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How can the study of biological processes help design new interventions for children with severe antisocial behavior?

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Abstract

Children with severe antisocial behavior have an increased risk of showing violently aggressive and other forms of problem behavior in adolescence and adulthood. It is well established that both biological and social factors are involved in the development of antisocial behavior. The primary aim of this paper is to discuss the evidence that specific neurobiological systems are involved in the etiology of childhood-onset antisocial behavior. These factors are responsible for the severity of the behavioral problems observed in antisocial children, but they also play a role in their persistence, because they influence children's interactions with their environment. We will discuss the possible causes of disruptions in neurobiological systems in childhood antisocial behavior and point out the implications of these findings for theory and clinical practice. We will argue that familial factors (e.g., genetic influences, early childhood adversity) are linked to negative behavioral outcomes (e.g., antisocial behavior problems) through the mediating and transactional interplay with neurobiological deficits. An investigation of neurobiological functioning in antisocial children might not only indicate which children are most likely to persist in engaging in severe antisocial behavior, but also guide the development of new interventions.

Aggressive and antisocial behavior that becomes a pervasive pattern affecting diverse domains of children's functioning is referred to in psychiatry as oppositional defiant disorder (ODD) or conduct disorder (CD; APA, 1994). The prevalence of these disorders is relatively high: 2% for CD and 3.2% for ODD (Lahey, Waldman, & McBurnett, 1999). The problem behavior of children with these disorders is often quite stable and persistent (Offord et al., 1992), and childhood-onset antisocial behavior is an important predictor of chronic and more serious forms of antisocial behavior (Hill & Maughan, 2001).

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Conduct problems in childhood are associated with a host of negative outcomes in adulthood; they predict not only future antisocial behavior (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001; Zoccolillo, Pickles, Quinton, & Rutter, 1992; Zoccolillo & Rogers, 1991), but also substance abuse and dependence in adulthood (Kazdin, 1995; Offord & Bennett, 1994), early pregnancy in antisocial girls (Bardone et al., 1998), persistent health problems (Bardone et al., 1998; Odgers et al., 2007), and other forms of psychiatric illness such as depression. As a result, children with externalizing behavioral problems are costly to society: the cumulative costs of public services used through to adulthood by individuals who show antisocial behavior in childhood are 10 times higher than those for individuals without these problems (Scott, Knapp, Henderson, & Maughan, 2001). The high costs are partly because of crimes committed, but also to extra educational provision,

foster and residential care, and state benefits. When one factors in the associated mental and physical health burden of CD in adulthood, the cost to society may be even greater than this estimate (Odgers et al., 2007).

Although the short-term effectiveness of intervention strategies (e.g., parent management training, cognitive behavioral therapy) has been demonstrated (Kazdin, 2001), the long-term effectiveness of treatment appears to be limited (Offord & Bennett, 1994). The high persistence and poor prognosis associated with ODD and CD, coupled with the limited effectiveness of current treatments of childhood antisocial behavior, are the main reasons why an investigation of biological correlates of antisocial behavior in childhood should be given more attention. An understanding of these factors should generate hypotheses concerning both the underlying neurobiological mechanisms and the etiology of antisocial behavior (Van Goozen, Fairchild, Snoek, & Harold, 2007). Furthermore, biological studies of antisocial behavior could lead to new approaches to the treatment of psychiatric conditions associated with aggression. Such approaches might involve pharmacological interventions to manipulate the biological substrates of aggression, or lead to hypotheses that influence the content of psychotherapy. We will argue that a neurobiological assessment of children with antisocial behavior could indicate that their underlying deficits are such that, for example, interventions involving "empathy induction" (if it has been established that the child is unresponsive to self-experienced or observed fear or sadness) or "learning from punishment" (making use of time-out or response cost) are unlikely to work. The implication of such a neurobiological approach is that one should cease investing public finances in so-called "blanket approaches," and replace these with targeted interventions that take the individual neurobiological profile into account. As Moffitt (2005) put it: "Valuable resources have been wasted because intervention programs have proceeded on the basis of risk factors without sufficient research to understand causal processes" (p. 534). An investigation of neurobiological mechanisms involved in severe antisocial behavior will identify not only different subgroups of antisocials in whom different causal processes initiate and maintain problem behavior, but also interventions that specifically target the deficits presented by each subgroup.

Causal Factors in Early-Onset Antisocial Behavior

Dispositional, child-specific (i.e., genetic, temperamental), and social factors contribute to the development and maintenance of antisocial behavior, although most research interest has focused on social factors. For example, life circumstances (e.g., bad neighborhoods), stress in the family because of adverse life events, and parental relationship problems and psychopathology all play a role (Conger, Ge, Elder, Lorenz, & Simons, 1994; Moffitt, 2005). These factors are likely to result in the affective neglect of the child (Erel & Burman, 1995). However, not all children exposed to social adversity develop antisocial behavior, and some children become antisocial despite a favorable social background. There is a growing literature showing that certain groups of children have an increased risk of developing psychiatric disorders, and this predisposition is presumably partly biologically determined. Specifically, research suggests that a number of different biological factors may be involved in antisocial behavior, and that these factors could play a role in the development and maintenance of antisocial behavior over time. Below we review the evidence that the stress response systems (i.e., hypothalamic–pituitary–adrenal [HPA] axis and autonomic nervous system [ANS]) and the neurotransmitter systems (5-hydroxytryptamine [5-HT, serotonin], dopamine [DA], and norepinephrine [NE]) are involved in childhood-onset antisocial behavior.

The Stress Response Systems

The starting point of research on the relationship between stress and antisocial behavior is that aggressive individuals are less sensitive to some forms of stress. This can be deduced from the fact that these individuals place themselves in risky, stressful, or dangerous situations more frequently than other people. Understanding the neurobiology of stress by focusing on which brain circuits are associated with the stress

response will provide important clues on how stress affects mood, cognition, and behavior.

The brain regions activated by acute stressors include multiple cortical areas, the hippocampus, nucleus accumbens, lateral septum, several hypothalamic nuclei, medial and cortical amygdaloid nuclei, dorsal raphe, locus coeruleus, and several brain stem nuclei (Campeau & Watson, 1997). There is some degree of specificity in response depending on the type of stimulus, and the elucidation of the pathways and brain regions involved in specific responses to various types of stressful stimuli is currently the focus of extensive investigation (Lopez, Akil, & Watson, 1999).

HPA axis hormones

The two major systems involved in the regulation of stress are the HPA axis and the catecholamine system (the locus coeruleus–NE/sympathetic nervous system [SNS]). Stress activates the locus coeruleus, the major catecholamine (specifically NE) containing nucleus in the brain and the SNS leading to the biological changes of the "fight or flight" reaction (De Bellis et al., 1999). Direct and indirect effects of this activation include increases in the catecholamine turnover in the brain, the SNS, and adrenal medulla leading to increases in heart rate (HR), blood pressure, metabolic rate, alertness, and in the circulating catecholamines (epinephrine, NE, and DA). During stress, the brain's hypothalamic corticotropin-releasing hormone (CRH) is released. CRH activates the HPA axis by stimulating the pituitary to secrete adrenocorticotropin hormone (ACTH). These events, in turn, promote cortisol release from the adrenal gland, stimulate the SNS, and centrally cause behavioral activation and intense arousal (Chrousos & Gold, 1992). The locus coeruleus also indirectly stimulates the HPA axis via connections through the limbic system. Cortisol, via negative feedback inhibition on the hypothalamus, pituitary, and other brain structures (hippocampus), suppresses the HPA axis, eventually leading to restoration of basal cortisol levels (homeostasis; De Bellis et al., 1999).

Most studies have focused on measuring cortisol levels as an index of HPA axis activity. Although the measurement of cortisol provides important information in this respect, cortisol is secreted by the adrenal cortex and therefore reflects a relatively late response. The HPA axis exhibits a pronounced diurnal rhythm. Cortisol is secreted in pulses, and the frequency of these pulses varies with time of day, the highest frequency being in the early morning, resulting in high early morning levels (Deuschle et al., 1997). As the day progresses, the pulses become less frequent and cortisol levels decrease. The diurnal rhythm of cortisol, with a peak of cortisol secretion in the early morning, can be discerned as early as 6 weeks of age (Larson, White, Cochran, Donzella, & Gunnar, 1998), although it becomes more stable over the course of the first months of life (Gunnar & Vasquez, 2001). The adult-type rhythm over the daytime hours emerges as children adopt adultlike sleeping patterns (i.e., give up napping during the day). For example, a recent study observed a normal circadian rhythm in 12- to 18-month-old infants (Goldberg et al., 2003).

The effects of stress operate through tonic (e.g., basal) and phasic (e.g., reactive) autonomic and neuroendocrine states. Most research (as shown in what follows) focuses on measuring baseline arousal/activity levels, but it can also be argued that stress reactivity represents an important, often overlooked, perspective in this area (Cacioppo, 1998). The same stressor can have profoundly different effects on physiological and neuroendrine activation across individuals or in individuals across different life circumstances, even when comparable levels of coping and perceived stress are expressed. This heterogeneity in stress response may help explain why some individuals are susceptible and others are resilient to physical disease and psychopathology (Cacioppo et al., 1998).

We mentioned that there are clear indications that stress plays an important role in explaining individual differences in antisocial behavior, particularly that aggressive individuals are less sensitive to some forms of stress. There are two possible explanations for a relationship between lower stress sensitivity and antisocial behavior. One theory claims that antisocial individuals have low levels of fear (Raine, 1996). A relative lack of fear would lead to antisocial or delinquent behavior because one is insensitive

to the negative consequences of one's own or other people's behavior in general and the experience of receiving punishment in particular. If this is the case, the implications for the treatment of these problem behaviors are clear: antisocial individuals will have problems in learning the association between behavior and punishment and pointing out the negative consequences of behavior, or punishing unacceptable behavior, is likely to have a reduced effect relative to other children.

