularly declarative memory (McEwen & Sapolsky, 1995; Sala et al., 2004). Impairment initially appears to be reparable, yet animal research suggests that more prolonged exposure can cause permanent damage to the hippocampus (McEwen & Sapolsky, 1995; Uno et al., 1994).

For example, a study of vervet monkeys showed that stereotaxically implanted glucocorticoids cause preferential damage in the hippocampus, including dendritic atrophy, shrinkage, condensation, and cell layer irregularities (Sapolsky, Uno, Rebert, & Finch, 1990). Others have corroborated enduring deficits in synaptic density in the hippocampus (e.g., Teicher et al., 2003). Elevated basal corticosterone is associated with a down-regulation of 5-HT_{1a} hippocampal receptors among subordinate male rats exposed chronically to dominant males (McKittrick, Blanchard, Blanchard, McEwen, & Sakai, 1995).

There is more controversy in the literature on humans. Smaller hippocampal volumes have been observed among (a) adults with PTSD following combat exposure or repeated childhood abuse, (b) some adults with current or recurrent depression, and (c) adults with borderline personality disorder, especially those with histories of childhood traumatic experiences (for a review, see Sala et al., 2004). A recent meta-analysis of structural MRI studies among adults with PTSD following diverse traumatic experiences showed significant pooled effects including 6.9% smaller left hippocampal volumes and 6.6% smaller right hippocampal volumes compared with controls (Smith, 2005). Differences were smaller when the comparison group had been exposed to similar traumatic events, and magnified when controls had no trauma history. Nonetheless, these results do not rule out the possibility that smaller hippocampi represent a vulnerability factor for PTSD and/or depression following trauma rather than a result of violence and stress exposure (e.g., Gilbertson et al., 2002).

Cross-sectional research among children has been less consistent. Two MRI studies showed no differences in hippocampal

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

volumes among children with PTSD following maltreatment (Carrion et al., 2001; De Bellis et al., 2002). Other studies have shown marginal effects for larger left hippocampal gray matter (De Bellis, Keshavan et al., 1999) and larger bilateral hippocampi volumes among children with maltreatment histories (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001). Tupler and De Bellis (2006) pooled data from two studies (De Bellis, Keshavan et al., 1999; De Bellis et al., 2002) and found significantly larger hippocampal white matter volumes after controlling for total cerebral white matter. This anatomical finding was correlated with total problems on the Child Behavior Checklist.

Longitudinal research among children has yet to provide consistent evidence of hippocampal damage due to violence exposure. However, the best evidence was found among 7- to 13-year-old maltreated children over 12–18 months (Carrion, Weems, & Reiss, 2007). Both PTSD symptoms and baseline cortisol predicted reductions in hippocampal volumes over time, controlling for individual differences at baseline. However, there was no control group in this sample. The only other longitudinal study among children uncovered no change in hippocampal volumes over a 9-month follow-up period (De Bellis et al., 2001).

Theorists have considered several possibilities for lack of expected hippocampal atrophy among children in these studies. Teicher et al. (2003) summarized these as follows: first, stress associated with PTSD may exert a gradual effect on hippocampal morphology, which is not detectable until adulthood. Second, alcohol and substance abuse problems, which do not arise until closer to adulthood, and are commonly associated with PTSD, may be the primary mechanism through which hippocampal atrophy occurs. Third, as already noted, reduced hippocampal volume may be a vulnerability marker for post trauma problems rather than a sequela of trauma.

Although more evidence is needed, there are two implications of potential hippocampal atrophy in developing children. First, such damage causes impairment in memory functions. This is difficult to construe as an adaptive response to stress, and may contribute in part to the relatively poor school performance observed among children with abuse histories compared with peers (Cicchetti & Toth, 1995). Second, hippocampal atrophy plays a role in subsequent HPA axis dysregulation by disrupting the negative feedback loop (see above). Fewer hippocampal cells translate into fewer glucocorticoid receptors. Consequently, stress hormones are released longer (Uno et al., 1994), damaging more hippocampal cells. It is clear that environmental stressors such as abuse are related to changes in the stress response. Some alterations may be adaptive to the immediate demands of threat. For example, chronically elevated cortisol facilitates alertness. Short-term adaptations may therefore result in long-term problems. This is even more apparent when considering the PFC.

PFC

Similar to the hippocampus, the frontal cortex has both a protracted developmental period and a high density of glucocorticoid receptors, making it vulnerable to early life stress. In addition, the frontal cortex is vulnerable to early disruption in subcortical structures because of its relatively long sensitive period, and both feed forward and feedback communication with lower brain regions. De Bellis and colleagues demonstrated structural abnormalities in the prefrontal cortices of maltreated children compared with controls, including smaller PFC volumes, less PFC cortical white matter, and larger prefrontal CSF volumes (De Bellis et al., 2002; De Bellis, Keshavan et al., 1999). These findings correlated positively with age of onset of maltreatment among children with PTSD.

Research indicates that stress exposure precipitates PFC impairment in both humans and animals (see Arnsten, 1998). For example, children with PTSD resulting from maltreatment perform worse on neuropsychological measures of attention and abstract reasoning/executive function, abilities controlled by frontal brain regions (Beers & De Bellis, 2002). Furthermore, children raised in Romanian orphanages show delayed cognitive and social skills (Kaler & Freeman, 1994; Rutter, O'Connor, & The English and Roman Adoptees Study Team, 2004). Although some children "catch-up" to adopted peers, children who experience longer periods of early neglect have sustained cognitive impairments 2.5 to 4 years later. In addition, executive functioning deficits observed in those with early maltreatment may partially mediate the relation between childhood maltreatment and later aggressive behaviors through deficits in inhibition, misinterpretation of others' intentions, increased selective attention to cues of threat, and general social and interpersonal deficits (Lee & Hoaken, 2007).

Both the high density of glucocorticoid and CRF receptors in primate cerebral cortices and excess cortisol may account for some of the observed impairments in PFC functions (Millan, Jacobowitz, Hauger, Catt, & Aguilera, 1986; Sánchez et al., 2001). In turn, reduction of glucocorticoid expression in the hippocampus and frontal cortex could account for elevated HPA axis activity after chronic stress exposure (Sánchez et al., 2001). Nonhuman primates exposed to early life stress show significantly diminished glucocorticoid receptors in the dorsolateral PFC, and a trend toward reduced receptors in the ventrolateral PFC (Patal, Katz, Karssen, & Lyons, 2008). These areas are involved in executive functions, cognitive and motor planning, and integrating and evaluating emotional information. Psychosocial conflict among tree shrews resulted in stress-induced increases in the number of CRH receptors in the frontal and cingulate cortices, but decreased affinity for binding sites (Fuchs & Flügge, 1995). Moreover, neuroendocrine changes in response to early stress, such as maternal separation, are associated with decreases in glucocortidoid receptor mRNA expression in the medial PFC (see Meaney et al., 1996; Sánchez et al., 2001). Furthermore, rats exposed to maternal separation also show decreased CRF_1 receptor binding in the frontal and parietal cortices (Ladd, Huot, Thrivikraman, & Plotsky, 1998, 1999). Sánchez et al. (2001) also suggest that early maternal separa-

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

tion leads to enhanced CRF neurotransmission within and from the amygdala, including the hypothalamic paraventricular nucleus, the central nucleus of the amygdale, and the LC. Thus, early stressful experiences must have effects on the circuits that connect these regions, as the amygdale mediates transmission to these areas, particularly the LC via CRF neurotransmission (Sánchez et al., 2001).

DA likely plays a role as well, and altered dopaminergic function in the frontal cortex leads to impairments in executive functioning (De Bellis, 2005). Although chronic stress is associated with hypodopaminergic function in the nucleus accumbens, stress may lead to *hyper*dopaminergic activity in the frontal cortex. Note that this is consistent with the hypodopaminergic functioning hypothesis of impulsivity described above, because the mesocortical and mesolimbic DA systems operate with considerable independence.

In addition, stress-induced working memory deficits are associated with increased catecholamine receptor stimulation in the PFC, yet these functional impairment are alleviated by DA antagonists (Arnsten, 1998; Arnsten & Goldman-Rakic, 1998). Similarly, infusion of D1 receptor agonists in the PFC induce spatial working memory deficits in rats (Zahrt, Taylor, Mathew, & Arnsten, 1997). Thus, PFC hyperdopaminergic functioning during stress may prevent frontal control of behavior, requiring more primitive subcortical structures to take over regulatory functions (Zahrt et al., 1997).

