Published in final edited form as:
Dev Psychopathol. 2010 ; 22(1): 1. doi:10.1017/S0954579409990228.

Neurobiological Adaptations to Violence across Development

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Abstract

Adaptation to violent environments across development involves 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) consider the impact of violence on the developing human stress and startle responses, and (c) brain development including the hippocampus and prefrontal cortex. This review integrates literature on the developmental effects of violence on rodents, non-human 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.

Keywords

abuse; adaptation; anxiety; depression; neurobiology

Adaptation to environmental contexts is often defined quite differently across scientific disciplines, depending on the level of analysis being studied. At the behavioral level, adaptation can be defined as an ability to adjust to the familial, cultural, and community contexts within which a person is raised. 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 adaptive in the context within which they develop, such behaviors can become liabilities in mainstream settings such as 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 familial, social, and cultural contexts.

The development of aggression in violent contexts has been called *pathological adaptation* (Schwab-Stone et al., 1995). Literature on community violence shows a moderately strong relation between youth exposure to violence and aggression, and weaker associations between exposure to violence and depression, anxiety, and post-traumatic stress disorder (Ng-Mak, Salzinger, Feldman, & Stueve, 2004). Male adolescents are more likely to become violent, whereas female adolescents are more likely to show signs of depression (Latzman & Swisher, 2005; Ng-Mak et al., 2004; Schwab-Stone et al., 1995). Interestingly, for a subset of adolescents exposed to violence, aggressive behavior is associated with less psychological distress (Ng-Mak et al., 2004). Other research shows that the association between negative affectivity and street violence holds only for males who do not engage in violence themselves (Latzman & Swisher, 2005).

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Such findings raise a fundamental question. Are the behavioral changes made in maladaptive environments such as violent families and communities truly *adaptive*? From a biological perspective, adaptation refers to changes that an organism or group of organisms undergo to increase their likelihood of survival within the environment that elicited the adaptation. Such adaptations may include changes in anatomical structures, physiological processes, or behavioral traits. In contrast, maladaptations are adaptations that are or have become less helpful than harmful (Sroufe, 1997). Thus, even if aggression and anxiety are useful adaptations for survival in violent contexts, they may be considered maladaptive in alternative contexts including school, occupational settings, and future family environments.

In contrast to behavioral perspectives on adaptation, which have been described in detail by others (e.g., Sroufe, 1997; Sroufe & Rutter, 1984), our primary objective in writing this article is to review biological mechanisms and sequelae of adaptation. Biological approaches to adaptation often focus on environmentally-elicited changes in the structure and/or function of neurobiological systems that confer advantages for coping or survival. Such adaptations are effected through and affected by a host of influences including genetic predispositions and vulnerabilities, environmental risk and protective factors, Gene × Environment interactions, and epigenetic changes in gene expression.

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 appear to exert 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 review see Cicchetti & Curtis, 2006). For example, among rats pups, differing lengths of postnatal maternal separation contribute to individual differences in the developing neuronal systems involved with the stress response (for review see Sánchez, Ladd, & Plotsky, 2001). From an evolutionary perspective, neurobiological variations associated with differing postnatal environments prepare the developing rat for probable analogous 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 within 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). Individuals 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 review what is currently known about neurobiological adaptations in contexts of violence across development. In the first two sections our focus is on the mechanisms underlying two broad behavioral predispositions that often follow from prolonged exposure to violence: aggression and vigilance/withdrawal. We examine how genetic vulnerabilities affect which behavioral pathway is expressed, and discuss how three associated neurotransmitter systems are affected. Next, we consider adaptations in the human stress response, the hippocampus and prefrontal cortex, and the startle response. Because we are interested primarily in the effects of violence on neurobiological systems subserving behavior, we draw primarily from the available literature on the experience of violence and stress among animals

and humans. We attempt to address wide forms of violence including effects of early physical abuse, and witnessing violence. We consider the generality of findings throughout the text. In the final sections we consider conclusions and future directions. We now describe different types of Gene× Environment interactions, some of which play an important role in the development of behavioral adaptations and maladaptations to violence exposure.

Gene× Environment interactions

Gene × Environment interactions arise when a specific genetic polymorphism confers vulnerability in one or more environmental context but not in others. We discuss below how exposure to violence moderates genetic effects on behavior for both antisocial and depressive outcomes. Gene × Environment interactions may be much more common than acknowledged previously (Moffitt et al., 2006) and may account for more variance in behavior than the main effects of genes and environment (Beauchaine et al., 2008). As noted by Moffitt et al. (2006), natural selection depends in part on individual differences in behavior that are elicited in response to similar environments. In the following section we discuss how Gene × Environment interactions elucidate protective and vulnerability factors for psychopathology. The literature that follows draws primarily from the maltreatment literature.

Maltreatment and Antisocial Behavior

Behavioral genetics

Recent research has explored the role of maltreatment in potentiating heritable vulnerabilities for child antisociality. Given similar environmental risk exposures to violence, not all children are affected equally. Some perpetuate violence, some become depressed, and others emerge functioning very well (Cicchetti & Toth, 1995; 2005). The studies reviewed below demonstrate a complex interplay of genetic vulnerability and maltreatment risk exposure on antisocial outcomes among children.

Jaffee and colleagues (Jaffee et al., 2005; Jaffee, Caspi, Moffitt, & Taylor, 2004a.; Jaffee et al., 2004b) showed that among 5-year-old twin pairs, 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 (MZ twin did not have CD), but by 24% among children at high genetic risk (MZ twin had CD). Parental antisocial behavior accounted for 56% of the effect of maltreatment on antisocial outcomes at age 7 (Jaffee et al., 2004a). Nonetheless, it is important to consider that research with MZ and DZ twins reared apart are the only studies that can truly factor out shared environmental effects.

One possible explanation for this finding is an evocative *r*GE correlation. In this case, children's behavior, which is influenced by genes, may elicit hostile parenting practices that potentiate antisocial behavior (see Patterson, DeGarmo, & Knutson, 2000). 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). Similarly, children with CD often 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). Fifty percent of the association between parental criticism and adolescent antisociality is attributable to heritable effects (Naruyste, Andershed, Neiderhiser, & Lichtenstein, 2007). Jaffee et al. (2004b) found that parents were more likely to use physical discipline strategies with children with a high genetic vulnerability for CD compared with children at low genetic risk. However, children's genetic vulnerability did not predict abuse.