A different theory involving stress focuses on sensation seeking (Zuckerman, 1979). Here it is argued that a certain level of stress is needed to feel pleasant, and that too little or too much stress is experienced as aversive. Aggressive individuals are considered to be underaroused and to have an elevated threshold for stress. In the following sections, we will briefly introduce the neurobiological pathways and systems associated with the hypofearfulness and underarousal theories of antisocial behavior, which might be disrupted in individuals with CD or ODD. We will then go on to examine more specifically the evidence that parameters associated with a dysfunctional HPA axis and/or ANS play a role in the development of antisocial behavior in children (for a more elaborate review, see Van Goozen et al., 2007).

The neurobiology of the underarousal theory

The underarousal theory of antisocial behavior holds that activity in a number of physiological arousal systems should be reduced under both resting conditions and during normal task performance in those with CD, and that this physiological hypoarousal is causally related to the development of aggression and antisocial behavior. It is most closely associated with lower basal activity in the HPA axis, the sympathetic adrenal medullary (SAM) system, and the pontine reticular formation (part of the brainstem circuit mediating the acoustic startle reflex; Lee, Lopez, Meloni, & Davis, 1996). It also suggests that central measures of arousal, such as electroencephalographic (EEG) activity, should show changes indicative of reduced arousal in those with CD, such as increased theta in the EEG power spectrum under resting conditions (Lindberg et al., 2005).

Research examining the underarousal theory has therefore focused on measuring individual differences in tonic or baseline functioning, and does not posit differential activity in the neural systems responding to threat or distress. Thus, antisocial individuals are predicted to have lower baseline cortisol secretion, HR, skin conductance (SC) level, and more slow-wave EEG activity, but normal increases in the activity of these systems when exposed to stress or stimuli connoting threat, despite the lower baselines. Similarly, they are predicted to have lower startle magnitudes, but to show normal increases in startle reflex magnitude when viewing distressing or fearful stimuli (i.e., intact affective modulation, although absolute startle magnitudes may still be reduced under these conditions because of the lower baseline level). Relevant to this point, Raine Venables, and Williams (1990) demonstrated that low arousal at age 15 as measured using cardiovascular activity, spontaneous fluctuations in SC level, and the EEG frequency spectrum predicted a criminal conviction by age 24. It is of interest that these measures of arousal were not significantly correlated with each other. A recent psychophysiological study reported reduced SC responses across all classes of International Affective Picture System slides (positive, neutral, and negative valence) in children with CD relative to controls, but still found larger SC responses to positive and negative pictures relative to neutral pictures in CD subjects (Herpertz et al., 2005). These data suggest a general autonomic hyporesponsivity in CD and persistent criminality, rather than a specific deficit in relation to negative or fear-inducing stimuli, and are therefore in line with predictions from the underarousal theory.

The neurobiology of fear dysfunction

The central tenet of the fearlessness theory is that antisocial individuals are relatively impaired in their perception of fear or threat, and that the neurobiological systems that normally process threat information are compromised (either structurally or functionally). This notion of threat stimuli includes signals that connote or predict punishment. Because they are insensitive to the negative consequences of one's own or other people's behavior in general,

and the experience of receiving punishment in particular, fearless individuals engage more readily in antisocial or delinquent behavior such as aggression.

The neural substrates implicated in this theory include the amygdala, which is thought to play a key role in the perception of threat signals in the environment (Amaral, 2003). This general principle has been supported by neuropsychological studies of humans with amygdala damage demonstrating that the recognition of fear and anger is impaired in these patients (Adolphs, Tranel, Damasio, & Damasio, 1994, 1995; Calder et al., 1996) and neuroimaging studies in which the amygdala has been shown to be activated by the viewing of fearful facial expressions (Morris et al., 1996; Whalen et al., 1998) and negatively valenced pictures (Lane et al., 1997). Patients with amygdala lesions show deficits in fear conditioning and affective decision making (Bechara, Damasio, Damasio, & Lee, 1999), reduced startle amplitudes to acoustic probes (Kettle, Andrewes, & Allen, 2006), and impaired modulation of the startle reflex by affective context (Funayama, Grillon, Davis, & Phelps, 2001).

There are a number of parallels between findings in amygdala patients and neuropsychological studies of children and adolescents with CD or psychopathic tendencies (or both). Deficits in the perception of facial and vocal expressions of fear and sadness have been reported in children with behavioral problems who are high in psychopathic traits (Blair, Budhani, Colledge, & Scott, 2005; Blair, Colledge, Murray, & Mitchell 2001). Adolescents with CD also show impaired fear conditioning and reduced startle amplitudes, although they exhibit normal affective modulation of the startle reflex (Fairchild, Van Goozen, Stollery, & Goodyer, 2008). Finally, two recent neuroimaging studies have reported amygdala dysfunction during the processing of negatively valenced stimuli (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005) and left amygdala volume reduction in early-onset CD (Sterzer, Stadler, Poustka, & Kleinschmidt, 2007). These studies also provided evidence for deficits in anterior insular cortex function or volume reductions in CD. Because the anterior insula is thought to be involved in generating anxiety states (Paulus & Stein, 2006), and shows exaggerated reactivity during the processing of affective stimuli in anxious individuals (Stein, Simmons, Feinstein, & Paulus, 2007), it seems plausible that dysfunction in this structure also contributes to the emotional deficits seen in CD.

Considered together, these data have led some authors to propose amygdala-based accounts of CD (particularly when this disorder is accompanied by high levels of psychopathic traits). Deficits in amygdala function are argued to render the individual relatively "fearless" and unable to recognize cues from the environment that signal either threat or submission (Van Goozen et al., 2007).

A further point of interest is that the prefrontal cortex and amygdala both exert considerable control over HPA axis activity (Herman et al., 2003; Wang et al., 2007). The amygdala has an excitatory influence on CRH-secreting cells in the paraventricular nucleus (PVN) of the hypothalamus that drive the HPA axis, whereas the prefrontal cortex inhibits HPA axis activation (Herman et al., 2003). Thus, an underactive amygdala (or at least its principal "output region," the central nucleus of the amygdala) or deficits in the functioning of prefrontal cortex–anterior cingulate–amygdala circuitry because of prefrontal cortex volume reductions (Kruesi, Casanova, Mannheim, & Johnson-Bilder, 2004; Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000), could underlie the problems in stress response system functioning observed in antisocial individuals (see later section). Alternatively, low reactivity of stress response systems could be because of fundamental changes in the functioning of these systems that are not because of changes in the activity of brain circuits that exert excitatory or inhibitory influences on the HPA axis, but instead are a result of genetic factors, for example. Thus, to prove that cortisol hyporeactivity during stress is because of "fearlessness" rather than physiological insufficiency, it will be necessary to (a) demonstrate that the HPA axis or the SAM system respond normally to physiological stimulation, and (b) show that the limbic circuits that normally activate these systems are less active during stress in those with CD, possibly using EEG or functional magnetic resonance imaging methods combined with an effective experimental stressor. This is a key question that would get at the locus of the neurobiological

dysfunction in CD, and has significant treatment implications.

As a guide, the fearlessness hypothesis predicts: no differences between CD and control participants in terms of basal cortisol secretion and HPA axis responses to physiological stressors, but attenuation of cortisol responses during psychological stress (because corticolimbic circuits, which evaluate the nature of the threat and their connections with the PVN of the hypothalamus, are impaired); no differences in basal HR, but an attenuated HR response to stress; no differences in absolute SC level but a reduced response to stress; reduced psychophysiological (e.g., HR and SC) responses to discrete, negatively valenced (and particularly fear-inducing) stimuli; reduced amygdala responses to negatively valenced stimuli (particularly those connoting threat); reduced or absent fear-potentiated startle; deficient autonomic fear conditioning; impaired subjective experience of fear; and possibly deficits in the recognition of fear states in others (which could be measured using tests measuring recognition of facial or vocal expressions of fear). Some of this has been described already (see above).

Animal models of stress-induced and pathological aggression

From everyday life, we know that stress is a primary factor in promoting aggression in humans. However, how stress mechanisms and the mechanisms involved in aggression interact on a neurobiological level has only recently received attention. Kruk, Halász, Meelis, and Haller (2004) demonstrated a fast positive feedback loop between the adrenocortical stress response and the brain area that controls aggression, that is, the hypothalamus. Specifically, stimulation of the aggressive area in the hypothalamus rapidly activated the HPA axis, even in the absence of an opponent. Hypothalamic aggression was also quickly facilitated by an injection of corticosterone. These findings have clear implications for aggression regulation and treatment. Hypothalamic aggression is selectively sensitive to serotonergic medication and the beta-blocker propranolol. Alternatively, regulation of the adrenocortical stress response with CRF antagonists or certain anxiolytics, which reduce different stress-induced behaviors, may be effective in counteracting acute stress-precipitated violence (Kruk et al., 2004). Thus, in normal animals and humans so-called "reactive" aggression is potentiated by high levels of arousal, an effect that is partly mediated by elevations in corticosteroid concentrations.

We already described evidence that "pathological" aggression appears to be related to HPA axis hyporeactivity. How, then, can these apparently opposing findings be reconciled? Haller and colleagues (Haller, Halász, Mikics, & Kruk, 2004; Halász, Liposits, Kruk, & Haller, 2002; Haller, Van de Schraaf, & Kruk, 2001) have developed a "hypoarousal-driven aggression" model in animals, which mimics human pathological aggression. In this model, the animal behaves in a predatory fashion and appears to interpret the presence of any conspecific as a threat, even if they are much smaller. Haller and colleagues showed that although the central amygdala is *not* involved in aggression relating to "hyperarousal" it is strongly activated in the glucocorticoid-deficient animal during fighting situations. Moreover, these rats exhibit abnormal levels of aggressiveness and attempt to inflict the maximum amount of damage to their opponent. Acute injections of corticosterone prior to exposure to the fighting situation prevent this abnormal pattern of aggressive behavior (Haller et al., 2001). The authors concluded that an acute increase in cortisol is important in making the correct interpretation of the type of social conflict one is dealing with. If one fails to initiate an acute cortisol response, it may be more difficult to evaluate the true nature of the conflict.