Several studies have revealed specific abnormalities in frontal cortex activation among those who have experienced childhood abuse (see Bremner, 2005; Bremner et al., 1999, 2003; De Bellis, Keshavan, Spencer, & Hall, 2000; Shin et al., 1999). In particular, the medial PFC, which includes the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), has been shown to be impaired in several positron emission studies among adults who experienced childhood trauma. The ACC has both cognitive and affective subdivisions, subserves numerous cognitive processes, and plays a critical role in decisions involving reward and punishment. In addition, it is involved in evaluating ongoing actions to facilitate adaptive behavior, self-monitoring, and processing emotion induced by pain, error detection, and other mental states (see Holroyd & Coles, 2002). The OFC plays a key role in social/emotional function and is involved in interpretation of others' emotional states and evaluating the magnitude of potential threats and rewards (Derryberry & Tucker, 2006; Gatzke-Kopp & Shannon, 2008). The ACC and OFC are highly interconnected with other limbic regions including the amygdala and hippocampus and are thus susceptible to the downstream effects of early stress (see Derryberry & Tucker, 2006; Mohanty et al., 2007).

Induced memories of traumatic experiences appear to be related strongly to decreases in ACC activation among those with PTSD following childhood sexual abuse (Bremner et al., 1999; Shin et al., 1999). In these studies, participants with abuse histories, but without current PTSD, show greater activation of the ACC compared to those with PTSD (Shin et al., 1999). Furthermore, De Bellis et al. (2000) found evidence of cell loss and lower neural integrity in the ACCs of maltreated children and adolescents with PTSD. Elevated NE release and subsequent decreased metabolism in medial and orbital frontal cortices may contribute to the recurrence of PTSD-related memories (Bremner et al., 1997).

Medial prefrontal regions of the brain are highly interconnected with the amygdala via cortical inhibitory inputs, which mediate amygdala and HPA axis responding (Bremner, 2005; Figueiredo, Bruestle, Bodie, Dolgas, & Herman, 2003). Thus, areas of the medial PFC have been hypothesized to play a role in inhibition and extinction of fear responses (for review, see LeDoux, 1998). Furthermore, it is likely that continued fear responses among those who have experienced trauma or abuse result from deficient ACC inhibition of the amygdala. When functioning properly, the ACC inhibits fearful responses when traumatic stimuli do not pose a real threat. However, among those with PTSD, who exhibit cued fear regardless of context, ACC–amygdala mediation may be lacking (Bremner, 2005).

Overall, the PFC is exquisitely sensitive to the untoward effects of early and/or sustained exposure to violence. Individual differences influenced by genetic variation likely influence who develops PTSD following violence exposure. The ACC plays a pivotal role. Future research could examine how genes that relate to psychopathology in violent contexts affect ACC activation. In the next section we explore the startle response, which is another system often affected by violence exposure related to PTSD. It is the final example of a neurobiological adaptation that can develop into a maladaptation.

Startle response

The startle response is an involuntary physiological reaction to unexpected and abrupt stimuli (e.g., loud noises, flashes of light), which facilitates interruption of ongoing behavior and the assumption of a protective body posture. The eye blink is the most consistent, sensitive, and well studied response of the startle reflexes (Klorman, Cicchetti, Thatcher, & Ison, 2003). It is measured by recording muscle activity with electromyography (EMG) from the orbicularis oculi, which overlie the eyes. Both nonspecific responses (i.e., those without preceding stimuli), and responses following a stimulus (the prepulse) have been examined. Inhibition of the startle response, known as prepulse inhibition, occurs following brief (20–200 ms) startling stimuli (Graham, 1975). In contrast, sustained prestimulation (≥2000 ms) facilitates the startle response.

Several investigators have found exaggerated startle responses without prepulse among those with PTSD, including war veterans (Butler et al., 1990; Morgan, Gillon, Southwick, Davis, & Charney, 1996), female sexual assault survivors (Morgan, Grillon, Lubin, & Southwick, 1997), and patients with diverse trauma histories (Shalev, Orr, Peri, Schreiber, & Pitman, 1992; Shalev, Peri, Orr, Bonne, & Pitman, 1997). These results are consistent with other studies demonstrating that war veterans with PTSD have potentiated EMG (nonpre-

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

pulse) startle responses and attenuated EMG prepulse inhibition during stressful conditions (Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1999). However, others have failed to find altered startle responses without prepulse among the aforementioned groups (Grillon & Morgan, 1999; Grillon, Morgan, Southwick, Davis, & Charney, 1996; Grillon et al., 1999; Metzger et al., 1999; Orr, Lasko, Metzger, & Pitman, 1997; Orr, Soloman, Peri, Pitman, & Shalev, 1997).

In an effort to resolve these discrepancies, Metzger reviewed 11 published studies and noted that 8 investigations produced medium to large effect sizes in startle responding. The mean weighted effect across all studies was medium (Cohen $d = 0.49$) for exaggerated startle when comparing participants with current PTSD to individuals without a trauma history. This suggests that despite some nonreplications, trauma-induced PTSD is associated with exaggerated startle responding. This behavior may be construed as a biological adaptation to life-threatening contexts insofar as it facilitates the initiation of defensive posturing. Yet the maintenance of an exaggerated startle response outside of high threat conditions could be considered a maladaptation.

Interestingly, two studies with youth have found opposite effects. Klorman et al. (2003) examined EMG in response to acoustic startle in 3- to 11-year-old maltreated children. Children were exposed to auditory probes of increasing loudness. Participating children were heterogeneous in terms of type of abuse experienced, but over 80% incurred maltreatment before the age of 2. A consistent pattern emerged when examining the data by sex and type of abuse experienced. Boys with histories of physical abuse responded to increases of startle probe loudness with smaller incremental changes in amplitude of the eye blink startle response, and smaller reductions of blink response latency compared with controls. In contrast, results for girls were inconsistent across ages. Although younger maltreated girls had smaller startle amplitudes and slower onset latencies than controls, older girls showed the opposite pattern.

The boys' responses from the Klorman et al. (2003) study are comparable with the only study of startle response among boys and girls with PTSD. Ornitz and Pynoos (1989) reported on a small group ($n = 6$) of 8- to 13-year-olds who experienced sniper fire on their school playground 17–21 months prior to the study. Children with PTSD displayed smaller startle responses to bursts of white noise than age- and sex-matched controls. However, under conditions of prepulse facilitation children with PTSD exhibited exaggerated responses.

One another study (Lipschitz et al., 2005) failed to find baseline acoustic startle, and modulated (prepulse facilitation and prepulse inhibition) differences between a group of female adolescents with mixed trauma exposure versus controls. The sample was diverse in both experience of current PTSD (61% met criteria) and exposure to trauma (87% had experienced multiple traumas).

Thus, preliminary results suggest that children may respond differently than adults who are exposed to threat. Instead of developing an exaggerated startle response, children appear to attenuate their responses. Cicchetti (2008) proposed that attenuated startle may be an indication of allostatic load. For children, attenuation of startle may be an indication of habituation, and an attempt to recalibrate their assessment of stimuli.

Several authors have noted that exaggerated startle could be either a short- or long-term adaptation to threatening environments, or alternatively, a vulnerability factor for the development of anxiety problems (e.g., Grillon et al., 1996). Grillon, Dierker, and Merikangas (1997) examined startle modulation among a group of children of parents with histories of anxiety and/or alcoholism. Children of parents with histories of anxiety had exaggerated startle responses at baseline. Thus, a causal relation between exposure to trauma and exaggerated startle cannot be assumed. Researchers have attempted to address the direction of causality of trauma and EMG exaggerated startle response (Guthrie & Bryant, 2005; Orr et al., 2003), but both studies failed to produce differences across trauma exposed and control groups. More recently, rodent studies have shown that startle responses are sensitive to changes in the environment; HPA hormones introduced pharmacologically in rats induce changes in the startle response (Doornbos et al., 2009; Keen-Rhinehart et al., 2009).

In summary, research indicates that among adults, PTSD is associated with exaggerated startle responses, despite some discrepancies in the literature. The literature on children shows the opposite pattern. It is unclear whether results reflect genetic predispositions versus environmentally elicited effects. However, recent animal studies appear to support the latter conclusion. This work also demonstrates that the startle response is sensitive to fluctuations in stress hormones associated with the HPA axis. Again, future work in this area could integrate measurement of specific genes with the startle response. Both 5-*HTT* and *MAOA* may play important roles. Specifically, individuals with s alleles of the *5-HTT* gene and lower *MAOA* activity alleles would be at risk for exaggerated startle responses.

Conclusions and Future Directions

Early development in violent contexts shapes behavioral adaptations across the life span. Our review has outlined a number of the neurobiological mediators of such adaptations. Genetic variability and vulnerability influence how individuals respond behaviorally. Recent advances in molecular genetics have led to the identification of genotypes as moderators of links between maltreatment and both antisocial behavior and depression. Future research will likely elucidate intervening neurobiological mechanisms underlying these links. Research focusing on neurotransmitter and neuroendocrine system plasticity during development implicates DA, 5-HT, NE, and glucocorticoids as key contributors to behavioral changes following exposure to violence. Although researchers appreciate that these systems interact, more integrated research approaches will prove useful. Experimental animal research is critical, yet quasi-experimental longitudinal studies of humans that focus on multiple central nervous system

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

measures may clarify inconsistencies in the literature. Ultimately, clarification of the neurobiological sequelae of violence may lead to earlier identification of children vulnerable to future behavioral maladaptations (Beauchaine et al., 2008).