In another set of analyses, Jaffee et al. (2004b) showed that physical maltreatment predicted antisocial outcomes across two 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 these results evidenced a passive *r*GE. However, a twin-parent design, rather than a twin-child design, is required to specify a gene-environment correlation. 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 gene-environment correlations 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 some more resilient) in the face of physical maltreatment than others. Molecular genetics research has attempted to specify the genetic vulnerability factor.

Molecular genetics

A polymorphism in the promoter region of the MAOA gene has gained considerable attention as a 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 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 interactions emerged. Alone, MAOA activity 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 inter-parental violence, and inconsistent discipline. Foley et al. found a main effect for adversity on CD, and a moderation effect for childhood adversity and the MAOA genotype. As in the Caspi et al. study, there was no main effect of MAOA on CD. Other researchers have failed to find a moderating effect 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 increasingly consistent results, evidence for MAOA × Maltreatment interactions on antisociality among non-white male populations is inconclusive to date. Widom and Brzustowicz (2006) failed to find a moderational effect among non-White abused individuals, but did find that MAOA activity buffered abused and neglected White males and females from of becoming violent and antisocial in adulthood. One-third of the sample was non-White and included African Americans, Latinos, American Indians, Pacific Islanders, among other racial minorities. The authors considered the possibility that their failure to replicate findings among ethnic minorities was due to low statistical power, which is feasible. An additional limitation

was combining non-White participants into a single group for analysis. This study and others (e.g., Balciuniene et al., 2001) have shown that the promoter gene polymorphism is not equally distributed across ethnicities. Thus, replication among other racial groups is important, and future research should recruit adequate sample sizes to support within racial group analyses.

Adaptivity of antisocial behavior

Aggression and impulsivity may be framed as adaptive behaviors in violent contexts. Individuals may use aggression for immediate self-protection, and more long term establishment of dominance in a social hierarchy. Indeed, on the behavior level aggression is likely 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. This strategy is clearly adaptive. It helps children protect themselves from pain and potentially death. As noted above, however, an aggressive response style applied in other more mainstream contexts becomes maladaptive.

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 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. We are unaware of research concerning the interaction of MAOA and other forms of violence (i.e., peer victimization, witnessing community violence). Inferences about whether MAOA moderates other types of violence exposure requires targeted research. However, what is clear from Caspi et al. (2002) and the other studies is that antisocial behavior is more likely among individuals with either severe or probable maltreatment. As such, it is possible that broad violence exposure moderates the effects of MAOA on antisocial outcomes. However, as demonstrated in the following literature concerning maltreatment and depression, it possible that other protective factors such as social support could mitigate such effects. Furthermore, when developing children are exposed to violence outside their homes they may be more likely to 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. Nonetheless, research conducted with depressed and abused children (Kaufman et al., 1998a), and research with depressed adults who are exposed to stressful life events (Kendler et al., 1995; Kendler & Karkowski-Shuman, 1997) suggests that the likelihood of developing depression after maltreatment may be partially heritable.

A population-based twin registry provides evidence for an interaction between heritability and stressful life events related to depression among adult women (Kendler et al., 1995). Among those at the lowest genetic risk (MZ twins unaffected) 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 (MZ twins, co-twin affected), probabilities of developing depression were 1.1% and 14.6% in the absence and presence of life events, respectively. Using discrete time survival analysis Kendler and Karkowski-Shuman (1997) showed that genetic risk factors for major depression increased the probability of exposure to stressful life events, suggesting an

evocative Gene-Environment correlation. This study provides evidence that heritable individual differences in vulnerability may influence the development of depression in the context of maltreatment leading to interest in candidate genes.

Molecular genetics

Exposure to maltreatment increases the probability of depression (e.g., Kaufman et al., 2004; Kaufman et al., 2006; Taylor et al., 2006), and a genetic polymorphism in the promoter region of the serotonin transporter (5-HTT) gene appears to moderate this relation. 5-HTT is involved in the reuptake of serotonin (5-HT) within brain synapses. The short (s) allele in the 5-HTT gene is related to lower transcriptional efficiency of the promoter and lower 5-HT uptake compared with the long (l) allele (Nakamura, Ueno, Sano, & Tanabe, 2000).

Using prospectively collected maltreatment and genotype data Caspi et al. (2003) explored depression outcomes among 26-year-old Caucasian New Zealanders. Although the 5-HTT gene did not have a direct association with depression, men and women with childhood maltreatment histories were more likely to endorse depressive symptoms as adults if they were homozygous for the s allele (s/s) or heretozygous (s/l) 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. Kaufman and colleagues (2004) found that among an ethnically diverse group of 5–15-year-old maltreated children, s/s individuals were more likely to report current depressive symptoms than both s/l and l/l children. However, the presence of social supports lowered the associated risk between the 5-HTT s/s genotype and depression. Social supports were independent from maltreatment status. In another report, Kaufman et al. (2006) investigated maltreatment, 5-HTT, and genotypes of the brain-derived neurotrophic factor (BDNF). BDNF is a protein that supports growth and differentiation of neurons, which has been associated with childhood-onset depression (Strauss, et al., 2004). A three way interaction between maltreatment, 5-HTT, and the val66/met polymorphism of the BDNF genotype was found for symptoms of depression in children. Children homozygous for the short allele of the 5-HTT gene who also possessed the val66/met BDNF genotype had the highest depression scores. Again, social support attenuated the associated risk between maltreatment and genetic vulnerability.

More general stress also impacts the link between 5-HTT and depressive outcomes. Research with female and male adults (Caspi et al., 2003; Kendler et al., 2005; Taylor, et al., 2006) and with female adolescents (Eley et al., 2004) has documented moderating effects of 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. Additionally, Caspi et al. (2003) ruled out the possibility of an evocative effects 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.

As with the MAOA gene, short alleles are not distributed equally across ethnic groups. Fifty percent of Caucasians have at least one short allele (Caspi et al., 2003) whereas African Americans are more likely to be homozygous for the long allele than both Caucasians and Latinos (Kaufman et al., 2004; Kaufman et al., 2006). Japanese individuals are more likely to carry a short allele than Caucasians (Kunugi, et al., 1997). This suggests that rates of depression following exposure to maltreatment (and other stressors) could vary as a function of race.