In a subsequent study, Haller's group (Halász et al., 2002) investigated the neural background of glucocorticoid dysfunction in defensive aggression. They found that the abnormal behavior as shown by adrenalectomized rats did not involve activation of the brain areas that are normally involved in the control of aggression (cortex, amygdala, septum, hypothalamus, periaquaductal grey, and locus coeruleus). Instead, the brain areas involved in mediating the stress response (the parvocellular part of the paraventricular nucleus of the hypothalamus) and fear reactions (central nucleus of the amygdala) were activated. Halász et al. (2002) concluded that abnormal aggressiveness because of glucocorticoid hypofunction is

related to *increased sensitivity to stressors* and fear-eliciting stimuli, possibly in the sense that signals coming from the opponents are misinterpreted, resulting in a behavioral response that is characteristic of more critical situations.

HPA axis and human aggression

Studies of antisocial adults have observed a negative relationship between cortisol levels and the amount of behavioral deviation shown (e.g., Virkkunen, 1985). Lower levels of cortisol could mean that these individuals are physiologically underaroused, that the negative feedback mechanisms acting on their HPA axes are hypersensitive, or that they have an increased threshold for stress (Kruesi, Schmidt, Donnelly, Hibbs, & Hamburger, 1989).

Studies in antisocial children have yielded mixed results. Some studies have found associations between reduced basal cortisol concentrations and aggressive behavior (e.g., McBurnett, Lahey, Rathouz, & Loeber, 2000; Pajer, Gardner, Rubin, Perel, & Neal, 2001; Shoal, Giancola, & Kirillova, 2003; Vanyukov et al., 1993); other studies found no such relationship (e.g., Azar et al., 2004; Kruesi, Schmidt, Donelly, Hibbs, & Hamburger, 1989; Schulz, Halperin, Newcorn, Sharma, & Gabriel, 1997; Van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & Van Engeland, 2000), or a positive relationship (Van Bokhoven et al., 2005). McBurnett et al. (1991) found that anxious CD children had higher cortisol levels than children with CD alone.

In the majority of studies referred to above, the findings have been correlational in nature, with the result that it has not been possible to draw causal inferences between low cortisol concentrations and antisocial behavior. There have been few studies with a design capable of showing that low cortisol levels *precede* the onset of antisocial behavior. Only two studies reported data indicating that low cortisol is a predictor of aggressive behavior or a marker for persistent aggression (McBurnett et al., 2000; Shoal et al., 2003).

Basal glucocorticoid concentrations are moderately heritable in humans (Inglis et al., 1999; Meikle, Stringham, Woodward, & Bishop, 1988), and parental antisocial personality symptom counts are inversely related to cortisol concentrations in their children (Vanyukov et al., 1993). This suggests that cortisol may be involved in the intergenerational transmission of antisocial behavior and provides further, indirect evidence that this steroid plays a role in the etiology of antisocial behavior.

Findings of reduced basal levels of cortisol in antisocial individuals could support the stimulation-seeking theory: antisocial children seek out stressful situations (e.g., fights) to increase their aversive, low basal cortisol levels. In contrast, the more often these children get involved in stressful situations, the more likely they are to habituate to these stimuli and subsequently show a blunted cortisol response to stress. The effect of frequent exposure (i.e., habituation) but also a lack of anticipatory fear, as suggested by the fearlessness theory, would be better studied under stressful conditions.

In two psychological challenge studies, Van Goozen et al. (1998, 2000) found that antisocial children with ODD had lower cortisol levels than normal controls (NC) when exposed to competition, frustration, and provocation. Specifically, the latter study reported that ODD children and NC participants did not differ in terms of baseline cortisol levels, but the stress-induced increase in salivary cortisol observed in the NC group was absent in the ODD group. Although increased cortisol reactivity to stress has been found in relation to aggressive behavior, this has only been reported in healthy subjects and community samples (Gerra et al., 1997; Scarpa, Fikretoglu, & Luscher, 2000). These results suggest that a pattern of low cortisol reactivity during stress is a specific characteristic of early-onset antisocial patients. Indeed, Snoek, Van Goozen, Matthys, Buitelaar, and Van Engeland (2004) found that child psychiatric patients suffering from attention-deficit/hyperactivity disorder (ADHD) showed a normal, stress-induced cortisol response, whereas children with ODD/CD did not.

It is known that CD children have often been exposed to adverse rearing circumstances involving neglect, abuse, and domestic violence, and that these experiences could affect their subsequent physiological reactivity to stress. Such enduring effects of early life adversity on cortisol reactivity are demonstrated by a study reporting that healthy adults reporting significant maltreatment in childhood showed attenuated

cortisol responses to psychosocial stress (Carpenter et al., 2007). However, there have also been reports of exaggerated physiological responses to stress in adult females exposed to sexual or physical abuse in childhood (Heim et al., 2000). This physiological hyperreactivity was particularly marked in abused participants who were currently suffering from affective or anxiety disorders (Heim et al., 2000). It is not known whether such effects are sexually dimorphic (hyporeactivity in males vs. hyperreactivity in females), or whether they vary according to the nature or course of the stressful experience (sexual or physical abuse vs. neglect). The effects of early adversity on developing stress systems may also vary according to the timing of the stressor and its duration (acute vs. chronic). As well as the possible consequences of early trauma, which is known to be more common in the backgrounds of children with CD, it is established that their own problem behavior elicits negative responses from peers, siblings, and parents, which might be experienced as stressful (Kazdin, 1995). It could be that frequent exposure to stressful situations has resulted in a habituation among these children to stress, and as a result, they show low stress reactivity (i.e., they care less or become less aroused by these events). In this context, it is important to study the individual's appraisal of the stressor to establish whether the subjective experience of antisocial children is in line with their physiological experience. In two of the studies described, antisocial children who failed to show a cortisol response during stress reported and showed intense emotional reactions, suggesting a mismatch between subjective and physiological arousal (Snoek et al., 2004; Van Goozen et al., 2000).

The observed differences in stress reactivity between CD and normally developing children could also be because of genetic factors, for example, polymorphic variation in genes that control aspects of HPA axis function. These could include the proopiomelanocortin gene and the CRH1 receptor genes; reduced activity or downregulation of either would mean that less ACTH is produced in response to CRH. There is also an emerging literature suggesting that specific polymorphisms of the glucocorticoid receptor and mineralocorticoid receptor genes may modulate cortisol reactivity during stress in healthy adults (Kumsta et al., 2007). Finally, it is likely that early experiences and genetic vulnerabilities interact to determine stress responsivity. Further investigation of the impact of early adversity on stress reactivity in childhood and adolescence, using genetically sensitive designs and detailed clinical assessments, is clearly warranted.

For the purposes of this special issue, it is important to note that another recent study showed that antisocial children with a blunted cortisol response to psychosocial stress showed the least improvement following a therapeutic intervention (Van de Wiel, Van Goozen, Matthys, Snoek, & Van Engeland, 2004). ODD/CD children who before treatment had similar levels of externalizing behaviors to cortisol nonresponders, but who exhibited a normal cortisol stress response to psychosocial challenge, responded more favorably to treatment. These findings show that, despite manifesting similar levels of aggressive or oppositional behavior as their disruptive peers, the children with attenuated HPA axis reactivity had a poorer prognosis. These data can be interpreted in two ways: (a) children with HPA axis dysfunction simply have a more serious and ingrained form of the disorder, despite showing similar rates of externalizing behavior as their peers, or (b) an impairment of HPA axis functioning may prevent the types of cognitive or emotional processing that play a critical role in the therapeutic process (Van Goozen et al., 2007). The latter interpretation suggests that children with early-onset antisocial behavior and either low basal cortisol levels or attenuated cortisol reactivity may be more effectively treated using pharmacologically based therapies that reinstate normal HPA axis functioning, perhaps as a precursor or an adjunct to psychological forms of treatment.

It is possible that glucocorticoid hypofunction in antisocial children enhances their stress reactions, resulting in an overreaction that leads to abnormal aggression. Indeed, Van Goozen et al. (2000) found that CD children, while showing no cortisol response to psychosocial challenge, reported more intense negative emotions than normal control children and reacted more aggressively toward their opponent. These findings fit with observed social-information processing

deficits in antisocial children (e.g., Milich & Dodge, 1984). Thus, antisocial children may interpret negative emotional situations incorrectly leading to more extreme, impulsive and aggressive behavior.

The neuroendorine and psychological findings in CD children also have clear parallels with the Haller data on adrenalectomized rodents. Although caution should be exercised in extrapolating from animal models to human behavior, it is possible to speculate that reduced basal cortisol levels and/or a failure in the ability of antisocial children to activate their HPA axis in response to stress may underlie their persistent aggressive behavior: they are more sensitive to stressful or fearful events, but at the same time do not comprehend (i.e., cognitively) or experience (physiologically) the negative consequences of their behavior. The animal studies also suggest that if a normal pattern of cortisol reactivity to stress were reinstated, this might reduce the level of aggression shown by CD children and help them to evaluate conflict situations more accurately.

To summarize, several studies support the notion that HPA axis activity is important in explaining the differences between disruptive, conduct-disordered children and nondisruptive children. Evidence for reduced basal cortisol secretion and cortisol hyporeactivity to stress has been reported in CD/ODD, although the latter appears to be more consistent across studies and different age groups than the former. Relatively little work has been carried out to examine the diagnostic specificity of this effect, but thus far cortisol hyporeactivity appears relatively specific to disruptive behavior disorders. Finally, cortisol hyporeactivity predicts poor response to therapeutic interventions, and work using rodent models suggests that restoration of a normal pattern of cortisol reactivity may attenuate abnormal aggression.