Finally, the adaptive (or maladaptive) value of neurobiological changes has been emphasized throughout this paper. As introduced, a behavior is adaptive insofar is it helps an organism survive. Within violent contexts, hyperarousal, vigilance, and aggression are clearly useful. The literature reviewed suggests that humans, among other mammals including rats and nonhuman primates, possess brains that are exquisitely sensitive to their environments and are equipped to adapt to early stress. However, many associated features of these adaptations confer risk in other contexts. Finally, adaptations such as vigilance may be useful for protection, but costly for other processes requiring sustained attention. Future work using the adaptational framework in examining development within violent contexts should take into account both short- and long-term effects, and consequences of behavior change.

Exposure to violence during development exacts diverse behavioral and neurobiological costs across a lifetime. The neurobiological changes we reviewed may explain at least some of the vulnerability to externalizing psychopathology, including oppositional and aggressive behaviors, delinquency and drug use, as well as internalizing psychopathology, including depression, PTSD, sleep dysregulation, and other anxiety problems. Described changes also contribute to school difficulties and dropout, and problems with job retention. Finally, the neurobiological sequelae of early exposure to violence likely contribute to the difficulties in peer and romantic relationships that some people experience across a lifetime. We encourage integrated research that can explain multiple problems related to early violence exposure.

References

Adams, E. K., Klimes-Dougan, B., & Gunner, M. (2007). Social regulation of the adrenocortical response to stress in infants, children, and adolescents. In D. Coch, G. Dawson, & K. W. Fischer (Eds.), *Human behavior, learning, and the developing brain* (pp. 264–304). New York: Guilford Press.

Anderson, K. E., Lytton, H., & Romney, D. M. (1986). Mothers' interactions with normal and conduct disordered boys: Who affects whom? *Developmental Psychology*, *22*, 604–609.

Arborelius, L., Hawks, B., Owens, M., Plotsky, P., & Nemeroff, C. (2004). Increased responsiveness of presumed 5-HT cells to citalopram in adult rats subjected to prolonged maternal separation relative to brief separation. *Psychopharmacology (Berlin)*, *176*, 248–255.

Arnsten, A. F. T. (1998). The biology of being frazzled. *Science*, *280*, 1711–1712.

Arnsten, A. F. T., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: Evidence for a hyperdopaminergic mechanism. *Archives of General Psychiatry*, *55*, 362–368.

Ayoub, C., & Rappolt-Schlichtmann, G. (2007). Child maltreatment and the development of alternate pathways in biology and behavior. In D. Coch, G. Dawson, & K. Fischer (Eds.), *Human behavior, learning, and the developing brain: Atypical development* (pp. 305–330). New York: Guilford Press.

Balciuniene, J., Syvänen, A. C., McLeod, H. L., Pettersson, U., & Jazin, E. E. (2001). The geographic distribution of monoamine oxidase haplotypes supports a bottleneck during the dispersion of modern humans from Africa. *Journal of Molecular Evolution*, *52*, 157–163.

Barr, C. S., Newman, T. K., Shannon, C., Parker, C., Dvoskin, R. L., Becker, M. L., et al. (2004). Rearing condition and rh5-HTTLPR interact to influence limbic–hypothalamic–pituitary–adrenal axis response to stress in infant macaques. *Biological Psychiatry*, *55*, 733–738.

Beauchaine, T. P. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology*, *13*, 183–214.

Beauchaine, T. P. (2009). Some difficulties in interpreting psychophysiological research with children. *Monographs of the Society for Research in Child Development*, *509*, 80–88.

Beauchaine, T. P., Hinshaw, S. P., & Gatzke-Kopp, L. (2008). Genetic and environmental influences on behavior. In T. P. Beauchaine & S. Hinshaw (Eds.), *Child and adolescent psychopathology* (pp. 58–90). Hoboken, NJ: Wiley.

Beauchaine, T. P., Katkin, E. S., Strassberg, Z., & Snarr, J. (2001). Disinhibitory psychopathology in male adolescents: Discriminating conduct disorder from attention-deficit/hyperactivity disorder through concurrent assessment of multiple autonomic states. *Journal of Abnormal Psychology*, *110*, 610–624.

Beauchaine, T. P., Klein, D. N., Crowell, S. E., Derbidge, C., & Gatzke-Kopp, L. M. (2009). Multifinality in the development of personality disorders: A Biology × Sex × Environment model of antisocial and borderline traits. *Development and Psychopathology*, *21*, 735–770.

Beauchaine, T. P., & Neuhaus, E. (2008). Impulsivity and vulnerability to psychopathology. In T. P. Beauchaine & S. Hinshaw (Eds.), *Child and adolescent psychopathology* (pp. 129–156). Hoboken, NJ: Wiley.

Beaver, K. M., DeLisi, M., Vaughn, M. G., & Barnes, J. C. (in press). Monoamine oxidase A genotype is associated with gang membership and weapon use. *Comprehensive Psychiatry*.

Beers, S. R., & De Bellis, M. D. (2002). Neuropsychologial function in children with maltreatment-related PTSD. *American Journal of Psychiatry*, *159*, 483–486.

Birmaher, B., Dahl, R. E., Perel, J., Williamson, D. E., Nelson, B., Stull, S., et al. (1996). Corticotropin-releasing hormone challenge in prepubertal depression. *Biological Psychiatry*, *39*, 267–277.

Bowden, C. L., Deutsch, C. K., & Swanson, J. M. (1988). Plasma dopamine-β-hydroxylase and platelet monoamine oxidase in attention deficit disorder and conduct disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *27*, 171–174.

Brenner, S., Beauchaine, T. P., & Sylvers, P. (2005). A comparison of psychophysiological and self-report measures of BAS and BIS activation. *Psychophysiology*, *42*, 108–115.

Bremner, J. D. (2005). Effects of traumatic stress on brain structure and function: Relevance to early responses to trauma. *Journal of Trauma and Dissociation*, *6*, 51–68.

Bremner, J. D., Innis, R. B., Ng, C. K., Staib, L., Duncan, J., Bronen, R., et al. (1997). PET measurement of cerebral metabolic correlates of yohimbine administration in posttraumatic stress disorder. *Archives of General Psychiatry*, *54*, 246–256.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry*, *156*, 1787–1795.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Staib, L., et al. (2003). Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder (PTSD) related to early childhood sexual abuse. *Biological Psychiatry*, *53*, 289–299.

Bugental, D. B., Martorell, G. A., & Barraza, V. (2003). The hormonal costs of subtle forms of infant maltreatment. *Hormones and Behavior*, *43*, 237–244.

Butler, R. W., Braff, D. L., Rausch, J. L., Jenkins, M. A., Sprock, J., & Geyer, M. A. (1990). Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. *American Journal of Psychiatry*, *147*, 1308–1312.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