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 depressive symptoms. Adolescents who were homozygous for the short 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 (*s/s*; *s/l*) *and* low MAOA activity had elevated depression, anxiety, and somatic symptoms. This research clarifies our understanding of the effect of 5-HTT on depression, with both stressful life events and MAOA activity acting as moderators.

Adaptivity of depression

Depression may be considered adaptive if it protects children from bodily damage, danger, and 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 help to detect future violence. Children who anticipate violence by reading warning signs among caregivers may escape abuse. More generally, anxiety and inhibition decreases the likelihood of approaching threatening situations. Nonetheless, like aggression, anxiety and depressive disorders become maladaptations and are costly when applied outside of violent contexts. For instance, depression is associated with poor social skills among children (Segrin, 2000). 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 long allele of the 5-HTTLPR polymorphism and high activity of MAOA are protective factors for depression among youth exposed to maltreatment. The short allele of the 5-HTTLPR polymorphism and low MAOA activity appear to be vulnerability factors for depression in violent contexts. Together with the review of MAOA, violent contexts, and aggression, these literatures suggest that low MAOA activity may confer risk for aggression primarily in males and depression primarily in females. Although this sex effect is poorly understood (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, in press), it may be rooted in differences in neurotransmitter expression.

As monoamine oxidase is responsible for degradation of all monoamine neurotransmitters, low activity MAOA genotype leads to heightened synaptic DA, NE, and 5-HT . The short allele of the 5-HTT transporter leads to less efficiency in 5-HT reuptake, and more synaptic 5-HT. Although tempting, it is far too complicated to simply conclude that more of these neurotransmitters leads to psychological difficulties in the developmental context of violence. Generally, individual differences in these neurotransmitters and their interaction influence temperament and stress responsivity. In turn, these differences affect how individuals cope with or react to exposure to violence. Next, we examine monoamine neurotransmitters that have been linked with regulation of behavior.

Effects of violence exposure on neurotransmitter function

Interactions between violence exposure and both MAOA and 5-HTT in predicting aggression and depression suggest potential roles for DA, NE, and 5-HT in the expression of these behaviors in high risk environments. This section addresses environmentally elicited changes in each neurotransmitter system. These monoamine neurotransmitters have been the focus of considerable theoretical and empirical work concerning behavior regulation and individual differences in personality (Cloninger, 1987) and psychopathology (Fowles, 1988; Gray, 1982; 1987; Gray & McNaughton, 2000, Rogeness, Javors, & Pliszka, 1992; Rogeness &

McClure, 1996; Quay, 1993; Quay; 1997). Gray (1982;1987) proposed that two neurobiological systems, the behavioral inhibition system (BIS) and the behavioral activation system (BAS), are responsible for 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 (NA) and 5-HT 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 neurotransmitter networks innervate many common brain regions (Rogeness & McClure, 1996). Thus, although we examine each neurotransmitter system independently, it is important to keep in mind that each system affects the others. We review each neurotransmitter with respect to behavior and sensitivity to violent contexts.

Dopamine

Non-human primate studies show that DA receptors, particularly within mesolimbic structures including 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 rapidly decline and ultimately reach stable levels. Dopaminergic receptors appear throughout the brain, but two areas are responsible for initiation of DA neurotransmission: the ventral tegmental area and the substantia nigra. These two areas project to three major dopaminergic pathways, which have distinct yet inter-related functions. Dopamine cells that arise from the ventral tegmental area project through the mesolimbic pathway to the nucleus accumbens. Dopamine signals then project forward through the mesocortical pathway to the anterior cingulate and medial prefrontal cortices (Gatzke-Kopp & Beauchaine; 2007; McArthur, McHale, & Gillies, 2007; Sagvolden, Johansen, Aase, & Russell, 2005). The mesolimbic pathway is involved in reward responding, approach motivation, and emotion, whereas the mesocortical pathway subserves cognition, working memory, self regulation, and planning (McArthur et al., 2007). Dopamine neurotransmission originating in the substantia nigra projects along the nigrastriatal (mesostriatal) pathway, which subserves sensirimotor integration and fight/flight responding.

The mesolimbic pathway comprises the BAS described by Gray (1987) and later by Gray and McNaughtan (2000). Consistent with Gray, Cloninger (1987) proposed that DA neurotransmission in this network is linked with individual differences in novelty-seeking behaviors, including exploration and impulsivity. Cloninger suggested that people high in novelty seeking would be likely to engage in approach behaviors under conditions of reward, and in active escape behaviors during conditions of punishment. Extending this work, Fowles (1988), Quay (1993), and Rogeness et al. (1992) proposed that DA dysfunction underlies unrestrained approach behaviors characteristic of 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 (PET) studies show that low levels of subcortical dopamine are linked with irritability and novelty seeking among healthy adults (Laasko et al., 2003, Suhara et al., 2001). Similarly, functional magnetic resonance imaging (fMRI) 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 activity among children and adolescents with ADHD and CD. Such effects appear to

be downstream consequences of mesolimbic DA dysfunction (see Brenner, Beauchaine, & Sylvers, 2005).

Importantly, several lines of research suggest that exposure to adverse environments—including those characterized by violence—can induce long term down regulation 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). Maestripieri and colleagues (2006a) reported a relation between low levels of homovanillic acid (HVA), a DA metabolite, and maternal rejection among cross fostered infant rhesus macaques. DA functioning may be altered similarly in deprived and violent contexts. However, this assumption has not been tested empirically.

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 et al. (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 areas is consistent with other investigations of the effects of chronic stress (e.g., Sheikh et al., 2007). Chronic exposure to stress hormones also inhibits DA metabolism (Lindley et al., 2002). Single and controllable stresses 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). There appears to also be a compensatory change in DAT expression. 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 DA transporter (DAT) in shrews. Subordinate male shrews evidenced elevated stress hormones and enlarged adrenal glands after repeated exposure to a dominant male. DAT binding sites were reduced in the caudate and the putamen, two structures located within the mesolimbic DA system, 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. This shift reduces DA reuptake, and increases DA availability in the synapse.

Altered DA functioning appears to be moderated, at least in part, by the social presence 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 with 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 reduction of DAT binding. Indeed, these rats showed an increase in DAT binding. Thus, the stress response appears to be implicated in altered DA functioning.