Promising as this work has been, it should be noted that these data are not without limitations. Although the measurement of salivary cortisol, as carried out in most human studies, provides us with information on HPA axis reactivity, cortisol is secreted by the adrenals and therefore reflects a relatively late response. It would therefore be instructive to investigate the functioning of higher levels of the HPA axis, for example, at the level of the pituitary (ACTH) and/or the hypothalamus (CRH). This could be achieved via CRH challenge tests to examine the sensitivity of pituitary CRH receptors by measuring ACTH and cortisol responses to CRH administration. Such studies would yield crucial information about the locus of the changes that lead to cortisol hyporeactivity in CD. If ACTH and cortisol responses to infusion of CRH were normal in children and adolescents with CD, it would suggest that the HPA axis itself is functioning normally, and that cortisol hyporeactivity is instead because of deficient corticolimbic innervation of the HPA axis (consistent with the fearlessness theory). This is analogous to the distinction made between "systemic" and "processive" stressors in the animal literature (Herman & Cullinan, 1997). Systemic stressors (such as hypoxia or bacterial infection) are context independent, do not require interpretation by the organism, and lead to HPA axis responses even in unconscious animals. In contrast, processive stressors (such as exposure to predator odor) are context dependent and require interpretation of their emotional meaning (i.e., apprehending on the basis of prior experience that a given stimulus connotes threat).

Clinical implications

There are at least two ways in which the findings on HPA axis function in antisocial children could be applied in clinical practice and future reseach. An examination of cortisol reactivity to stress could be used to assess of the probability of successful treatment outcome, and in the selection of more targeted interventions. As discussed above, Van de Wiel et al. (2004) showed that cortisol reactivity to stress predicted response to a standard psychotherapeutic intervention (i.e., a combination of cognitive behavioral therapy and parent management training). It was found that the problem behavior of ODD/CD children who showed cortisol hyporeactivity was not altered, whereas the behavior of children exhibiting normal cortisol reactivity improved significantly. Thus, if the individual's HPA axis is normally reactive, traditional interventions such as those involving cognitive and emotional processing and utilizing negative feedback could be predicted to have an increased chance of success. However, in the absence

of a normal cortisol stress response, psychotherapy is unlikely to be effective and pharmacological interventions, for example influencing levels of HPA axis steroids, should be considered.

Because this was the first study to examine the effect of a specific neurobiological risk factor (i.e., cortisol stress hyporeactivity) on prognosis and outcome of a therapeutic intervention, the results need to be replicated in studies involving groups of CD outpatients and community-sampled CD children, and using different forms of psychological intervention (e.g., cognitive–behavioral therapy and multisystemic therapy).[1] If the findings are confirmed, it should be possible in the future to select the best possible treatment option for an individual based on the outcomes of a biological screening procedure. Individuals lacking this biological vulnerability could be expected to profit more from traditional psychological procedures, whereas those with an elevated biological risk should instead be treated by interventions aimed at adjusting the biological deficits. Clearly, studies on the identification of biological predictors of treatment outcome in behavior-disordered children are of heuristic and clinical value: stress reactivity and clinical outcome is not only an important and understudied area in child psychiatry, but the proposed line of research would also influence the development of treatment protocols for children with behavioral disorders, and has the potential to detect chronic or persistent cases using physiological measurements.

A second clinical implication follows directly from the animal work conducted by Haller and colleagues (2004). They showed that restoration of the stress hormonal response via injections of corticosterone prevented abnormal aggressive behavior, and proposed that an increase in stress hormones is important in the appraisal of conflict situations. One prediction arising from the model is that reinstatement of normal HPA axis functioning should ameliorate some forms of disruptive behavior and enhance the response to therapeutic interventions. By restoring stress response systems (this also applies to our discussion of the physiological arousal system that will follow) to a relatively normal state of activity, it should be possible to repair the apparent disjunction between strong emotional reactions (often inappropriate or seemingly out of proportion to the precipitating conditions) and weak or nonexistent stress responses to situations that normally elicit anger, embarrassment, or fear. This connection between the cognitive/emotional components of an experience and the accompanying physiological reaction may be crucial for some aspects of emotional regulation and development. The importance of experiencing "somatic feedback" in decision-making and risk-taking behavior has been outlined by other authors (Damasio, Tranel & Damasio, 1990).

However, to accomplish a reinstatement of stress reactivity, we need to know more about the development and functioning of stress response systems in normal children and adolescents and those with disruptive behavior disorders (see also later section on "A developmental perspective"). In particular, further research is required to investigate the regulatory mechanisms acting on the HPA axis in this latter group, because low basal cortisol concentrations or reduced cortisol reactivity could result from changes at several different levels of the axis (e.g., blunting of the ACTH response to CRH, CRH receptor downregulation in the anterior pituitary, ACTH receptor downregulation in the adrenal cortex, or increased sensitivity of the negative feedback mechanisms that restrain HPA axis activity). CRH/dexamethasone (DEX) challenge tests, to be described below, along with the development of novel CRH antagonist drugs, might be considered in this connection. Alternatively, cortisol hyporeactivity might result from deficits in so-called "processive" neural pathways, which are involved in the cognitive and emotional interpretation of stress-eliciting situations (Herman & Cullinan, 1997). Such an approach would implicate the brain regions involved in activating the HPA axis, such as the paraventricular nucleus of the hypothalamus, amygdala, and prefrontal cortex, rather than components of the axis itself.

1. Studies in physically abused posttraumatic stress disorder children also suggest that increased corticol is a predictor of resiliance (Cicchetti & Rogosch, 2007). Although maltreated children on average tend to have attenuated cortisol secretion, the subgroup of abused children who are still able to elevate corticol to adapt to stressors in their lives are demonstrating greater striving for competence.

Despite this uncertainty regarding the origins of cortisol hyporeactivity in children with severe antisocial behavior, the research by Haller's group provides an impetus to discover what would happen if we were able to restore a normal cortisol stress response in such individuals. There are several potential methods that could be used to achieve this outcome. One could more closely examine the beneficial effects of physical exercise, because exercise increases cortisol secretion acutely. If one were to find that antisocial children show a reduced cortisol response to psychosocial stress, but are able to generate a cortisol increase during exercise, one could examine the behavioral effects of this increase. Although physical exercise is commonly used in penitentiary and reformatory settings, to our knowledge no systematic studies have investigated whether any benefical effects of exercise regimes on antisocial behavior are because of the concomitant effects on the HPA axis.

A different approach would be to examine the pathophysiology of antisocial behavior more specifically and then use the resulting information to design pharmacological interventions. The combined DEX/CRH test (Sher, 2006) and the prednisolone suppression test (Pariante et al., 2002) have been shown to be useful neuroendocrine tools to evaluate enhanced or impaired glucocorticoid-mediated negative feedback on the HPA axis in different groups of psychiatric patients; the expectation in antisocial children would be one of enhanced negative feedback leading to hypocortisolism.

Administering cortisol directly, as was done by Haller et al. (2004) in animals, is problematic because of the many adverse side effects of externally administered cortisol. Moreover, to examine the cognitive, emotional, and behavioral effects of a cortisol surge during stress in antisocial children, in an attempt to replicate the aggression-inhibiting effects of cortisol administration in adrenalectomized rats, cortisol would have to be injected. Given these practical problems, it would be interesting to consider the possibility of administering cortisol via a nasal spray. Nasal sprays for the delivery of corticosteroids are widely available.

The ANS

The ANS, through its sympathetic and parasympathetic branches, regulates critical life functions on a moment to moment basis and governs the fight or flight reaction. In physiological terms, the parasympathetic nervous system is concerned with the conservation and restoration of energy; it causes a reduction in HR and blood pressure, and facilitates digestion and absorption of nutrients, and consequently, the excretion of waste products. In contrast, the SNS enables the body to prepare for fear, flight, or fight. Sympathetic responses include an increase in HR, blood pressure, and cardiac output.

Earlier, we discussed the fearlessness theory, which claims that low levels of arousal are markers of low levels of fear (Raine, 1993), and the stimulation-seeking theory (Zuckerman, 1979), which argues that individuals with tonically low arousal levels are motivated to seek out stimulation to raise their arousal to a more optimal level.

An extensive body of research has accumulated on ANS correlates, particularly SC and HR, of antisocial, delinquent, criminal, psychopathic, and violent behavior, largely showing that the activity of the ANS is lower in these individuals (Ortiz & Raine, 2004; Raine, 1996). It is of interest, and in contrast to the cortisol literature, that a number of studies have used a design capable of showing that low physiological arousal precedes the onset or predicts the persistence of antisocial behavior.

In one study (Raine et al., 1990), HR and SC were measured in 100 15-year-old boys. When the boys were 24 years old, the researchers established who had committed a crime in the intervening 9-year period. The HR and SC values of adolescents who had been convicted for committing a crime were lower than those of boys who had not committed a crime. Furthermore, a longitudinal study carried out in Mauritius demonstrated that low basal HR at age 3 years was consistently associated with increased aggressive behavior at age 11 (Raine, Venables, & Mednick, 1997).

Similarly, a recent study showed that a low resting SC level, measured in childhood, was the best predictor of poor outcome and a CD diagnosis in adolescence. These data were collected within a group of youths who all met the diagnostic criteria for CD or ODD in childhood (Van Bokhoven, Matthys, Van Goozen, & Van Engeland, 2005).