Cabib, S., & Puglisi-Allegra, S. (1996). Stress, depression, and the mesolimbic dopamine system. *Psychopharmacology (Berlin)*, *128*, 331–342.
Cahill, L., Prins, B., Weber, M., & McGaugh, J. (1994). Beta-adrenergic activation and memory for emotional events. *Nature*, *371*, 702.
Caldji, C., Tannenbaum, B., Sharma, S., Francis, D., Plotsky, P. M., & Meaney, M. J. (1998). Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proceedings of the National Academy of Sciences of the United States of America*, *95*, 5335–5340.
Carrasco, G. A., & Van de Kar, L. D. (2003). Neuroendocrine pharmacology of stress. *European Journal of Pharmacology*, *463*, 235–272.
Carrion, V., Weems, C., Eliez, S., Patwardhan, A., Brown, W., Ray, R. D., et al. (2001). Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biological Psychiatry*, *50*, 943–951.
Carrion, V., Weems, C., Ray, R., Glaser, B., Hessl, D., & Reiss, A. (2002). Diurnal salivary cortisol in pediatric posttraumatic stress disorder. *Biological Psychiatry*, *51*, 575–582.
Carrion, V., Weems, C., & Reiss, A. L. (2007). Stress predicts brain changes in children: A pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics*, *119*, 509–516.
Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297*, 851–854.
Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the *5-HTT* gene. *Science*, *301*, 386–389.
Castellanos, F. X., Elia, J., Kruesi., M. J., Gulotta, C. S., Mefford, I. N., Potter, W. Z., et al. (1994). Cerebrospinal fluid monoamine metabolites in boys with attention-deficit hyperactivity disorder. *Psychiatry Research*, *52*, 305–316.
Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. *American Journal of Psychiatry*, *161*, 195–216.
Cicchetti, D. (2008). A multiple levels of analysis perspective on research in development and psychopathology. In T. P. Beauchaine & S. Hinshaw (Eds.), *Child and adolescent psychopathology* (pp. 27–57). Hoboken, NJ: Wiley.
Cicchetti, D., & Curtis, W. J. (2006). The developing brain and neural plasticity: Implications for normality, psychopathology, and resilience. In D. Cicchetti & D. Cohen (Eds.), *Developmental psychopathology: Vol. 2. Developmental neuroscience* (2nd ed., pp. 1–64). Hoboken, NJ: Wiley.
Cicchetti, D., & Rogosch, F. A. (2001a). Diverse patterns of neuroendocrine activity in maltreated children. *Development and Psychopathology*, *13*, 677–693.
Cicchetti, D., & Rogosch, F. A. (2001b). The impact of child maltreatment and psychopathology on neuroendocrine functioning, *Development and Psychopathology*, *13*, 783–804.
Cicchetti, D., Rogosch, F. A., & Sturge-Apple, M. L. (2007). Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: Depressive symptomatology among adolescents from low socioeconomic status backgrounds. *Development and Psychopathology*, *19*, 1161–1180.
Cicchetti, D., & Toth, S. L. (1995). A developmental psychopathology perspective on child abuse and neglect. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*, 541–565.
Cicchetti, D., & Toth, S. L. (2005). Child maltreatment. *Annual Review of Clinical Psychology*, *1*, 409–438.
Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants. A proposal. *Archives of General Psychiatry*, *44*, 573–588.
Coccaro, E. F., Siever, L. J., Klar, H. M., Maurer, G., Cochrane, K., Cooper, T. B., et al. (1989). Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. *Archives of General Psychiatry*, *46*, 587–599.
Coplan, J. D., Andrews, M. W., Rosenblum, L. A., Owens, M. J., Friedman, S., Gorman, J. M., et al. (1996). Persistent elevations of cerebrospinal fluid concentrations of corticotrophin-releasing factor in adult nonhuman primates exposed to early-life stressors: Implications for the pathophysiology of mood and anxiety disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 1619–1623.
Coplan, J. D., Trost, R. C., Owens, M. J., Cooper, T. B., Gorman, J. M., Nemeroff, C. B., et al. (1998). Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions. *Archives of General Psychiatry*, *55*, 473–477.
Covington, H. E., & Miczek, K. A. (2005). Intense cocaine self-administration after episodic social defeat stress, but not after aggressive behavior: Dissociation from corticosterone activation. *Psychopharmacology (Berlin)*, *183*, 331–340.
Cravchik, A., & Goldman, D. (2000). Neurochemical individuality: Genetic diversity among human dopamine and serotonin receptors and transporters. *Archives of General Psychiatry*, *57*, 1105–1114.
Crowell, S., Beauchaine, T. P., Gatzke-Kopp, L., Sylvers, P., Mead, H., & Chipman-Chacon, J. (2006). Autonomic correlates of attention-deficit/hyperactivity disorder and oppositional defiant disorder in preschool children. *Journal of Abnormal Psychology*, *115*, 174–178.
Cubells, J. F., & Zabetian, C. P. (2004). Human genetics of plasma dopamine beta-hydroxylase activity: Applications to research in psychiatry and neurology. *Psychopharmacology (Berlin)*, *174*, 462–476.
Cummins, R. A., & Livesey, P. (1979). Enrichment-isolation, cortex length, and the rank order effect. *Brain Research*, *178*, 88–98.
De Bellis, M. (2005). The psychobiology of neglect. *Child Maltreatment*, *10*, 150–172.
De Bellis, M. D., Baum, A. S., Birmaher, B., Keshavan, M. S., Eccard, C. H., Boring, A. M., et al. (1999). Developmental traumatology part I: Biological stress systems. *Biological Psychiatry*, *45*, 1259–1270.
De Bellis, M. D., Chrousos, G. P., Dorn, L. D., Burke, L., Helmers, K., Kling, M. A., et al. (1994). Hypothalamic–pituitary–adrenal axis dysregulation in sexually abused girls. *Journal of Clinical Endocrinology and Metabolism*, *78*, 249–255.
De Bellis, M. D., Hall, J., Boring, A. M., Frustraci, K., & Moritz, G. (2001). A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biological Psychiatry*, *50*, 305–309.
De Bellis, M. D., Keshavan, M. S., Clark, D. B., Casey, B. J., Giedd, J. N., Boring, A. M. (1999). Developmental traumatology part II: Brain development. *Biological Psychiatry*, *45*, 1271–1284.
De Bellis, M. D., Keshavan, M. S., Shifflett, H., Iyengar, S., Beers, S. R., Hall, J., et al. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: A sociodemographically matched study. *Biological Psychiatry*, *52*, 1066–1078.
De Bellis, M. D., Keshavan, M. S., Spencer, S., & Hall, J. (2000). *N*-Acetylasparatate concentration in the anterior cingulated in maltreated children and adolescents with PTSD. *American Journal of Psychiatry*, *157*, 1175–1177.
De Bellis, M. D., Lefter, L., Trickett, P. K., & Putnam, F. W., Jr. (1994). Urinary catecholamine excretion in sexually abused girls. *Journal of the American Academy of Child & Adolescent Psychiatry*, *33*, 320–327.
Delahanty, D. L., Nugent, N. R., Christopher, N. C., & Walsh, M. (2005). Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. *Psychoneuroendocrinology*, *30*, 121–128.
Derryberry, D., & Tucker, D. M. (2006). Motivation, self-regulation, and self-organization. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology: Vol. 2. Developmental neuroscience* (2nd ed., pp. 502–533). Hoboken, NJ: Wiley.
Dettling, A., Pryce, C. R., Martin, R. D., & Döbelli, M. (1998). Physiological responses to parental separation and a strange situation are related to parental care received in juvenile Goeldi's monkeys (*Callimico goeldii*). *Developmental Psychobiology*, *33*, 21–31.
Dodge, K. A. (1993). Social–cognitive mechanisms in the development of conduct disorder and depression. *Annual Review of Psychology*, *44*, 559–584.
Doornbos, B., Fokkema, D. S., Molhoek, M., Tanke, M. A. C., Postema, F., & Korf, J. (2009). Abrupt rather than gradual hormonal changes induce postpartum blues-like behavior in rats. *Life Sciences*, *84*, 69–74.
Dozier, M., Peloso, E., Lindhiem, O., Gordon, M. K., Manni, M, Sepulveda, S., et al. (2006). Developing evidence-based interventions for foster children: An example of a randomized clinical trial with infants and toddlers. *Journal of Social Issues*, *62*, 767–785.
Drevets, W. C., Frank, J. C., Kupfer, D. J., Holt, D., Greer, P. J., Huang, Y., et al. (1999). PET imaging of serotonin 1A receptor binding in depression. *Biological Psychiatry*, *46*, 1375–1387.
Drevets, W. C., Thase, M. E., Moses-Kolko, E. L., Price, J., Frank, E., Kupfer, D. J., et al. (2007). Serotonin-1A receptor imaging in recurrent depression: Replication and literature review. *Nuclear Medicine and Biology*, *34*, 865–877.
Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*, 257–269.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

Eley, T. C., Sugden, K., Corsico, A., Gregory, A. M., Sham, P., McGuffin, P., et al. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry*, *9*, 908–915.

Figueiredo, H. F., Bruestle, A., Bodie, B., Dolgas, C. M., & Herman, J. P. (2003). The medial prefrontal cortex differentially regulates stress-induced c-FOS expression in the forebrain depending on type of stressor. *European Journal of Neuroscience*, *18*, 2357–2364.

Fisher, P. A., Gunnar, M. R., Chamberlain, P., & Reid, J. B. (2000). Preventive intervention for maltreated preschool children: Impact on children's behavior, neuroendocrine activity, and foster parent functioning. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*, 1356–1364.

Flory, J. D., Newcorn, J. H., Miller, C., Harty, S., & Halperin, J. M. (2007). Serotonergic function in children with attention-deficit hyperactivity disorder: Relationship to later antisocial personality disorder. *British Journal of Psychiatry*, *190*, 410–414.

Flügge, G., van Kampen, M., & Mijnster, M. J. (2004). Perturbations in brain monoamine systems during stress. *Cell and Tissue Research*, *315*, 1–14.

Foley, D. L., Eaves, L. J., Wormley, B., Silberg, J. L., Maes, H. H., Kuhn, J., et al. (2004). Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Archives of General Psychiatry*, *61*, 738–744.

Fowles, D. (1988). Psychophysiology and psychopathology: A motivational approach. *Psychophysiology*, *25*, 373–391.

Francis, D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*, *286*, 1155–1158.