Finally, social defeat sensitizes the mesolimbic DA system, as demonstrated by the behavioral effects of cocaine and amphetamines (Miczek, Covington, Nikulina, & Hammer, 2004). For example, Covington and Miczek (2005) showed that male rats that had lost in an aggressive interaction demonstrated enhanced motoric behavior after amphetamine challenge compared

with both rats that had won the aggressive interaction and control rats. Additionally, rats that experienced social defeat self-administered more cocaine than those in the other two social conditions. Thus, social defeat appears to sensitize the mesolimbic DA system to certain reinforcers.

In summary, evidence from rat studies shows that central DA systems are altered by chronic stress, which down-regulates central DA functioning. Other literature 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 dopamine has yet to be elucidated. 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 development, violent contents will likely guide future research in this area. For now, it is clear that DA is affected by the stress response, which is activated by acute and chronic exposure to diverse forms of violence, and that early adverse experiences moderate the impact of low levels of MAOA on future antisocial behavior. Additionally, there is evidence that hypodopaminergic functioning relates to impulsive behavior.

Norepinephrine

NE is released both centrally from the locus coeruleus (LC), which is situated within the pons of the brainstem, and peripherally from the adrenal medulla. Notably, NE is synthesized from DA, implying that DA and NE levels are interdependent. Two notable enzymes in the conversion are tyrosine hydroxylase, which limits the rate of synthesis (Lewis, 2001), and dopamine-beta-hydroxylase (DBH), which catalyzes the oxidation of DA into norepinephrine. 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 particularly 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. For example, 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 non-human primates (Maestripieri, McCormack, Lindell, Higley, & Sánchez, 2006b).

The LC-NE serves as a general arousal system. Acute stress activates the LC-NE system via corticotrophin releasing factor, a major hormone of the HPA axis (Charney, 2004; Tsigos & Chrousos, 2002). This process stimulates the sympathetic nervous system, resulting in increased heart rate and HPA axis reactivity. Concurrently, NE release also suppresses parasympathetic and neurovegetative functions such as eating and sleeping (Charney, 2004; Tsigos & Chrousos, 2002; Porges, 1995). High levels of activation of the LC-NE system inhibit activation of the prefrontal cortex, which can lead to the dominance of instinctual over higher order cognition (Charney, 2004). The LC-NE system stimulates the amygdala during acute stress and enhances memory in the hippocampus (Tsigos & Chrousos, 2002). Norepinephrine production is also 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). Furthermore, animal studies show that physical stress increases (a) conversion of NE into adrenaline in the brainstem (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 review see Carrasco & Van de Kar, 2003). NE released in response to acute stressors enhances classical conditioning and is involved in the provocation 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 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. found that maternally separated neonates had elevated NE as adults during pre-stress conditions. In response to restraint stress, maternally deprived neonates displayed elevated NE, whereas those handled exhibited attenuated NE in the hypothalamus as adults compared with a control group. In vitro audio-radiographic 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-NE negative feedback loop via a down regulation of α_2 noradrenergic receptors. In turn, this likely contributes to elevations in HPA axis reactivity.

Research has indicated elevated cisternal CSF CRF among adult bonnet macaques raised under variable foraging conditions as infants (Coplan et al., 1996; Coplan et al., 1998). However, this rearing condition has not shown changes in CSF MHPG (Coplan et al., 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). Intermittent mildly, rather than extremely, stressful periods during early development can lower 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 measured behavior indices (Parker et al., 2007).

Among humans, children with PTSD related to diverse maltreatment histories show elevated 24-hour urinary NE compared to children without maltreatment histories, children without psychiatric problems, and children with overanxious anxiety disorders (De Bellis et al., 1999a). Urinary NE has been correlated with the duration of trauma and PTSD symptoms (De Bellis et al., 1999a) and predicted PTSD symptoms six weeks post trauma (Delahanty, Nugent, Christopher, & Walsh, 2005). Girls with sexual abuse histories have exhibited elevated urinary concentrations of the NE metabolite vanillyl mandelic acid (VMA) in the absence of elevated NE (De Bellis, et al., 1994). This group of children also displayed increased rates of dysthymia, suicidal ideation, and suicide attempts. Notably, participants had a mean age of 11 years, had experienced sexual abuse for several months beginning at around age 6, but had been in safe homes for at least one year. Among adults, women with childhood abuse histories and current PTSD also show elevated urinary NE (Lemieux & Coe, 1995).

Elevated catecholamines have been observed among children with less direct experiences violence. For example, Gottman and Katz (1989) observed a positive relation between parental discord and child urinary catecholamines. Elevated daily NE has been correlated with experiencing, seeing, or even hearing about violence among adolescents (Wilson, Kliewer, Teasley, Plybon, & Sica, 2002). Elevated epinephrine related to violence exposure is consistent with research among both depressed children and adults (for review see Heim & Nemeroff, 2001).

Stress, DBH levels and behavior have also been investigated. The enzyme is detectable in plasma and cerebrospinal fluid, and is associated with fluctuations in DA and NE levels (Cubells & Zabetian, 2004). Low levels of DBH are characterized by elevated ratios of DA to NE (Kim et al., 2002). Studies have associated peripheral levels of DBH with aggressive behaviors, particularly among males (Bowden, Deutsch, & Swanson, 1986, Gabel, Stadler, Bjorn, Shindledecker, & Bowden, 1993; Rogeness, Hernandez, Macedo, Amrung, and Hoppe, 1986). Consistent with such findings, Bowden et al. (1986) 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 (i.e., stress associated with unpredictable and unremitting maltreatment), appears to suppress the enzyme. Rogeness, Amrung, and Harris (1984) provided the first clinical evidence of this effect, finding low serum levels of DBH among boys who were abused physically and/or neglected. However, Rogeness et al. (1986) did not find an association between abuse and serum enzyme activity 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 also 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 had 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, the data suggest that lowered NE is associated with aggression among boys, and may be related to early abuse. This is consistent with conceptualization of the LC-NE as a contributor to the behavioral inhibition system. Normal NE activity under the non-reward and punishment conditions acts to inhibit behavior. Lowered NE, in turn, fails to inhibit behavior in the face of aversive stimuli, while heightened NE contributes to excessive inhibition and anxiety.

Although interesting, these findings do not inform us directly about neurotransmitter levels, and 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, causality cannot be determined. Indeed, recent molecular genetic research suggests that plasma DBH variability is determined in large part by heritability, and is stable across time (Cubells & Zabetian, 2004).