Although there have also been studies that failed to demonstrate a relationship between HR and/or SC, on the one hand, and aggressive or antisocial behavior, on the other hand (Fowles & Furuseth, 1994; Raine & Venables, 1984), results of a recent meta-analysis indicate that low resting HR is one of the best replicated biological markers of antisocial and aggressive behavior in childhood and adolescent community samples, with an average effect size of −0.44 from 40 independent studies comprising a total of 5,868 children (Ortiz & Raine, 2004). The effect size for studies measuring the increase in HR during a stressor was even greater in magnitude (−0.76 from nine independent studies). There is also some indication that low HR is diagnostically specific to antisocial behavior, because no other psychiatric condition has been linked to low HR. In another recent meta-analysis, Lorber (2004) found that conduct problems in children were associated with low resting HR but increased HR reactivity. Conduct problems were also associated with lower levels of SC, both at rest and during task performance (Lorber, 2004).

To summarize, these meta-analyses provide strong evidence that low resting HR and SC are robust correlates of antisocial behavior in children. There is less agreement regarding the direction of changes in HR reactivity or HR during stress, but lower SC levels during task performance are consistently associated with conduct problems in children. This pattern is of interest because autonomic hypoarousal is another characteristic of the glucocorticoid-deficiency model developed by Haller and colleagues (described above). In addition to abnormal fighting patterns, these animals showed much smaller HR increases in both a social stress test and the elevated-plus maze test, which induces anxiety (Haller et al., 2004). This appears consistent with the "fearlessness" interpretation of low autonomic activity in antisocial behavior.

Apart from the strong relation between lower ANS levels and antisocial behavior, it is also important to report that the reverse relationship has been found: children with increased ANS (re)activity levels are more fearful (Kagan, Reznick, & Snidman, 1987). Within the domain of antisocial behavior this is an important finding. In a 14-year prospective study, Raine, Venables, and Williams (1995) measured physiological arousal and orienting in 101 15-year-old male schoolchildren. They found that antisocial adolescents who desisted from criminality had significantly greater physiological arousal and orienting than antisocial adolescents who became adult criminals. They concluded that biological factors can protect against the development of criminal behavior. Brennan and coworkers (1997) conducted a study among sons of criminal fathers. It is known that these boys have an elevated risk of becoming delinquent. The study showed that boys who did not engage in criminal activity as adults had higher HR and SC levels than boys who did become criminal. The researchers concluded that the former group of boys were biologically protected by their heightened autonomic responsivity.

Clinical implications

The implications of these findings for the prevention and intervention of severe antisocial behavior are very similar to the ones we proposed for the HPA axis. They involve conducting detailed diagnostic assessments with at-risk or antisocial children to examine the presence of ANS dysfunction(s), and the conditions under which these become apparent. We presented evidence that decreased levels of ANS activity, tonically and phasically, are related to a worse prognosis, probably because these individuals have a greater drive to seek challenging events and are less sensitive to punishment feedback (Brennan et al., 1997; Raine et al., 1990; Van Bokhoven et al., 2005). The clinical implications of these findings are clear: punishment-based socialization strategies will not be effective in those antisocial children who have reduced ANS levels, and pointing out the adverse consequences of bad behavior is unlikely to lead to substantial behavioral change.

Future Directions

Thus far we have reviewed evidence that children with severe antisocial behavior suffer from reduced reactivity of different stress systems. A few studies have also provided indirect evidence of reduced functioning of the amygdala in children with severe antisocial behavior or psychopathic tendencies. For example, two

studies showed that children and adolescents with CD had a blunted response to auditory stimuli that normally elicit a startle reflex, but showed a normal pattern of affective modulation by emotional pictures (Fairchild et al., 2008; Van Goozen, Snoek, Matthys, Van Rossum, & Van Engeland, 2004). At present, it is unclear whether these data fit with the underarousal or fearlessness hypothesis; reduced startle reflex amplitudes but a normal pattern of affective modulation suggests that the startle reflex circuit may be compromised (e.g., reduced tonic activity in the pontine reticular formation).

The interpretation that these findings are because of amygdala impairment, and therefore support the fearlessness theory, is consistent with a report showing that damage to the right amygdala dramatically reduces startle amplitude to an aversive auditory stimulus and prevents the potentiating effect of negatively valenced pictures on the startle response (Angrilli et al., 1996; Kettle et al., 2006). Given the evidence of reduced or impaired functioning of different brain systems that play a role in emotional processing and emotional learning, it is worth asking whether it might be possible to directly intervene in those systems by modulating brain activity as a way of improving antisocial symptoms. For example, would it be possible to specifically normalize activity in the neural circuitry involving the orbitofrontal cortex (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001), dorsal anterior cingulate (Sterzer et al., 2005), and amygdala (Blair, Mitchell, & Blair, 2005)?

At the moment there are two methods that show promise for future use in improving some of the functional deficits observed in antisocial behavior. Transcranial magnetic stimulation (TMS) is a procedure in which a magnetic coil is used to induce electric fields in the brain and is a noninvasive and well-tolerated method of altering cortical physiology. TMS disrupts the normal pattern of cortical processing by adding "neural noise" (Walsh & Rushworth, 1999). High-frequency TMS excites neural activity and low-frequency TMS inhibits neural activity in a localized fashion (George, 2006). Although single-pulse stimulation is generally considered to be a safe procedure, caution is needed when using repetitive pulse TMS (rTMS) because of a small risk that it can cause seizures (Wasserman & Lisanby, 2001). In psychiatry, TMS has mostly been used in the treatment of depression, and the available evidence supports the antidepressant (i.e., mood-improving) effect of rTMS when applied to the dorsolateral prefrontal cortex. There are several potential mechanisms by which rTMS may affect mood: it may produce neuroendocrine effects, stimulate striatal DA release, modulate neurotransmitter and neuromodulator release, and increase cerebral blood flow in stimulated regions and those connected to them (Anand & Hotson, 2002).

We are not aware of studies that used TMS/rTMS to *increase* cortical excitability. Our hypothesis would be that such an increase, applied to selected areas of the PFC, would enhance inhibitory function and result in more controlled, less impulsive behavior. For the moment, the fact that ventral areas in the brain that are important in emotional processing, such as the orbitofrontal and anterior cingulate cortices, are not easily or directly accessible to transcranial stimulation is likely to limit the clinical efficacy of rTMS (Wasserman & Lisanby, 2001). However, time will hopefully bring technical advancement in terms of being able to target subcortical regions and ventral PFC (see Schutter & van Honk, 2006). TMS could play a future role in tackling some of the problems observed in severe antisocial behavior, provided (a) specific, testable pathophysiological hypotheses based on robust neuropsychological assessments are developed, (b) future participants can be properly screened for the safe application of r-TMS/TMS, and (c) we have the means to precisely localize and target those areas in the brain that need this form of intervention.

A second method that involves changing brain activity is neurofeedback (NF). NF is a form of biofeedback training in which one learns, through a process of immediate feedback and positive reinforcement, to modulate electrical activity in one's brain as a way of improving symptoms (Heinrich, Gevensleben, & Strehl, 2007). NF training has mostly been used in treatment of ADHD and epilepsy. For example, children with ADHD who show underarousal of central and frontal brain regions, have been shown to be able to learn to decrease activity in one EEG frequency band (i.e., theta) and increase activity in another EEG frequency band (i.e., beta), thus activating and maintaining a

state of cortical arousal ("tonic activation"). In one study, Levesque, Beauregard, and Mensour (2006) trained 15 medication-free ADHD children in NF; 5 other ADHD children were controls. They not only showed that the NF-trained children suffered less from problems related to inattention, impulsivity, and hyperactivity, but also confirmed by functional magnetic resonance imaging that the enhanced performance was attributable to a normalization of neural activity in the anterior cingulate cortex, the key neural substrate of selective attention.

As is the case for other neuropsychiatric disorders characterized by self-regulation deficits, children and teenagers with severe antisocial behavior could profit from NF, given their problems with impulse control and emotional regulation. This method of treatment is a noninvasive, but nevertheless a technical and time-consuming procedure. It could be considered after a thorough assessment of underlying pathophysiology and, if possible, administered in combination with other available treatment options (e.g., parent management training, cognitive behavioral therapy).

Neurotransmitters

We will now discuss the role of different neurotransmitters in antisocial behavior. Although between 50 and 100 molecules have been identified as neurotransmitters in the central nervous system, only the monoamines (i.e., 5-HT, NE, and DA) have been systematically studied with respect to human aggression, and of these three monoamines, the most extensively studied is 5-HT.

NE

It has been suggested that the NE system affects both arousal and the degree of sensitivity an organism displays toward the environment, which may prepare an organism to respond aggressively to novel or threatening environmental stimuli (Siever et al., 1991). Animal research (e.g., Higley et al., 1992) provides evidence of a positive correlation between NE activity and aggressive behavior. In humans, increased NE activity has been associated with measures of sensation-seeking, extraversion, and risk-taking behaviors (e.g., Roy, Adinoff, & Linnoila, 1988). Furthermore, Brown, Goodwin, Ballenger, Goyer, and Major (1979) have found a positive relationship between cerebrospinal fluid (CSF) 3-methoxy-4-hydroxyphenylglycol (MHPG), a central NE metabolite, and a history of aggression in males. In CD or aggressive ADHD children, higher levels of MHPG or a positive correlation between MHPG and aggression have also been found (Castellanós et al., 1994; Gabel, Stadler, Bjorn, Shindledecker, & Bowden, 1993).