Fuchs, E., & Flügge, G. (1995). Modulation of binding sites for corticotrophin-releasing hormone by chronic psychosocial stress. *Psychoneuroendocrinology*, *20*, 33–51.

Gabel, S., Stadler, J., Bjorn, J., Shindledecker, R., & Bowden, C. (1993). Dopamine-beta-hydroxylase in behaviorally disturbed youth. Relationship between teacher and parent ratings. *Biological Psychiatry*, *1*, 434–442.

Galvin, M., Shekhar, A., Simon, J., Stilwell, B., Ten Eyck, R., Laite, G., et al. (1991). Low dopamine-beta-hydroxylase: A biological sequela of abuse and neglect? *Psychiatry Research*, *39*, 1–11

Galvin, M., Ten Eyck, R., Shekhar, A., Stilwell, B., Fineberg, N., Laite, G., et al. (1995). Serum dopamine beta hydroxylase and maltreatment in psychiatrically hospitalized boys. *Child Abuse & Neglect*, *19*, 821–832.

Galvin, M., Stilwell, B. M., Shekhar, A., Kopta, S. M., & Goldfarb, S. M. (1997). Maltreatment, conscience functioning and dopamine beta hydroxylase in emotionally disturbed boys. *Child Abuse & Neglect*, *21*, 83–92.

Gatzke-Kopp, L., & Beauchaine, T. P. (2007). Central nervous system substrates of impulsivity: Implications for the development of attention-deficit/hyperactivity disorder and conduct disorder. In D. Coch, G. Dawson, & K. Fischer (Eds.), *Human behavior and the developing brain: Atypical development* (pp. 239–263). New York: Guilford Press.

Gatzke-Kopp, L. M., & Shannon, K. E. (2008). Brain injury as a risk factor for psychopathology. In T. P. Beauchaine & S. P. Hinshaw (Eds.), *Child and adolescent psychopathology* (pp. 208–233). Hoboken, NJ: Wiley.

Gershon, A., Vishne, T., & Grunhaus, L. (2007). Dopamine D2-like receptors and the antidepressant response. *Biological Psychiatry*, *61*, 145–153.

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., et al. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, *5*, 1242–1247.

Glaser, D. (2000). Child abuse and neglect and the brain—A review. *Journal of Child Psychology and Psychiatry*, *41*, 97–116.

Goodyer, I. M., Herbert, J., & Altham, P. M. (1998). Adrenal steroid secretion and major depression in 8- to 16-year-olds, III. Influence of cortisol/DHEA ratio at presentation on subsequent rates of disappointing life events and persistent major depression. *Psychological Medicine*, *28*, 265–273.

Gottman, J. M., & Katz, L. (1989). Effects of marital discord on young children's peer interaction and health. *Developmental Psychology*, *25*, 373–381.

Graham, F. K. (1975). The more or less startling effects of weak prestimulation. *Psychophysiology*, *12*, 238–248.

Gray, J. A. (1982). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system*. New York: Oxford University Press.

Gray, J. A. (1987). Perspectives on anxiety and impulsivity: A commentary. *Journal of Research in Personality*, *21*, 493–509.

Gray, J. A., & McNaughton, N. (2000). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system* (2nd ed.). New York: Oxford University Press.

Grillon, C., Dierker, L., & Merikangas, K. R. (1997). Startle modulation in children at risk for anxiety disorders and/or alcoholism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*, 925–932.

Grillon, C., & Morgan, C. A. (1999). Fear-potentiated startle conditioning to explicit and contextual cues in Gulf War veterans with posttraumatic stress disorder. *Journal of Abnormal Psychology*, *108*, 134–142.

Grillon, C., Morgan, C. A., Davis, M., & Southwick, S. M. (1999). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry*, *44*, 1027–1036.

Grillon, C., Morgan, C. A., Southwick, S. M., Davis, M., & Charney, D. S. (1996). Baseline startle amplitude and prepulse inhibition in Vietnam veterans with posttraumatic stress disorder. *Psychiatry Research*, *64*, 169–178.

Guthrie, R. M., & Bryant, R. A. (2005). Auditory startle response in firefighters before and after trauma exposure. *American Journal of Psychiatry*, *162*, 283–290.

Gunnar, M. R., & Vasquez, D. M. (2006). Stress neurobiology and developmental psychopathology. In D. Cicchetti & D. Cohen (Eds.), *Developmental psychopathology: Vol. 2. Developmental neuroscience* (pp. 533–577). New York: Wiley.

Haberstick, B. C., Lessem, J. M., Hopfer, C. J., Smolen, A., Ehringer, M. A., Timberlake, D., et al. (2005). Monoamine oxidase A (MAOA) and antisocial behaviors in the presence of childhood and adolescent maltreatment. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *135*, 59–64.

Halperin, J. M., Newcorn, J. H., Schwartz, S. T., Sharma, V., Siever, L. J., Koda, V. H., et al. (1997). Age-related changes in the association between serotonergic function and aggression in boys with ADHD. *Biological Psychiatry*, *41*, 682–689.

Hart, J., Gunnar, M., & Cicchetti, D. (1995). Salivary cortisol in maltreated children: Evidence of relations between neuroendocrine activity and social competence. *Development and Psychopathology*, *7*, 11–26.

Hart, J., Gunnar, M., & Cicchetti, D. (1996). Altered neuroendocrine activity in maltreated children related to symptoms of depression. *Development and Psychopathology*, *8*, 201–214.

Hatalski, C. G., Guirguis, C., & Baram, T. Z. (1998). Corticotropin releasing factor mRNA expression in the hypothalamic paraventricular nucleus and the central nucleus of the amygdale is modulated by repeated acute stress in the immature rat. *Journal of Neuroendocrinology*, *10*, 663–669.

Heim, C., & Nemeroff, C. B. (2001). Childhood trauma, depression, and anxiety. *Biological Psychiatry*, *49*, 1023–1039.

Hidalgo, R. B., & Davidson, J. R. (2000). Selective serotonin reuptake inhibitors in post-traumatic stress disorder. *Journal of Psychopharmacology*, *14*, 70–76.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*, 679–709.

Huizinga, D., Haberstick, B. C., Smolen, A., Menard, S., Young, S. E., Corley, R. P., et al. (2006). Childhood maltreatment, subsequent antisocial behavior, and the role of monoamine oxidase a genotype. *Biological Psychiatry*, *60*, 677–683.

Imperato, A., Cabib, S., & Puglisi-Allegra, S. (1993). Repeated stressful experiences differently affect the time-dependent responses of the mesolimbic dopamine system to the stressor. *Brain Research*, *60*, 333–336.

Isovich, E., Mijnster, M. J., Flügge, G., & Fuchs, E. (2000). Chronic psychosocial stress reduces the density of dopamine transporters. *The European Journal of Neuroscience*, *12*, 1071–1078.

Jaffee, S. R., Caspi, A., Moffitt, T. E., Dodge, K. A., Rutter, M., Taylor, A., et al. (2005). Nature × Nurture: Genetic vulnerabilities interact with physical maltreatment to promote conduct problems. *Development and Psychopathology*, *17*, 67–84.

Jaffee, S. R., Caspi, A., Moffitt, T. E., Polo-Tomas, M., Price, T. S., & Taylor, A. (2004). The limits of child effects: Evidence for genetically mediated child effects on corporal but not on physical maltreatment. *Developmental Psychology*, *40*, 1047–1058.

Jaffee, S. R., Caspi, A., Moffitt, T. E., & Taylor, A. (2004). Physical maltreatment victim to antisocial child: Evidence of an environmentally mediated process. *Journal of Abnormal Psychology*, *113*, 44–55.

Kaler, S., & Freeman, B. (1994). Analysis of environmental deprivation: Cognitive and social development in Romanian orphans. *Journal of Child Psychology and Psychiatry*, *35*, 769–781.

Kaufman, J. (1991). Depressive disorders in maltreated children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *30*, 257–265.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

Kaufman, J., Birmaher, B., Brent, D., Dahl, R., Bridge, J., & Ryan, N. D. (1998). Psychopathology in the relatives of depressed-abused children. *Child Abuse and Neglect*, *22*, 171–181.

Kaufman, J., Birmaher, B., Perel, J., Dahl, R., Moreci, P., Nelson, B., et al. (1997). The corticotropin-releasing challenge in depressed abused, depressed non-abused, and normal children. *Biological Psychiatry*, *42*, 669–679.

Kaufman, J., Birmaher, B., Perel, J., Dahl, R., Stull, S., Brent, D., et al. (1998). Serotonergic functioning in depressed abused children: Clinical and family correlates. *Biological Psychiatry*, *44*, 973–981.

Kaufman, J., Yang, B.-Z., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., et al. (2006). Brain-derived neurotrophic factor–5-*HTTLPR* gene interactions and environmental modifiers of depression in children. *Biological Psychiatry*, *59*, 673–680.