What is clear from animal research is that norepinephrine functioning is altered based on a wide range of stress exposures, including chronic, indirect violence exposure (e.g., Wilson et al., 2002). Consistent with inferences about dopamine, we expect that genetic polymorphisms contribute to individual variability. Future research exploring the genetic expression of norepinephrine will likely elucidate specific mechanisms. MAOA is a likely candidate gene given its impact on NE and DA, and the fact that NE is synthesized from DA.

Serotonin

Serotonergic neural circuits originate in the raphe nuclei of the brainstem and project throughout the central nervous system (Rogeness et al., 1992). 5-HT is synthesized from the amino acid tryptophan. Tryptophan is the precursor amino acid; and tryptophan hydroxylase is the rate-limiting converting enzyme. As a widespread neurotransmitter, 5-HT plays a role in modulating and gating the responses of other neurotransmitters, including DA. Additionally, 5-HT contributes to the regulation of arousal, mood, and impulse control. There are at least 7 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 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 septo-hippocampal 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 septo-hippocampal system is also involved in inhibition and anxiety. The septo-hippocampal system includes the septum, hippocampus, dentate gyrus, entorhinal cortex, subicular area and the posterior cingulated cortex. Gray proposed that this system detects conflict in goals, monitoring punishment and non-rewarding stimuli. This detection leads to increased attention and passive avoidance of threat.

Like Gray, Cloninger (1987) linked 5-HT functioning to harm avoidance, or trait anxiety. Anxiety disorders have been linked convincingly with 5-HT dysfunction, as has depression. Most pharmacological treatments for depression target the central 5-HT system (Hidalgo & Davidson, 2000). Many selective serotonin reuptake inhibitors (SSRIs) also have anxiolytic effects (Carrasco & Van de Kar, 2003). Furthermore, 5-HT_{1a} receptor densities are reduced among depressed patients during both depressive episodes and during 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 is also implicated in aggression. Research with rodents and non-human primates shows that depletion of 5-HT leads to aggressive behavior (for review see Lucki, 1998). Among children, cross sectional research has linked lower peripheral 5-HT to aggression (Kruesi et al., 1990). Similar findings have been reported in longitudinal studies (Kruesi et al., 1992). More recent research has linked reduced 5-HT reactivity to fenfluramine among children with antisocial personality traits nine 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, relates to blunted prolactin responses to the fenfluramine challenge (Coccaro, 1989). Fenfluramine activates 5-HT release and inhibits 5-HT reuptake. Prolactin is released by 5-HT stimulation, and is therefore an index of 5-HT activity (Pine et al., 1997). However, there are inconsistencies in the literature (Castellanos, et al., 1994; Halperin et al., 1997; Pine et al., 1997; Schulz et al., 2001,).

Serotonin 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 review in 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 is also affected by early life stress. 5-HT_{1A} receptors are down-regulated under conditions of elevated stress hormones (Charney, 2004). This functions to lower the threshold for anxious reactions to events.

Effects of neonatal handling on both basal 5-HT levels 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 the hippocampus (Papaioannou, Dafni, Alikaridis, Bolaris, & Stylianopoulou, 2002). In response to short term stress, rats show increased levels of 5-HT in the hypothalamus. The same research group has also found increased 5-HT levels in the hypothalamus and striatum, and increased 5-HT turnover in the striatum, hippocampus, and hypothalamus among neonatally handled rats exposed to single and repeated stressors in adulthood (Panagiotaropoulos et al., 2004).

Separation stress exerts opposite effects on the developing brain. Arborelius, Hawks, Owens, Plotsky, and Nemeroff (2004) demonstrated that prolonged separation stress during neonatal development can lead to decreased 5-HT release in the raphe nuclei of rats in response to increasing doses of citalopram, a SSRI. Adult rats that were separated from their mothers also show passive coping styles to stressful events (Veenema, Blume, Niederle, Buwalda, & Neumann, 2006). Additionally, they exhibit a reduction in 5-HT immunoreactivity and correlated inter-male aggression (Veenema et al., 2006). Maternal rejection early in life has been linked with lower cerebrospinal fluid levels of the 5-HT metabolite, 5-HIAA, and higher indices of anxiety in cross-fostered female rhesus macaques (Maestripieri, et al., 2006a). Variable maternal foraging conditions have been related to decreased behavioral responsiveness to a 5-HT agonist *m*CPP among bonnet macaques (Rosenblum et al., 1994). Such rearing conditions have also revealed decreased baseline 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 have shown elevated CSF concentrations of the 5-HT metabolite, 5-HIAA (Coplan et al., 1998; Mathew et al., 2002). Another study 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 results are not uniform, 5-HT dysregulation—particularly hypo-responsivity—appears to be related to early adversity (Mathew, 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 with a control group and non-abused depressed group of children (Kaufman, et al., 1998b). Boys with adverse rearing experiences also have shown elevated prolactin responses, and no cortisol change 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 stimulators. Interestingly, a group of adult women with borderline personality disorder demonstrated blunted responses to the 5-HT agonist, *m*CPP (Rinne, Westenberg, den Boer, and 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 control participants. These results are consistent with animal research on adult 5-HT functioning and early adversity. Heim and Nemeroff suggested that the impact of early life stress may include a developmental switch. Initial 5-HT hyperactivity may lead to a down regulation and 5-HT hypoactivity in adulthood. Longitudinal prospective research is needed to clarify this possibility.

What is clear is that 5-HT system regulation is sensitive to early rearing environment, particularly abusive rearing environments. 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 to violence could alter 5-HT functioning, as suggested by one finding cited above. This literature suggests that lower efficiency of the 5-HTT leads to greater vulnerability in developmental contexts of violence. Furthermore, environmental eliciteded changes in all three neurotransmitters 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 (i.e., the flight or fight response). In such a moment, the individual's primary goal 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 hypothalamic-pituitary-adrenal (HPA) axis form two interrelated effectors of the mammalian stress response (Adam, Klimes-Dougan, & Gunnar, 2007; Gunnar & Vazquez, 2006). The PNS also plays an important role (Porges, 1995). Threats of violence lead to the activation of all three systems. Fear activates the amygdala, which sends messages to the brain stem and the hypothalamus (Glaser, 2000). The sympathetic response is affected through brainstem nuclei, which project to the adrenal gland. The medulla of the adrenal gland secretes epinephrine and NE. These hormones raise heart rate and blood pressure, and increase sweating. The PNS contributes to this effect through vagal withdrawal, which leads to instantaneous acceleration of heart rate (Porges, 1995). The HPA axis supports the SNS through regulation of basal activity and its own negative feedback system. Similarly, the PNS is responsible for maintenance of homeostasis in the absence of stress, and subjugation of internal needs (i.e., through vagal withdrawal) during threatening conditions (Porges, 1995). The sympathetic and parasympathetic responses to stress occur within seconds, whereas the HPA response may take several minutes, and has temporally longer effects (Glaser, 2000; Sapolsky, 1998).