In contrast, it has been proposed that the anxiogenic effects associated with elevated NE should act as an inhibitor of aggressive behavior (Rogeness, Javors, Maas, & Macedo, 1990; Rogeness, Javors, & Pliszka, 1992). Virkkunen, Nuutila, Goodwin, and Linnoila (1987) found decreased CSF MHPG levels in arsonists and violent offenders relative to controls. Rogeness, Javors, Maas, Macedo, and Fischer (1987) found negative correlations between MHPG and conduct symptoms, but no difference in plasma MHPG between CD and non-CD groups. Kruesi et al. (1990) found inverse correlations between CSF MHPG and aggressive symptoms in children. DA beta-hydroxylase (DBH), the enzyme that converts DA to NE, is also used as an indirect measure of NE functioning. Rogeness et al. (1987, 1990) found low levels of DBH in CD children. Other studies, however, have failed to find a relation between CD and peripheral measures of NE functioning in children (Pliszka, Rogeness, & Medrano, 1988; Pliszka, Rogeness, Renner, Sherman, & Broussard, 1988). In one study examining levels of different monoamine metabolites in CD children, no evidence of abnormal MHPG levels was found (Van Goozen, Matthys, Cohen-Kettenis, Westenberg, & Van Engeland, 1999).

DA

DA is considered to play a role in behavioral activation, reward mechanisms, and goal-directed behaviors. Increased activity in this system, it has been suggested, leads the organism to seek out pleasurable stimuli. It is hypothesized that the system is highly responsive to signals in the environment that indicate the presence of reward (Schultz, 1998). Results from animal studies indicate that increased DA functioning is usually

associated with increased aggressive behavior (Spoont, 1992). However, studies of CSF homovanillic acid (HVA), a DA metabolite, have been highly inconsistent in aggressive child and adult populations. Two studies of CSF HVA (Linnoila et al., 1983; Virkkunen et al., 1994) showed decreased levels in impulsive offenders compared with controls, although other studies of antisocial adults have found no relation between HVA and aggression (Brown et al., 1979; Lidberg, Tuck, Asberg, Scalia-Tomba, & Bertilsson, 1985; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). Kruesi et al. (1990, 1992) also found no relationships between CSF HVA levels and aggressive behavior in children with CD/ODD and/or ADHD. Gabel et al. (1993) and Van Goozen et al. (1999) found lower plasma levels of HVA in young CD boys. In contrast, Castellanós et al. (1994) found a positive relationship between HVA and aggression in ADHD children.

Clinical evidence

Although biochemical studies in children do not provide clear evidence of a relationship between NE or DA, on the one hand, and aggressive behavior, on the other, clinical findings do support an involvement of these monoamines in aggressive behavior. For example, there are studies showing that methylphenidate (MPH), which stimulates the release of NE and DA, reduces aggressive behavior (Kolko, Bukstein, & Barron, 1999). MPH treatment is especially effective in children with ADHD. Because early-onset CD often shows comorbidity with ADHD, it could be that the improvement in aggressive behavior is dependent on ADHD symptoms (Klein et al., 1997). However, one study found significantly reduced ratings of antisocial behavior by MPH treatment (Klein et al., 1997) in CD children independent of ADHD symptoms. In addition, beta-adrenergic blockers such as propanolol have been reported to be effective in reducing aggressive behavior in children (see Kavoussi, Armstead, & Coccaro, 1997). Furthermore, as mentioned before, the dopaminergic system is implicated in the mediation of reward-driven behavior (Pliszka, 1999). The knowledge that the reward system and DA are implicated in the neurobiology of addiction (Dackis & O'Brien, 2001) and that CD children are at considerable risk of substance abuse (Kazdin, 1995) is consistent with an involvement of DA in the modulation of aggressive behavior in children. Quay (1993) hypothesized that CD children seek out exciting, potentially rewarding and novel situations because of an overly active DA-mediated reward system (also called behavioral activation system [BAS]). A dominance of the BAS (which activates behavior in response to cues for probable reward and nonpunishment) over the more 5-HT-mediated behavioral inhibition system (BIS, which inhibits ongoing behavior in the presence of cues for probable punishment and nonreward) in CD children has been supported (Matthys, Van Goozen, de Vries, Cohen-Kettenis, & Van Engeland, 1998; Matthys, Van Goozen, Snoek, & Van Engeland, 2004). However, dominance of BAS over BIS can also result from a poorly functioning BIS because of lowered 5-HT (Matthys et al., 2004). In conclusion, more research is needed to clarify the precise role of NE and DA in the instigation and regulation of aggressive behavior in children.

Serotonin and aggression

In an important paper, Spoont (1992) argued that serotonin stabilizes information processing in neural systems, resulting in controlled behavioral, affective, and cognitive output, whereas disturbances in 5-HT activity result in altered information processing tendencies. Exactly how 5-HT activity influences aggressive or impulsive behavior in humans is not yet understood, although diminished serotonergic function is thought to disinhibit aggression directed against the self and others, perhaps by sharpening sensitivity to stimuli that elicit irritation and aggression, and blunting sensitivity to cues that signal punishment (Spoont, 1992).

A substantial body of evidence suggests that 5-HT plays a role in aggression directed toward others, other people's property (e.g., arson), and toward oneself (e.g., suicide; see Tuinier, Verhoeven, & Van Praag, 1996, for a review of clinical findings). For example, inverse relationships between CSF 5-hydroxyindoleacetic acid (5-HIAA, a major metabolite of 5-HT) and aggressive or violent behavior have been reported in a number of antisocial and clinical and nonclinical samples, including alcoholics (Limson

et al., 1991), arsonists (Virkunnen et al., 1987), and men who murdered their sexual partners (Lidberg et al., 1985). It has been suggested that a deficit in 5-HT availability and/or turnover is mainly associated with impulsive forms of aggression. To date, only three studies have measured CSF 5-HIAA in children. Kruesi et al. (1990) found lower 5-HIAA levels in disruptive and/or ADHD children and inverse correlations with ratings of aggressive behavior. At 2-year follow-up, CSF 5-HIAA levels were found to be a predictor of the severity of physical aggressive behavior and poor outcome (Kruesi et al., 1992). In contrast, Castellanós et al. (1994) found in their study of 29 boys with ADHD that CSF 5-HIAA levels were positively correlated with measures of aggression and impulsivity. The authors noted that their ADHD group was more hyperactive and less aggressive than the Kruesi et al. (1990) sample, and speculated that 5-HT measures may only correlate negatively with aggression in groups of children with a core aggression problem.

Studies of aggressive children using whole-blood serotonin assays, a peripheral measure of 5-HT, have yielded mixed results: some reported a negative correlation with aggression (Hanna, Yuwiler, & Coates, 1995); others found higher levels or positive relationships with whole-blood 5-HT (Hughes, Petty, Sheikha, & Kramer, 1996; Pliszka, Rogeness, Renner, et al. 1988; Unis et al., 1997), or no differences compared to normal or psychiatric controls (Cook, Stein, Ellison, Unis, & Leventhal, 1995; Rogeness, Hernandez, Macedo, & Mitchell, 1982). In two studies, Van Goozen et al. (1999) found that plasma 5-HIAA was significantly lower in ODD/CD children than in NC and strongly inversely correlated with aggression as observed by others and as elicited experimentally.

"Pharmacochallenge" measurement techniques provide a useful alternative method of assessing the relationship between central 5-HT and aggression. In several studies of antisocial adults, the prolactin response to fenfluramine has been shown to be inversely correlated with aggression, impulsivity, and irritability (e.g., Coccaro, Kavoussi, Cooper, & Hauger, 1997; O'Keane et al., 1992). Some challenge studies (the majority using fenfluramine) have been conducted in aggressive children or adolescents but the findings are less clear-cut than those in adults. In two studies (Halperin et al., 1994, 1997) a significantly enhanced prolactin response to fenfluramine was observed in young (<9.1 years) aggressive ADHD boys, whereas the older (>9.1 years) aggressive ADHD boys did not show an elevated response. The authors suggested that aggressive ADHD children, who initially have an enhanced prolactin response to fenfluramine, fail to undergo normal developmental changes in 5-HT function and subsequently have a blunted response. In line with this pattern of enhanced reactivity are the results of Pine et al. (1997), who investigated the serotonergic function in 34 younger brothers of convicted delinquents. They found that aggressive behavior, but also adverse rearing circumstances, were positively correlated with the prolactin response to fenfluramine challenge. Another study investigated the neuroendocrine response to the selective 5-$HT_{1B/1D}$ receptor agonist, sumatriptan (Snoek et al., 2002). This receptor subtype is of interest because animal studies have suggested that the 5-$HT_{1B/1D}$ receptor has a privileged role in the etiology of impulsive aggression (Saudou et al., 1994). Consistent with previous reports in children, the study showed that the growth hormone response to sumatriptan was enhanced in CD children (Snoek et al., 2002). This suggests that the sensitivity of postsynaptic 5-$HT_{1B/1D}$ receptors is increased in CD children, perhaps as a result of a primary deficit in brain 5-HT levels that subsequently leads to upregulation of 5-HT receptor number.

To conclude, there is compelling evidence in adults for an inverse relationship between 5-HT measures (CSF 5-HIAA and prolactin response to fenfluramine challenge) and antisocial behavior, but the direction of the relationship in children is less straightforward. The majority of the results of pharmacological challenge studies in children point to a positive relationship between the hormonal responses and aggressive behavior, and age has been suggested to be an important factor in explaining these inconsistencies (Halperin et al., 1997; Pine et al., 1997). Future challenge studies focusing on well-defined antisocial groups and using selective neurotransmitter agonists that activate specific receptor subtypes are needed to explore the 5-HT–aggression relationship more closely (Van Goozen et al., 2007).