Kaufman, J., Yang, B.-Z, Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., et al. (2004). Social support and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy Sciences of the United States of America*, *101*, 17316–17321.

Keen-Rhinehart, E., Michopoulos, V., Toufexis, D. J., Martin, E., Nair, H., Ressler, K. J., et al. (2009). Continuous expression of corticotrophin-releasing factor in the central nucleus of the amygdale emulates the dysregulation of the stress and reproductive axes. *Molecular Psychiatry*, *19*, 37–50.

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., et al. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry*, *152*, 833–842.

Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A., & Riley, B. (2005). The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication. *Archives of General Psychiatry*, *62*, 529–535.

Kendler, K. S., & Karkowski-Shuman, L. (1997). Stressful life events and genetic liability to major depression: Genetic control of exposure to the environment? *Psychological Medicine*, *27*, 539–547

Kim, C. H., Zabetian, C. P., Cubells, J. F., Cho, S., Biaggioni, I., Cohen, B. M., et al. (2002). Mutations in the dopamine beta-hydroxylase gene are associated with human norepinephrine deficiency. *American Journal of Medical Genetics*, *108*, 140–147.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., et al. (2006). MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta analysis. *Molecular Psychiatry*, *11*, 903–913.

Kliewer, W. (2006). Violence exposure and cortisol responses in urban youth. *International Journal of Behavioral Medicine*, *13*, 109–120.

Klimes-Dougan, B., Hastings, P. D., Granger, D. A., Usher, B. A., & Zahn-Waxler, C. (2001). Adrenocortical activity in at-risk and normally developing adolescents: individual differences in salivary cortisol basal levels, diurnal variation, and responses to social challenges. *Development and Psychopathology*, *13*, 695–719.

Klorman, R., Cicchetti, D., Thatcher, J. E., & Ison, J. R. (2003). Acoustic startle in maltreated children. *Journal of Abnormal Child Psychology*, *31*, 359–370.

Kruesi, M. J., Hibbs, E. D., Zahn, T. P., Keysor, C. S., Hamburger, S. D., Bartko, J. J., et al. (1992). A 2-year prospective follow-up study of children and adolescents with disruptive behavior disorders. Prediction by cerebrospinal fluid 5-hydroxyindoleacetic acid, homovanillic acid, and autonomic measures? *Archives of General Psychiatry*, *49*, 429–435.

Kruesi, M. J., Rapoport, J. L., Hamburger, S. D., Hibbs, E. D., Potter, W. Z., Lenane, M., et al. (1990). Cerebrospinal fluid monoamine metabolites, aggression, and impulsivity in disruptive behavior disorders of children and adolescents. *Archives of General Psychiatry*, *47*, 419–426.

Kunugi, H., Hattori, M., Kato, T., Tatsumi, M., Sakai, T., Sasaki, T., et al. (1997). Serotonin transporter polymorphisms: Ethnic difference and possible association with bipolar affective disorder. *Molecular Psychiatry*, *2*, 457–462.

Laasko, A., Wallius, E., Kajander, J., Bergman, J., Eskola, O., Solin, O., et al. (2003). Personality traits and striatal dopamine synthesis capacity in healthy subjects. *American Journal of Psychiatry*, *160*, 904–910.

Ladd, C. O., Owens, M. J., & Nemeroff, C. B. (1996). Persistent changes in corticotrophin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology*, *137*, 1212–1218.

Ladd, C. O., Huot, R. L., Thrivikraman, K. V., & Plotsky, P. M. (1998). Persistent alterations in the negative feedback regulation of the hypothalamic–pituitary–adrenal (HPA) axis in maternally-separated adult Long–Evans hooded rats. *Society for Neuroscience Abstracts*, *24*, 117.

Ladd, C. O., Huot, R. L., Thrivikraman, K. V., & Plotsky, P. M. (1999). Reversal of the maternal separation phenotype by reboxetine. *Society for Neuroscience Abstracts*, *25*, 1456.

Lanfumey, L., Mannoury La Cour, C., Froger, N., & Hamon, M. (2000). 5-HT–HPA interactions in two models of transgenic mice relevant to major depression. *Neurochemical Research*, *25*, 1199–1206.

Latzman, R. D., & Swisher, R. R. (2005). The interactive relationship among adolescent violence, street violence, and depression. *Journal of Community Psychology*, *33*, 355–371.

LeDoux, J. (1998). Fear and the brain: Where have we been, and where are we going? *Biological Psychiatry*, *44*, 1229–1238.

Lee, V., & Hoaken, P. N. S. (2007). Cognition, emotion, and neurobiologial development: Mediating the relation between maltreatment and aggression. *Child Maltreatment*, *12*, 281–298.

Lemieux, A. M., & Coe, C.L. (1995).Abuse-related posttraumatic stress disorder: Evidence for chronic neuroendocrine activation in women. *Psychosomatic Medicine*, *57*, 105–115.

Lewis, D. A. (2000). The catecholamine innervation of primate cerebral cortex. In M. V. Solanto, A. F. T. Arnsten, & F. X. Castellanos (Eds.), *Stimulant drugs and ADHD: Basic and clinical neuroscience*. Oxford: Oxford University Press.

Lindley, S. E., Bengoechea, T. G., Wong, D. L., & Schatzberg, A. F. (2002). Mesotelencephalic dopamine neurochemical responses to glucocorticoid administration and adrenalectomy in Fischer 344 and Lewis rats, *Brain Research*, *958* 414–422.

Lindley, S. E., She, X., & Schatzberg, A. F. (2005). Monoamine oxidase and catechol-*o*-methyltransferase enzyme activity and gene expression in response to sustained glucocorticoids. *Psychoneuroendocrinology*, *38*, 785–790.

Lipschitz, D. S., Mayes, L. M., Rasmusson, A. M., Anyan, W., Billingslea, E., Gueorgueva, R., et al. (2005). Baseline and modulated acoustic startle responses in adolescent girls with posttraumatic stress disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*, 807–814.

Liu, D., Caldji, C., Sharma, S., Plotsky, P.M., & Meaney, M. J. (2000). Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinephrine release in the hypothalamic paraventricular nucleus. *Journal of Neuroendocrinology*, *12*, 5–12.

Liu, D., Diorio, J., Tannanbaum, B., Caldji, C., Francis, D., Freedman, A., et al. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. *Science*, *277*, 1659–1662.

Lucas, L. R., Celen, Z., Tamashiro, K. L. K., Blanchard, R. J., Blanchard, D. C., Markham, C., et al. (2004). Repeated exposure to social stress has long term effects on indirect markers of dopaminergic activity in brain regions associated with motivated behavior. *Neuroscience*, *124*, 449–457.

Lucas, L. R., Wang, C.-J., McCall, T. J., & McEwen, B. S. (2007). Effects of immobilization stress on neurochemical markers in the motivational system of the male rat. *Brain Research*, *1155*, 108–115.

Lucki, I. (1998). The spectrum of behaviors influenced by serotonin. *Biological Psychiatry*, *44*, 151–162.

Maestripieri, D., Higley, J. D., Lindell, S. G., Newman, T. K., McCormack, K., & Sánchez, M. M. (2006). Early maternal rejection affects the development of monoaminergic systems and adult abusive parenting in rhesus macaques (*Macaca mulatta*). *Behavioral Neuroscience*, *120*, 1017–1024.

Maestripieri, D., McCormack, K., Lindell, S. G., Higley, J. D., & Sánchez, M. M. (2006). Influence of parenting style on the offspring's behavior and CSF monoamine metabolite levels in crossfostered and noncrossfostered female rhesus macaques. *Behavioral Brain Research*, *175*, 90–95.

Margolin, G. (2005). Children's exposure to violence: Exploring diverse pathways. *Journal of Interpersonal Violence*, *20*, 72–81.

Mathew, S. J., Coplan, J. D., Sith, E. L. P., Schare, B. A., Owens, M. J., & Nemeroff, C. B. (2002). Cerebrospinal fluid concentrations of biogenic amines and corticotrophin-releasing factor in adolescent non-human primates as a function of the timing of adverse early rearing. *Stress*, *5*, 185–193.

McArthur, S., McHale, D., & Gillies, G. E. (2007). The size and distribution of midbrain dopaminergic populations are permanently altered by perinatal glucocorticoid exposure in a sex region and time related manner. *Neuropsychopharmacology*, *32*, 1462–1476.

McEwen, B. S., & Sapolsky, R. M. (1995). Stress and cognitive function. *Current Opinion in Neurobiology*, *5*, 205–216.