Physical threats to life activate the HPA axis primarily through NE neurons in the brainstem, including the locus coeruleus (Adam, Klimes-Dougan, & Gunnar, 2007). Corticotropin releasing factor (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 adrenocorticotropic hormone (ACTH). In turn, the ACTH released into the blood reaches the adrenal glands, which release a class of steroids called glucocorticoids (cortisol in humans and other primates, corticosterone in rodents).

Cortisol is a catabolic hormone, which activates 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 responsiveness via changes in the brain. Glucocorticoids also suppress the immune, growth, and reproductive systems (Charney, 2004; Sánchez, 2006). Fluctuations are not

exclusively stress induced as cortisol has a circadian periodicity. Humans experience a daily peak of cortisol about 30 minutes after waking and a gradual decrease over the day (Tarullo & Gunnar, 2006). Cortisol contributes to the inhibition of the HPA axis activity through a negative feedback system. Cortisol binds to glucocorticoid receptors in the hippocampus, hypothalamus, and the pituitary, which leads to suppression of CRH, ACTH, and glucocorticoids.

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 on maternal care behaviors have shown reduced ACTH and corticosterone in response to stress (Liu et al., 1997). As adults their offspring display increased hippocampal glucocorticoid receptor mRNA expression (Weaver et al., 2004; Liu et al., 1997), enhanced glucocorticoid negative feedback sensitivity (Liu et al., 1997), and decreased CRH mRNA levels (Francis et al., 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 is delicately sensitive to normal variation in maternal behavior.

It follows that exposure to more extreme developmental contexts, including exposure to violence, alters HPA axis functioning. These functional changes are observed both at rest and during stress reactivity. Much of the 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). That is, an individual's stress response system may adapt 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 attenuated by maternal care giving behaviors (for review see Sánchez, Ladd, & Plotsky, 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 ameliorate these patterns (Adam, Klimes-Dougan, & Gunnar, 2007). Thus, the stress response is regulated socially, and early life stress affects, but does not completely determine future functioning.

Child maltreatment studies provide further evidence that the stress response is altered both in response to development in violent contexts. There are several recent reviews that address this topic (e.g., Adam, Klimes-Dougan, & Gunnar, 2007; Gunnar & Vazquez, 2006; Tarullo & Gunnar, 2006). These reviews suggest that discrepancies may be clarified by considering methodology, developmental status, and the participants' current psychiatric symptoms.

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 et al., 1999a). Other reports have failed to find differences in morning cortisol levels (Hart, Gunnar, & Cicchetti, 1995; Hart, Gunnar & Cicchetti., 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 et al. (1999a) reported that duration of abuse was a predictor of cortisol 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 with non-maltreated 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, 2002).

Current behavioral functioning is correlated with neuroendocrine functioning among older children. Cicchetti & 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 psychopathology, and (c) children with psychopathology without abuse histories. Similarly, both Carrion et al. (2002) and De Bellis et al. (1999a) 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, et al., 1998; Klimes-Dougan, et al., 2001). Thus, internalizing problems appear related to higher cortisol levels in children.

Overall, maltreated children with externalizing problems do not show basal cortisol differences compared with 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 non-maltreated 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 with 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 daily 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 intravenously injected. These studies show conflicting results. De Bellis 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 non-human 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 down-regulation 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, & 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, 2002). Greater cortisol reactivity is consistent with non-human primate studies among abused and harshly treated young (Dettling, Pryce, Martin, & Döbelli, 1998) and among young 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 down regulation 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.

Adaptivity of the stress response to violence

Acute release of stress hormones serves a clear adaptive purpose—the diversion of energy from processes irrelevant to immediate survival toward organs that demand energy to respond to threat. Cortisol reactivity among adults with abuse histories suggests a down regulation 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, but not adaptation Furthermore, both hyper- and hypo-responding are deleterious (Sapolsky, 1998). Chronic stress and associated elevations in circulating glucocorticoids have negative impacts on the body, including proportion of cardiovascular disease, ulcers, amenorrhea, and immune system dysfunction, (Sapolsky 1998, 2000).

Individual responses are likely influenced by genetic vulnerability and protective factors. For example, animal studies implicate the 5-HT transporter gene. Serotonin is involved in the activation and the feedback of the HPA axis and 5-HT transporter knockout mice display elevated corticosterone responses to chronic stress (Lanfumey, Mannoury La Cour, Froger, & Hamon, 2000). Furthermore, possession of two copies of the long 5-HT transporter gene led to smaller ACTH responses during separation stress among macaques that had been reared by peers (Barr et al., 2004). This indicates a Rearing Condition × Gene interaction, which may inform the link between violence exposure and depression. Research among humans could investigate HPA responsivity with regard to violence exposure and genetic vulnerabilities to better elucidate correlations 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, namely the hippocampus and the prefrontal cortex. Functional changes in these brain regions are also mediated by environmentally elicited alterations in the monoamine neurotransmitter systems. These 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 consider 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 more evolutionarily newer structures develop, such as the cerebral cortex (Perry, 2008). The brain develops hierarchically and sequentially, and different areas of the brain develop and mature at different points throughout the lifespan. Thus, exposure to violence can have dramatically different effects depending on timing, and length of exposure. Throughout infancy and childhood the brain continues to form connections and to prune synapses in a use- and experience-dependent fashion (Cummins & Livesey, 1979; Perry, 2008). Because the most primitive structures of the brain develop first, including sympathetic and parasympathetic nervous systems, disruption due to stress may have a profound effect on structures and functions that develop later, such as those that mediate emotional responses, abstract thinking, and social interaction, namely, the limbic system and cortex. Although dramatic changes in brain structure cease after childhood, the frontal cortex and the hippocampus continue to develop well into early adulthood. In contrast with more primitive functions such as sensory inputs, cortically mediated functions are likely to have a relatively long sensitive period (Perry, 2008). Therefore, early violence exposure may adversely affect the development of structures that mature later in time, if lower level structures have been disrupted. Additionally, lengthier periods of stress exposure confer greater risk for maladaptation within higher brain structures that have yet to mature.