Effects of serotonin manipulation on human aggression

Establishing a causal relationship between low 5-HT levels and aggression can only be achieved by experimental studies in which it is shown that manipulations of the serotonergic system have a direct effect on aggressive behavior. Pharmacological manipulation of the 5-HT system through tryptophan depletion or supplementation (tryptophan is an amino acid necessary for the synthesis of 5-HT) results in changes in the predicted direction in aggressive individuals tested under laboratory conditions (Bjork, Dougherty, Moeller, Cherek, & Swann, 1999; Bjork, Dougherty, Moeller, & Swann, 2000). Various psychopharmacological agents including antipsychotics, lithium, anticonvulsants, benzodiazepines, and amphetamines have been shown to alter aggressive behavior in adults and children (Mann, 1995; McDougle, Stigler, & Posey, 2003; Stoff & Vitiello, 1996). In addition to the effect of these agents on several different neurotransmitter systems, many of them may have marked effects on the 5-HT system. A few studies investigating the antiaggressive effect of agents that primarily affect the 5-HT system, like selective serotonin reuptake inhibitors (SSRIs), have demonstrated their efficacy in reducing impulsive aggression in adult psychiatric patients (Coccaro & Kavoussi, 1997; Fava et al., 1993; Kavoussi, Liu, & Coccaro, 1994; Salzman et al., 1995).

In children, however, the results are less clear. Controlled studies of the effects of serotonergic agents on aggression in pediatric samples are few in number. Most of the available data come from single case reports and open label trials with limited numbers of patients. Two open label studies have described favorable effects of trazodone in the treatment of aggressive behavior in pediatric inpatients (Ghaziuddin & Alessi, 1992; Zubieta & Alessi, 1992). An open label, pilot study showed a reduction in impulsive aggression in 11 children with CD/ODD after treatment with the SSRI citalopram (Armenteros & Lewis, 2002). However, another open label study found no improvement in aggressive behavior when investigating the effect of three different SSRIs (fluoxetine, paroxetine, and sertraline) on the aggressive behavior of 19 hospitalized adolescent psychiatric patients (Constantino, Liberman, & Kincaid, 1997). In addition, an unpublished study showed that an 8-week treatment with the SSRI fluvoxamine had only limited effects on aggressive and oppositional symptoms in a group of 15 hospitalized CD children (Snoek, 2002). Fluvoxamine also did not affect the GH response to the 5-$HT_{1B/1D}$ receptor agonist sumatriptan, which suggests that changes in the sensitivity of postsynaptic 5-$HT_{1B/1D}$ receptors in CD children are relatively long-lasting and not easily corrected by restoring normal levels of 5-HT.

To summarize, very few studies have examined the effects of specific 5-HT receptor agonists and antagonists on disruptive behavior in children. Although evidence from studies investigating the antiaggressive properties of currently available SSRIs suggests that these drugs are of limited use in treatment of CD children, it is possible that novel antidepressant drugs with actions on the 5-HT system will be useful in their treatment in the future (Van Goozen et al., 2007).

Clinical implications

Although pharmacological agents that directly affect the 5-HT system are available, we noted that no medication is currently able to deal specifically with the kinds of behavioral problems shown by antisocial individuals.

Increasing serotonin function to examine its inhibitory effect on aggressive or impulsive behavior can be achieved by administering the serotonin precursor tryptophan. Results from studies using acute tryptophan depletion suggest that this procedure increases aggression in humans (Bjork et al., 1999, 2000; Cleare & Bond, 1995). Studies investigating the effects of tryptophan administration in the treatment of pathological aggression are extremely rare. One study found that tryptophan reduced uncontrollable aggression relative to placebo, but the patient group was different from the one discussed here because they also suffered from schizophrenia (Morand, Young, & Ervin, 1983). Moskowitz, Pinard, Zuroff, Annable, and Young (2001) treated 98 healthy adults for 12 days with tryptophan (Tryptan, 1 g/day) and for 12 days with placebo in a double-blind crossover study. They found no effects on mood, but enhancing 5-HT increased dominance and decreased quarrelsome behavior.

Although these findings are preliminary and the conclusions therefore remain tentative, studies examining the effects of tryptophan administration should be extended to groups suffering from severe behavioral problems.

Genetic Factors in Antisocial Behavior

It is well established that persistent antisocial behavior and criminality are concentrated in a relatively small proportion of families (Farrington, Jolliffe, Loeber, Stouthamer-Loeber, & Kalb, 2001), and that children with disruptive behavior disorders are more likely than controls to have parents who show antisocial behavior themselves (Lahey et al., 1987). A logical extension of these findings is to ask whether a predisposition toward antisocial behavior can be inherited.

Recent meta-analyses have concluded that heritable factors explain 40–50% of population variation in antisocial behavior (Miles & Carey, 1997; Rhee & Waldman, 2002), although the proportion may be greater (60–65%) for aggressive antisociality (Tackett, Krueger, Iacono, & McGue, 2005) or personality factors related to severe antisocial behavior, such as callous and unemotional traits (Viding, Blair, Moffitt & Plomin, 2005). Further evidence for a genetic influence on criminality and antisocial behavior comes from adoption studies. These studies document the fact that adoptees from biological parents with a criminal conviction show higher rates of criminality than adoptees whose biological parents did not have a conviction, even though both groups were separated from their biological parents shortly after birth (Bohman, Cloninger, Sigvardsson, & Knorring, 1982; Cadoret, Yates, Troughton, Woolworth, & Stewart, 1995). Another point of interest is that genetics and rearing environment interact powerfully to moderate the likelihood of developing antisocial behavior or criminality. An illustration of this is provided by Bohman's (1996) adoption study of petty criminality. It was shown that individuals lacking either a genetic predisposition or environmental risk factors had only a 3% chance of becoming repeat offenders. Those exposed to environmental risk (e.g., as a result of having antisocial adoptive parents) had a 6% rate of criminality, whereas those with a genetic predisposition had a 12% incidence of criminality. In contrast, the incidence of criminality in those with both genetic and environmental risk factors present was as high as 40%. A number of other studies document the importance of considering Gene × Environment interactions in the development of aggressive or antisocial behavior (e.g., Cadoret et al., 1995; see Raine, 2002, for a review).

In trying to identify specific genes that confer an increased risk of antisocial behavior, significant attention has focused on the monoamine oxidase-A (*MAOA*) gene, on the basis of animal work showing increased aggression in mice lacking this gene (Cases et al., 1995) and studies showing increased aggression in humans with a point mutation in the same gene (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993). *MAOA* is an enzyme that degrades serotonin, NE, and DA following their reuptake from the synaptic cleft, and it may be particularly important in early life because its homolog enzyme, *MAOB*, does not reach functional maturity until later in development (Shih, Chen, & Ridd, 1999). There are two common polymorphisms of the *MAOA* gene in humans: a high activity and a low activity form (found, respectively, in approximately 65 and 35% of the male population; Caspi et al., 2002; Kim-Cohen et al., 2006). Althogh recent evidence suggests a weak main effect of *MAOA* genotype on vulnerability to psychopathology in the direction of worse outcomes in those with *high MAOA* activity (Kim-Cohen et al., 2006), an impressive series of studies have shown that the *MAOA* genotype strongly moderates the impact of early adversity on risk for antisocial behavior (Caspi et al., 2002; Foley et al., 2004; Nilsson et al., 2005). Individuals with a combination of low MAOA activity and exposure to childhood maltreatment show dramatically increased rates of CD and violent offending relative to those with low MAOA activity but no exposure to social adversity, whereas the effect of maltreatment exposure is substantially weaker in those with high MAOA activity (Caspi et al., 2002[2]).

2. It is interesting that other work by Caspi et al. (2003) has shown a similar G × E effect for depression in those who possess the low activity form of the 5-HT transporter gene.

Genetics, Development, Environment, and the Stress Response

An individual's stress response is determined by multiple factors. Abnormal reactivity of the stress system is associated with increased vulnerability to psychopathology, and this may be the result of genetic, developmental, and environmental factors. Depending on the genetic background of the individual and his/her exposure to adverse stimuli in prenatal and/or postnatal life (i.e., developmental influences), one might fail to cope with life's stressors. In addition, genetic polymorphisms, for example those of CRH, and its receptors and/or regulators, are expected to account for some the observed variability in the functioning of the stress system (Charmandari, Tsigos, & Chrousos, 2005). Constitutional vulnerability or resilience can be altered by exposure of the individual to early environmental stressors. The prenatal life, but also infancy, childhood, and adolescence are periods of increased plasticity for the stress system, and are therefore particularly sensitive periods. Excessive or sustained activation of the stress system during these critical periods may have profound, even permanent, effects on the functioning of the stress system of the individual.

Neurobiological effects of early adversity

We presented evidence that genes and neurobiological systems play a role in antisocial behavior. Next we describe how environmental factors impact on neurobiological development and functioning, and thus contribute to antisocial behavior. Some environmental risk factors are prenatal, such as exposure to maternal smoking in utero (Silberg et al., 2003; Thapar et al., 2003); others are postnatal, such as maltreatment (Caspi et al., 2002), or adversity, consisting of a combination of parental neglect, interparental violence, and inconsistent discipline (Foley et al., 2004). Some of the best candidate environmental risk factors are those that are most likely to have an effect on the biological systems involved in psychopathology; stress responsiveness, variations in quality of parental care, parental psychopathology, poverty, child abuse, and neglect (Moffitt, 2005).

Animal studies in nonhuman primates and rodents consistently show that early life stressors have long-term neurobiological consequences, including effects on the HPA axis and the noradrenergic, dopaminergic, and serotonergic systems, that persist into adult life (reviewed by Bremner & Vermetten, 2001; Sanchez, Ladd, & Plotsky, 2001). Kraemer, Ebert, Schmidt, and McKinney (1989) showed in their study of rhesus monkeys that disruption of early social attachment produced changes in CSF measures of biogenic amine system activity. Rosenblum et al. (1994) administered the noradrenergic agonist yohimbine and the serotonergic agonist *meta*-chlorphenylpiparazine (*m*-CPP) to two groups of adult primates that had been reared under conditions of normal or disrupted social development. The animals exposed to social deprivation were hyperresponsive to yohimbine and hyporesponsive to *m*-CPP. Liu et al. (1997) found that, as adults, the offspring of mothers that exhibited more licking and grooming of pups during the first 10 days of life showed reduced plasma ACTH and glucocorticoid responses to acute stress, increased hippocampal glucocorticoid receptor messenger RNA expression, enhanced glucocorticoid feedback sensitivity, and decreased levels of hypothalamic CRH messenger RNA. The authors concluded that maternal behavior serves to "program" HPA responses to stress in the offspring and variations in maternal care may affect the development of individual differences in neuroendocrine responses to stress in rats. Although it has been more difficult to demonstrate lasting alterations in primate HPA axis functioning following exposure to early adversity, in recent years it has become clear that manipulations that disrupt the quality of mother–infant interactions (such as unpredictable foraging demand conditions or repeated separation of the mother from the infant's social group) are capable of inducing long-term changes in HPA axis activity. CSF cortisol concentrations in infant primates were reported to be reduced following maternal exposure to chronic stress (Coplan et al., 1996), whereas urinary cortisol levels were lower following a period of repeated maternal separation (Dettling, Feldon, & Pryce, 2002).