McKittrick, C. R., Blanchard, D. C., Blanchard, R. J., McEwen, B. S., & Sakai, R. R. (1995). Serotonin receptor binding in a colony model of chronic social stress. *Biological Psychology*, *37*, 383–393.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

Meaney, M. J., Brake, W., & Gratton, A. (2002). Environmental regulation of the development of mesolimbic dopamine systems: A neurobiological mechanism for vulnerability to drug abuse? *Psychoneuroendocrinology*, *27*, 127–138.

Meaney, M. J., Diorio, D., Francis, J., Widdowson, J., LaPlante, P., Caldji, C., et al. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Developmental Neuroscience*, *18*, 49–72.

Metzger, I. J., Orr, S. P., Berry, N. J., Ahern, C. E., Lasko, N. B., & Pitman, R. K. (1999). Physiologic reactivity to startling tones in women with posttraumatic stress disorder. *Journal of Abnormal Psychology*, *108*, 347–352.

Miczek, K. A., Covington, H. E., Nikulina, E. M., & Hammer, R. P. (2004). Aggression and defeat: Persistent effects on cocaine self-administration and gene expression in peptidergic and aminergic mesocorticolimbic circuits. *Neuroscience and Biobehavioral Reviews*, *27*, 787–802.

Millan, M A., Jacobowitz, D. M., Hauger, R. L., Catt, K. J., & Aguilera, G. (1986). Distribution of corticotrophin-releasing factor receptors in primate brain. *Proceedings of the National Academy of Sciences of the United States of America*, *83*, 1921–1925.

Mirescu, C., Peters, J. D., & Gould, E. (2004). Early life experience alters response of adult neurogenesis to stress. *Nature Neuroscience*, *7*, 841–846.

Mohanty, A., Engels, A. S., Herrington, J. D., Heller, W., Ringo Ho, M., Banich, M. T., et al. (2007). Differential engagement of anterior cingulate cortex subdivisions for cognitive and emotional function. *Psychophysiology*, *44*, 343–351.

Morgan, C. A., Grillon, C., Lubin, H., & Southwick, S. M. (1997). Startle reflex abnormalities in women with sexual assault-related posttraumatic stress disorder. *American Journal of Psychiatry*, *154*, 1076–1080.

Morgan, C. A., Grillon, C., Lubin, H., Southwick, S. M., Davis, M., & Charney, D. S. (1995). Fear-potentiated startle in posttraumatic stress disorder. *Biological Psychiatry*, *38*, 378–385.

Morgan, C. A., Grillon, C., Southwick, S. M., Davis, M., & Charney, D. S. (1996). Exaggerated acoustic startle reflex in Gulf War veterans with posttraumatic stress disorder. *American Journal of Psychiatry*, *153*, 64–68.

Nakamura, M., Ueno, S., Sano, A., & Tanabe, H. (2000).The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. *Molecular Psychiatry*, *5*, 32–38.

Narusyte, J., Andershed, A.-K., Neiderhiser, J. M., & Lichtenstein, P. (2007). Aggression as a mediator of genetic contributions to the association between negative parent–child relationships and adolescent antisocial behavior. *European Child & Adolescent Psychiatry*, *16*, 128–137.

Neiderhiser, J. M., Reiss, D., Pedersen, N. L., Lichtenstein, P., Spotts, E. L., Hansson, K., et al. (2004). Genetic and environmental influences on mothering of adolescents: a comparison of two samples. *Developmental Psychology*, *40*, 335–351.

Neumeister, A., Bain, E., Nugent, A. C., Cason, R. E., Bonne, O., & Luckenbough, D. A. (2004). Reduced serotonin type 1_A receptor binding in panic disorder. *Journal of Neuroscience*, *24*, 589–591.

Nesse, R. M. (2000). Is depression an adaptation? *Archives of General Psychiatry*, *57*, 14–20.

Ng-Mak, D. S., Salzinger, S., Feldman, R. S., & Stueve, C. A. (2004). Pathologic adaptation to community violence among inner-city youth. *American Journal of Orthopsychiatry*, *74*, 196–208.

O'Connor, T., Deater-Deckard, K., Fulker, D., Rutter, M., & Plomin, R. (1998). Genotype–environment correlations in late childhood and early adolescence: Antisocial behavior problems and coercive parenting. *Developmental Psychology*, *34*, 970–981.

Ornitz, E. M., & Pynoos, R. (1989). Startle modulation in children with posttraumatic stress disorder. *American Journal of Psychiatry*, *146*, 866–870.

Orr, S. P., Lasko, N. B., Metzger, L. J., & Pitman, R. K. (1997). Physiologic responses to non-startling tones in Vietnam veterans with post-traumatic stress disorder. *Psychiatry Research*, *73*, 103–107.

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Hu, F. B., Shalev, A. Y., et al. (2003). Physiologic responses to sudden loud tones in monozygotic twins discordant for combat exposure. *Archives of General Psychiatry*, *60*, 283–288.

Orr, S. P., Soloman, Z., Peri, T., Pitman, R. K., & Shalev, A. Y. (1997). Physiologic responses to loud tones in Israeli veterans of the 1973 Yom Kippur War. *Biological Psychiatry*, *41*, 319–326.

Panagiotaropoulos, T., Pondiki, S., Papaioannou, A., Alikaridis, F., Stamatakis, A., Gerozissis, K., et al. (2004). Neonatal handling and gender modulate brain monamines and plasma corticosterone levels following repeated stressors in adulthood. *Neuroendocrinology*, *80*, 181–191.

Papaioannou, A., Dafni, U., Alikaridis, F., Bolaris, S., & Stylianopoulou, F. (2002). Effects of neonatal handling on basal and stress-induced monoamine levels in the male and female rat brain. *Neuroscience*, *114*, 195–206.

Parker, K. J., Rainwater, K. L., Buckmaster, C. L., Schatzberg, A. F., Lindley, S. E., & Lyons, D. M. (2007). Early life stress and novelty seeking behavior in adolescent monkeys. *Psychoneuroendocrinology*, *32*, 785–792.

Patel, P. D., Katz, M., Karssen, A. M., & Lyons, D. M. (2008). Stress-induced changes in corticosteroid receptor expression in primate hippocampus and prefrontal cortex. *Psychoneuroendocrinology*, *33*, 360–367.

Patterson, G. R. (1982). *Coercive Family Processes: Vol. 3. A social learning approach*. Eugene, OR: Castilia.

Patterson, G. R., Capaldi, D., & Bank, L. (1991). An early starter model for predicting delinquency. In D. Pepler & K. H. Rubin (Eds.), *The development and treatment of childhood aggression* (pp. 139–168), Hillsdale, NJ: Erlbaum.

Patterson, G. R., DeGarmo, D. S., & Knutson, N. (2000). Hyperactive and antisocial behaviors: Comorbid or two points in the same process? *Development and Psychopathology*, *12*, 91–106.

Perry, B. D. (2008). Child maltreatment: A neurodevelopmental perspective on the role of trauma and neglect in psychopathology. In T. P. Beauchaine & S. P. Hinshaw. (Eds.), *Child and adolescent psychopathology* (pp. 93–128). Hoboken, NJ: Wiley.

Pezawas, L., Verchinski, B. A., Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., et al. (2004). The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *Journal of Neuroscience*, *24*, 10099–10102.

Pine, D. S., Coplan, J. D., Wasserman, G. A., Miller, L. S., Fried, J. E., Davies, M., et al. (1997). Neuroendocrine response to fenfluramine challenge in boys: Associations with aggressive behavior and adverse rearing. *Archives of General Psychiatry*, *54*, 839–846.

Porges, S. W. (1995). Cardiac vagal tone: A physiological index of stress. *Neuroscience and Biobehavioral Reviews*, *19*, 225–233.

Quay, H. C. (1993). The psychobiology of undersocialized aggressive conduct disorder: A theoretical perspective. *Development and Psychopathology*, *5*, 165–180.

Quay, H. C. (1997). Inhibition and attention deficit hyperactivity disorder. *Journal of Abnormal Child Psychology*, *25*, 7–13.

Rinne, T., Westenberg, H. G. M., den Boer, J. A., & van den Brink, W. (2000). Serotonergic blunting to *meta*-chlorophenylpiperazine (*m*-CPP) highly correlates with sustained childhood abuse in impulsive and autoaggressive female borderline patients. *Biological Psychiatry*, *47*, 548–556.

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., et al. (2009). Interaction Between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis. *Journal of the American Medical Association*, *301*, 2462–2471.

Rogeness, G. A., Amrung, S. A., & Harris, W. R. (1984). Clinical characteristics of emotionally disturbed boys with very low activities of dopamine beta hydroxylase. *Journal of the American Academy of Child & Adolescent Psychiatry*, *23*, 203–208.

Rogeness, G. A., Hernandez, J. M., Macedo, C. A., Amrung, S. A., & Hoppe, S. K. (1986). Near-zero plasma dopamine-β-hydroxylase and conduct disorder in emotionally disturbed boys. *Journal of the American Academy of Child & Adolescent Psychiatry*, *25*, 521–527.