The hippocampus

The hippocampus is particularly vulnerable to stress exposure because it has a protracted postnatal development period, a high density of glucocorticoids receptors, and includes postnatal neurogenesis (Teicher et al., 2003). As noted in the introduction of this section, the hippocampus is involved in regulation of 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, in particular 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 and condensation, and cell layer irregularity (Sapolsky, Uno, Rebert, & Finch, 1990). Others have corroborated the enduring deficit in synaptic density in the hippocampus (e.g., Teicher et al., 2003). Elevated basal corticosterone has also been associated with a downregulation 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 within the human literature. Smaller hippocampal volumes have been observed among (a) adults with PTSD stemming from 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 review see Sala et al., 2004). A recent meta-analysis of structural MRI among adults with PTSD related to 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 attenuated when the comparison group had been exposed to similar traumatic events and magnified when controls had no trauma history. Nonetheless, these results cannot rule out the possibility that smaller hippocampi represent a vulnerability factor rather than a result of violence and stress exposure (e.g., Gilbertson, et al., 2002).

Cross-sectional research among children has been inconsistent with research among adults. Two MRI studies (Carrion et al., 2001; De Bellis et al., 2002) showed no differences in hippocampal volume among children with PTSD related to maltreatment. Other studies have shown marginal effects for larger left hippocampal gray matter (De Bellis et al., 1999b) and larger bilateral hippocampi (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001) among children with maltreatment histories. Tupler and De Bellis (2006) pooled data from De Bellis et al. (1999b), (2002) and revealed a significant effect for larger hippocampal white matter 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 convincing evidence of hippocampal damage due to violence exposure. The best evidence was found among 7–13-year-old maltreated children over 12–18 months (Carrion, Weems, & Reiss, 2007). PTSD symptoms and baseline cortisol predicted reductions in hippocampal volume over time. Hippocampal volume at baseline was not predictive of change over time. However, there was no control group in this sample. The only other longitudinal study among children failed to find changes in hippocampal volume over a nine 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 the reasons 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, are commonly associated with PTSD and adults with child abuse histories and may be the primary mechanism in adult hippocampal atrophy studies. Third, again, reduced hippocampal volume may be a vulnerability marker for post trauma problems rather than a sequelae of trauma.

Although more evidence is needed, implications of potential hippocampal atrophy in developing children are two-fold. First, such damage causes impairment in memory functions. This in no way can be construed as an adaptive response to stress, instead, an untoward side effect. This may contribute in part to the relative 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. The hippocampus contributes to the HPA's negative feedback. Fewer hippocampal cells translates to fewer glucocorticoid receptors. Consequently, stress hormones are released longer (Uno et al, 1994), and damage more hippocampal cells. It is clear that environmental stressors such as abuse are related to changes in the stress response. It may be possible to construe some alterations as 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 prefrontal cortex.

Prefrontal Cortex

The frontal cortex has both a protracted developmental period and a high density of glucocorticoid receptors, making it vulnerable to early life stress. Additionally, the frontal cortex is vulnerable to early disruption in lower level structures because of its relatively long sensitive period and feedforward and feedback communication with lower levels of the brain. De Bellis and colleagues have demonstrated structural abnormalities in the prefrontal cortex (PFC) of maltreated children compared with controls, including smaller PFC volumes, smaller PFC cortical white matter, and larger prefrontal CSF volume (De Bellis et al., 1999b; De Bellis et al., 2002). Findings correlate positively with age of onset of maltreatment in 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 regions (Beers & De Bellis, 2002). Furthermore, children raised in neglectful 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 experienced longer periods of early neglect have sustained cognitive impairments 2 ½ - 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 behavior, through deficits in inhibition, misinterpretation of others' intentions, increased selective attention to cues of threat, and general social and interpersonal deficits (Lee & Hoaken, 2007).

The high density of glucocorticoid and corticotrophin-releasing factor (CRF) receptors in primate cerebral cortex and excess cortisol may account for some of the observed impairments in prefrontal cortex functions (Millan, Jacobowitz, Hauger, Catt, & Aguilera, 1986; Sánchez, Ladd, & Plotsky, 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). Non-human primates exposed to early life stress have shown significantly diminished glucocorticoid receptors in the dorsolateral prefrontal cortex, and a trend toward reduced receptors in the ventrolateral prefrontal cortex (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 a decreased affinity for the binding site (Fuchs & Flügge, 1995). Neuroendocrine changes in response to early stress, such as maternal separation, are associated with decreases in glucocortidoid receptor mRNA expression in medial prefrontal cortex (see Sánchez et al.,

2001; Meaney, Diorio, Francis, Widdowson, LaPlante, Caldji, Sharma, Seckl, & Plotsky, 1996). Furthermore, rats reared in 180 min maternal separation also showed a decrease CRF_1 receptor binding in frontal and parietal cortices (Ladd, Huot, Thrivikraman, & Plotsky, 1998, 1999, as cited in Sánchez, Ladd, & Plotsky, 2001). Sánchez et al. (2001) also suggested that early maternal separation leads to enhanced CRF neurotransmission within and from the amygdala, including the hypothalamic paraventricular nucleus (PVN), central nucleus of the amygdale (CeA), and the locus coeruleus (LC). Thus, early stressful experience must have an effect 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).

Dopamine likely plays a role as well. Chronic stress may lead to hyperdopaminergic activity in the frontal cortex, as reviewed above, leading to impairments in executive functioning (De Bellis, 2005). Stress induced working memory deficits are associated with increased catecholamine receptor stimulation in the prefrontal cortex, and these functional impairment are alleviated by dopamine antagonists (Arnsten, 1998; Arnsten & Goldman-Rakic, 1998). Similarly, infusion of a D1 receptor agonist in the PFC induces spatial working memory deficits in rats (Zahrt, Taylor, Mathew, & Arnsten, 1997). The authors suggest that hyperdopaminergic functioning may serve to take the PFC “offline” to allow posterior and subcortical structures, responsible for lower-level functions, to take over (Zahrt et al., 1997).Note that this is not inconsistent with the hypodopaminergic functioning hypothesis described above, since the mesocortical and mesolimbic dopamine systems operate with considerable independence.

Several studies have found specific abnormalities in frontal cortex activation among those who have experience childhood abuse (see Bremner, 2005; Bremner et al., 2003; Bremner et al., 1999; De Bellis, Keshavan, Spencer, & Hall, 2000; Shin et al., 1999). In particular, the medial prefrontal cortex (mPFC), which includes the ACC and orbitofrontal cortex, has been shown to be impaired in several positron emission (PET) studies among adults who experienced childhood trauma. The ACC has both cognitive (dACC) and affective (rACC) subdivisions, and subserves numerous cognitive processes, and plays a critical role in decisions that rely on reward and punishment information. 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 orbitofrontal cortex plays a key role in social/emotional function and is involved in interpretation of other’s emotional state and evaluating the magnitude of a potential threat (Derryberry & Tucker, 2006; Gatzke-Kopp & Shannon, 2008). The ACC and orbitofrontal cortex 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 related to childhood sexual abuse (Shin et al., 1999, Bremner et al., 1999. In these studies, participants with abuse histories, but without current PTSD showed greater activation of the ACC compared to the PTSD group (Shin et al., 1999). Furthermore, De Bellis et al. (2000) found evidence of cell loss and lower neural integrity and in the ACC of maltreated children and adolescents with PTSD. Elevated norepinephrine release and subsequent decreased metabolism in medial and orbital frontal cortices may contribute to PTSD related memories (Bremner et al., 1997).

Medial prefrontal regions of the brain are highly interconnected with the amygdala via cortical inhibitory connections, which mediate amygdala and HPA-axis responding (Bremner, 2005; Figueiredo, Bruestle, Bodie, Dolgas, & Herman, 2003). Thus, areas of the mPFC have been hypothesized to play a role in inhibition and extinction of fear responses (for review see LeDoux 1998), and it is likely that the continued fear response among those who have experienced trauma or abuse, results from a deficient ACC inhibition on the amygdala. When functioning

appropriately, ACC activation inhibits a fearful response when traumatic stimuli do not pose a true threat. However, in those with PTSD, cued fear inappropriate to the context, may be subserved by lack of ACC-amygdala mediation (Bremner, 2005).

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

Startle Response

Startle responding is also potentiated in violent contexts. 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 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 responses without preceding stimuli, and following a stimulus (the prepulse) are traditionally examined. Inhibition of the startle response, known as pre-pulse inhibition, occurs following brief (20–200 msec) startling stimuli (Graham, 1975). In contrast, sustained pre-stimulation (≥ 2000 msec) facilitates the startle response.

Several investigators have found exaggerated startle responses without pre-pulse among people 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 that show that war veterans with PTSD have potentiated EMG (non-pre-pulse) startle responses and attenuated EMG pre-pulse inhibition (less inhibition of startle) during stressful conditions (Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1999). In contrast, others have failed to find altered startle responses without pre-pulse among all the aforementioned groups (Grillon & Morgan, 1999; Grillon, Morgan, Southwick, Davis, & Charney, 1996; Grillon, Morgan, Davis, & Southwick, 1999; Meztger 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. The mean weighted effect across all studies was medium (Cohen's d=0.49) for exaggerated startle when comparing participants with current PTSD to individuals without trauma history. This suggests that, in spite of a number of null findings in the literature, trauma-induced PTSD is associated with exaggerated startle response. This behavior may be construed as a biological adaptation to life-threatening contexts insofar as it facilitates the initiation of defensive posturing. Nonetheless, 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 3–11-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% experienced maltreatment before two years of age. 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 eye blink startle

response, and smaller reductions of blink response latency compared with control. Results for girls were inconsistent across ages. Although younger maltreated girls had smaller startle amplitude and slower onset latency than controls, older girls showed the opposite pattern.

The boys' responses from the Klorman et al. 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 an age- and sex-matched control group. However, under conditions of pre-pulse facilitation children with PTSD exhibited exaggerated responses.

One another study, Lipschitz et al. (2005) failed to find baseline acoustic startle, and modulated (pre-pulse facilitation and pre-pulse inhibition) differences between a group of female adolescents with mixed trauma exposure and control participants. The study 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 attenuate their responses. Cichetti (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, & Merikangas (1997) examined startle modulation among a group of children of parents with histories of anxiety and/or alcoholism. They found that children of parents with histories of anxiety problems had exaggerated startle responses during baseline conditions. Thus, a causal relation between exposure to trauma and exaggerated startle cannot be assumed. More recently, researchers have attempted to address the direction of causality of trauma and EMG exaggerated startle response (Guthrie & Bryant, 2005; Orr et al., 2003). However, both studies failed to produce differences across trauma exposed and control groups.

In summary, research indicates that among adults, PTSD induced by life threatening conditions is associated with exaggerated startle responses, despite some discrepancies in the literature. The literature on children shows the opposite pattern of results. It's unclear if this is a genetic predisposition versus an environmentally elicited effect. Again, future work in this area could integrate measurement of specific genes with the startle response. We anticipate that 5-HTT and MAOA may play important roles. More specifically, we expect that individuals with short alleles of 5-HTT and lower MAOA activity would be at risk for exaggerated startle responses. There is substantial evidence that, whether a vulnerability factor or a trauma induced change, startle is associated with a wide range of traumatic experiences. That is, both direct and witnessed violence are powerful experiences on the developing brain.

Conclusions and Future Directions

Early development in violent context shapes behavioral adaptations across the lifespan. Our review has outlined a number of the neurobiological mediators of adaptation. 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

dopamine, serotonin, norepinephrine, 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 measures may clarify inconsistencies in the literature. Ultimately, the clarification of the neurobiological effects of developmental violence may lead to earlier identification of children vulnerable for future maladaptive functioning.

Finally, the adaptive value of neurobiological changes has been emphasized throughout this paper. As introduced, a behavior is adaptive insofar is it helps an organism survive. Within a violent context, hyperarousal, vigilance, and aggression are clearly useful. The literature reviewed suggests that humans, among other mammals including rats and 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 development in maltreatment or violent contexts should take into account both short and long term benefits, and consequences of behavior change.

Exposure to violence during development initiates diverse behavioral costs across a lifetime. The neurobiological changes we covered can explain externalizing psychopathology, including oppositional and aggressive behavior, delinquency and drug use, and internalizing psychopathology, including depression, PTSD, sleep dysregulation, and other anxiety problems. Described changes also contribute to school difficulties and dropout, and problems with job retainment. Finally, the neurobiological sequelae of early exposure to violence relate 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.

Acknowledgments

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

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