Rogeness, G. A., Javors, M. A., & Pliszka, S. R. (1992). Neurochemistry and child and adolescent psychiatry. *Journal of the American Academy of Child & Adolescent Psychiatry*, *31*, 765–781.

Rogeness, G. A., & McClure, E. B. (1996). Development and neurotransmitter–environment interactions. *Development and Psychopathology*, *8*, 183–199.

Rosenblum, L. A., Forger, C., Noland, S., Trost, R. C., & Coplan, J. D. (2001). Response of adolescent bonnet macaques to an acute fear stimulus as a function of early rearing conditions. *Developmental Psychobiology*, *39*, 40–45.

Rosenblum, L. A., & Paully, G. S. (1984). The effects of varying environmental demands on maternal and infant behavior. *Child Development*, *55*, 305–314.

Rosenblum, L. A., Coplan, J. D., Friedman, S., Bassoff, T., Gorman, J. M., & Andrews, M. W. (1994). Adverse early experiences affect noradrenergic and serotonergic functioning in adult primates. *Biological Psychiatry*, *35*, 221–227.

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene–environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry*, *47*, 226–261.

Rutter, M., O'Connor, & the English and Roman Adoptees (ERA) Study Team. (2004). Are there biological programming effects for psychological development? Findings from a study of Romanian Adoptees. *Developmental Psychology*, *40*, 81–94.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press

Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences*, *28*, 397–468.

Sala, M., Perez, J., Soloff, P., Ucelli di Nemi, S., Caversazi, E., Soares, J. C., et al. (2004). Stress and hippocampal abnormalities in psychiatric disorders. *European Neuropsychopharmacology*, *14*, 393–405.

Saltzman, K. M., Holden, G. W., & Holahan, C. J. (2005). The psychobiology of children exposed to marital violence. *Journal of Clinical Child and Adolescent Psychology*, *34*, 129–139.

Sánchez, M. M. (2006). The impact of early adverse care on HPA axis development: Nonhuman primate models. *Hormones and Behavior*, *50*, 623–631.

Sánchez, M. M., Ladd, C. O., & Plotsky, P. M. (2001). Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. *Development and Psychopathology*, *13*, 419–449.

Sapolsky, R. M. (1998). *Why zebras don't get ulcers: An updated guide to stress, stress-related diseases, and coping*. New York: W. H. Freeman.

Sapolsky, R. M. (2000). Stress hormones: Good and bad. *Neurobiology of Disease*, *7*, 540–542.

Sapolsky, R. M., Uno, H., Rebert, C. S., & Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience*, *10*, 2897–2902.

Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder, *Biological Psychiatry*, *61*, 720–724.

Schulz, K. P., Newcorn, J. H., McKay, K. E., Himelston, J., Koda, V. H., Siever, L. J., et al. (2001). Relationship between central serotonergic function and aggression in prepubertal boys: Effect of age and attention-deficit/hyperactivity disorder. *Psychiatry Research*, *101*, 1–10.

Schwab-Stone, M. E., Ayers, T. S., Kasprow, W., Voyce, C., Barone, C., Shriver, T., et al. (1995). No safe haven: A study of violence exposure in an urban community. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*, 1343–1352.

Segrin, C. (2000). Social skills deficits associated with depression. *Clinical Psychology Review*, *20*, 379–403.

Shalev, A. Y., Orr, S. P., Peri, T., Schreiber, S., & Pitman, R. K. (1992). Physiologic responses to loud tones in Israeli posttraumatic stress disorder patients. *Archives of General Psychiatry*, *11*, 870–875.

Shalev, A. Y., Peri, T., Orr, S. P., Bonne, O., & Pitman, R. K. (1997). Auditory startle responses in help-seeking trauma survivors. *Psychiatry Research*, *69*, 1–7.

Sheikh, N., Ahmad, A., Siripurapu, K. B., Kumar Kuchibhotla, V. K., Singh, S., & Palit, G. (2007). Effect of *Bacopa monniera* on stress induced changes in plasma corticosterone and brain monoamines in rats. *Journal of Ethnopharmacology*, *111*, 671–676.

Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., et al. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *American Journal of Psychiatry*, *156*, 575–584.

Shin, L. M., Kosslyn, S. M., McNally, R. J., Alpert, N. M., Thompson, W. L., Rauch, S. L., et al. (1997). Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Archives of General Psychiatry*, *54*, 233–237.

Smith, M. E. (2005). Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: A meta-analysis of structural MRI studies. *Hippocampus*, *15*, 798–807.

Snyder, J., Edwards, P., McGraw, K., Kilgore, K., & Holton, A. (1994). Escalation and reinforcement in mother–child conflict: Social processes associated with the development of physical aggression. *Development and Psychopathology*, *6*, 305–321.

Snyder, J., Schrepferman, L., & St. Peter, C. (1997). Origins of antisocial behavior: Negative reinforcement and affect dysregulation of behavior as socialization mechanisms in family interaction. *Behavior Modification*, *21*, 187–215.

Sroufe, A. (1997). Psychopathology as an outcome of development. *Development and Psychopathology*, *9*, 251–268.

Sroufe, A., & Rutter, M. (1984). The domain of developmental psychopathology. *Child Development*, *55*, 17–29.

Stone, E., & McCarty, R. (1983). Adaptation to stress: Tyrosine hydroxylase activity and catecholamine release. *Neuroscience and Biobehavioral Reviews*, *7*, 29.

Strauss, J., Barr, C. L., George, C. J., King, N., Shaikh, S., Devlin, B., et al. (2004). Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. *American Journal of Medical Genetics: Neuropsychiatric Genetics*, *131*, 16–19.

Suhara, T., Yasuno, F., Sudo, Y., Yamamoto, M., Inoue, M., Okubo, Y., et al. (2001). Dopamine D2 receptors in the insular cortex and the personality trait of novelty seeking. *Neuroimage*, *13*, 891–895.

Tanaka, M., Yoshida, M., Emoto, H., & Ishii, H. (2000). Noradrenaline systems in the hypothalamus, amygdala, and locus coeruleus are involved in the provocation of anxiety: Basic studies. *European Journal of Pharmacology*, *405*, 397–406.

Tarullo, A. R., & Gunnar, M. R. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior*, *50*, 632–639.

Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. L. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry*, *60*, 671–676.

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience and Biobehavioral Reviews*, *27*, 33–44.

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, *53*, 865–871.

Tupler, L. A., & De Bellis, M. D. (2006). Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biological Psychiatry*, *59*, 523–529.

Twitchell, G. R., Hanna, G. L., Cook, E. H., Fitzgerald, H. E., Little, K. Y., & Zucker, R. A. (1998). Overt behavior problems and serotonergic function in middle childhood among male and female offspring of alcoholic fathers. *Alcoholism: Clinical and Experimental Research*, *22*, 1340–1348.

Uno, H., Eisele, S., Sakai, A., Shelton, S., Baker, E., DeJesus, O., et al. (1994). Neurotoxicity of glucocorticoids in the primate brain. *Hormones and Behavior*, *28*, 336–348.

Veenema, A. H., Blume, A., Niederle, Buwalda, B., & Neumann, I. D. (2006). Effects of early life stress on adult male aggression and hypothalamic vasopressin and serotonin. *European Journal of Neuroscience*, *24*, 1711–1720.

Weaver, I. A. C., Cervoni, N., Champagne, F. A., Alessio, A. C. D., Sharma, S., & Seckl, J. R. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, *7*, 847–854.

Wichers, M., Kenis, G., Jacobs, N., Mengelers, R., Derom, C., Vlietinck, R., et al. (2008). The BDNF $Val^{66} \times$ 5-HTTLPR $\times$ Child Adversity interaction and depressive symptoms: An attempt at replication. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*, 120–123.

Widom, C. S., & Brzustowicz, L. M. (2006). MAOA and the "cycle of violence": Childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. *Biological Psychiatry*, *60*, 684–689.

Wilson, D. K., Kliewer, W., Teasley, N., Plybon, L., & Sica, D. A. (2002). Violence exposure, catecholamine excretion, and blood pressure nondipping status in African American male versus female adolescents. *Psychosomatic Medicine*, *64*, 906–915.

Young, S. E., Smolen, A., Hewitt, J. K., Haberstick, B. C., Stallings, M. C., Corley, R. P., et al. (2006). Interaction between MAO-A genotype and maltreatment in the risk for conduct disorder: Failure to confirm in adolescent patients. *American Journal of Psychiatry*, *163*, 1019–1025.

Zahrt, J., Taylor, J. R., Mathew, R. G., & Arnsten, A. F. T. (1997). Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. *Journal of Neuroscience*, *17*, 8528–8535.

https://doi.org/10.1017/S0954579409990228 Published online by Cambridge University Press