The few studies of the effects of early stress on neurobiological systems conducted in clinical populations of traumatized children have generally been consistent with findings from animal studies. Studies of various adult psychiatric

patients with a history of early childhood abuse have revealed long-term changes in HPA axis activity (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001), noradrenergic function (see Bremner & Vermetten, 2001) and the serotonergic system (Rinne, Westenberg, den Boer, & Van den Brink, 2000). There is also evidence for long-term changes in HPA axis functioning in children and adolescents with a history of abuse (Cicchetti & Rogosch, 2001; De Bellis et al., 1999; Duval et al., 2004; Gunnar, Fisher, and the Early Experience, Stress, and Prevention Network, 2006). Different studies of severely socially deprived children raised in Romanian orphanages during the Ceaucescu era showed that these children failed to show a normal daily pattern of cortisol secretion, compared to healthy children raised at home with their parents (Carlson & Earls 1997; Gunnar et al., 2006; Gunnar, Morison, Chisholm, & Schuder, 2001).

Returning to the issue of antisocial children, children with CD are more likely to come from more adverse rearing environments involving atypical caregiver–child interaction, parental psychopathology, or exposure to abuse and neglect (Rutter & Silberg, 2002). We also know that CD children are more likely to experience compromised pre- or perinatal development because of maternal smoking, poor nutrition, or exposure to alcohol and/or drugs. It is possible that these prenatal and early postnatal influences have had lasting effects on developing neurobiological systems in the brain, including the HPA axis and neurotransmitter systems, and resulted in a child with a more difficult temperament. For these reasons, it can be predicted that interventions in early life will be most successful in achieving lasting change through their enduring effects on developing neurobiological systems.

An intriguing issue is why some individuals exposed to early adversity exhibit elevated basal cortisol levels, exaggerated HPA axis reactivity (i.e., increased glucocorticoid secretion), and autonomic responses to psychosocial stress, and are therefore at risk of developing mood and anxiety disorders (Heim et al., 2000, 2001), whereas others appear to show the opposite pattern of reduced basal cortisol and attenuated physiological and endocrine responses to stress (Carlson & Earls, 1997; Gunnar & Donzella, 2002; Gunnar et al., 2001, 2006). Although to our knowledge no research with a design capable of finding how these opposite patterns of neurobiological functioning develop over time has been published (see our later section on "A developmental perspective"), we can think of some factors which might be involved in (part) of the explanation.

A first factor that could be involved in the development of opposite patterns of HPA functioning is gender. There are clear gender differences in the prevalence rates for psychopathology, with females being more prone to develop internalizing disorders, such as depression, anxiety, and eating disorders, and males showing a greater tendency to develop externalizing disorders, such as ODD and CD (Cyranowski, Frank, Young, & Shear, 2000). These internalizing and externalizing disorders are associated with opposite patterns of HPA axis functioning. Research has shown that males and females not only differ in their neuroendocrine responses to stress (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Uhart, Chong, Oswald, Lin, & Wand, 2006), but also in sensitivity to different types of stressors (Stroud, Salovey, & Epel, 2002). Thus gender could play a moderating role in the relation between early adversity and psychopathology.

A second factor is that the type of stressor involved could make a difference, for example, physical or sexual abuse, neglect or maltreatment. Recently, Lee, Geracioti, Kascow, and Coccaro (2005), examining retrospectively physical and emotional abuse, and physical and emotional neglect in men with personality disorders, found a positive relationship specifically between emotional neglect and CSF CRH concentration, which is suggestive of an increased HPA axis function. According to these authors, emotional neglect is analogous to the disruptions in maternal care as administered in the rodent handling and separation paradigms (Meaney et al., 1996) and the primate variable foraging paradigms (Coplan et al., 1996). Future research should address this issue and examine the effects of different types of stressors on neurobiological development and functioning.

A third factor that could influence long-term neurobiological functioning is the timing or the duration of the stressor (-s). Again, to our knowledge, no human research has examined the neurobiological effects of stress at different

developmental stages. The animal literature would suggest that the timing of exposure to adversity, and its intensity, has a critical influence on the eventual outcome. For example, rats separated for 24 hr at postnatal day (PND) 3–4 exhibited an enhanced ACTH response to a mild stressor relative to controls, whereas those separated at PND 11–12 showed an attenuated ACTH response (Van Oers, de Kloet, & Levine, 1998). Furthermore, animals subjected to long-term social isolation after weaning showed reduced responses to restraint stress (Sanchez, Aguado, Sanchez-Toscano, & Saphier, 1998). This is in sharp contrast with animals experiencing repeated maternal separation at PND 2–20, who showed an exaggerated HPA axis response to stress (Ladd, Owens, & Nemeroff, 1996). These studies illustrate the importance of examining the consequences of different types of early life stress and the timing of such experiences in naturalistic studies in humans. With respect to chronicity, Heim, Ehlert, and Hellhammer (2000) describe evidence that hypocortisolism is observed in otherwise healthy individuals living under conditions of ongoing stress. A pattern of decreased ACTH and corticosterone secretion and reduced responsiveness to challenge has also been found in rodents living under conditions of chronic stress because of exposure to continuous electric shocks or immobilization. In recognizing that antisocial children often come from problematic backgrounds, and that many of them have been neglected or abused (Kazdin, 1995), it is reasonable to assume that they have often been exposed to prolonged or uncontrollable stress, and that these experiences have had a lasting effect on the developing neurobiological systems of the brain, including the HPA axis and the 5-HT system. At present, however, it is unclear whether such experiences, if it can be established (retrospectively) that these have occurred in children with antisocial behavior, have altered their basal cortisol secretion (daily rhythm), their HPA axis response to stress, or both. This is clearly an important topic for future research.

Early brain development: The effect of nutrition

Interest in the effects of nutrition on brain function has been growing in recent years. Nutritional deficiencies during important phases of neurodevelopment can affect brain maturation and functioning because deficits in protein, iron and zinc levels may impair brain activity in regions such as the prefrontal cortex that are important in emotion regulation and behavioral inhibition (see, e.g., Liu, Raine, Venables, & Mednick, 2004).

Neugebauer, Hoek, and Susser (1999) found that men prenatally exposed to severe maternal nutritional deficiency because of the wartime famine in 1944 in The Netherlands had an increased risk of being diagnosed with antisocial personality disorder at age 18 years. Liu et al. (2004) conducted a prospective longitudinal study in Mauritian birth cohort ($n = 1{,}795$) to examine the effects of poor nutrition on externalizing behavior in childhood and adolescence. They found that children who were malnourished at age 3 years ($n = 353$) were more aggressive and hyperactive at age 8 years, showed more externalizing behavior at age 11, and were more likely to be diagnosed with CD at age 17.

Another promising line of research shows that manipulations involving nutrition can have positive effects for preventing and reducing antisocial behavior. Raine, Mellingen, Liu, Venables, and Mednick (2003) exposed 83 3-year-old Mauritian children to an environmental enrichment program for 2 years and assessed antisocial and criminal behavior (among other outcomes) at ages 17 and 23 years. They found that the enrichment-exposed children had lower rates of antisocial and criminal behavior at follow up and that the beneficial effects of the intervention were greatest for the children who had shown signs of malnutrition at age 3.

A double-blind, placebo-controlled, randomized experimental trial showed that supplementation of adult prisoners' diets with vitamins, minerals, and essential fatty acids significantly reduced antisocial and violent behavior by an average of 26–35% (Gesch, Hammond, Hampson, Eves, & Crowder, 2002). Clearly, dietary interventions may prove useful in reducing antisocial behavior in those already affected, but it may also represent a relatively easy and inexpensive way to prevent antisocial behavior from developing in at-risk groups by providing them with better early nutrition (Liu et al., 2004).

More recent work (Hibbeln, Fergusan, & Blasbalg, 2006) draws specific attention to the role of omega-3 essential fatty acids because of their direct relationships with the 5-HT system. It is proposed that early deficiencies in omega-3 essential fatty acids may lower 5-HT levels at critical periods of neurodevelopment and result in a cascade of suboptimal development of different neurotransmitters systems, resulting in suboptimal regulation of the frontolimbic system. Although the authors cite numerous animal studies on the effects of fatty acid deficiencies and supplementation, they acknowledge that studies assessing serotonergic changes following fatty acid supplementation in a double-blind, randomized, placebo-controlled way have not yet been conducted in humans.

To summarize, the limited data on the role of nutritional deficiencies in aggressive, antisocial behavior suggest that nutrients are a factor that should be taken into account when considering intervention or prevention programs for antisocial behavior. Well-designed studies are needed to elucidate the precise neurobiological effects of different types of nutrients (e.g., vitamins, omega-3 fatty acids) in reducing antisocial behavior. In the meantime, especially given that these nutrients are inexpensive, nontoxic, and readily available in specific foods, dietary interventions (including dietary education and improved dietary intake during pregnancy) should be given proper consideration, especially in the case of those most at risk for transferring or developing psychopathology.

Clinical Implications: Neurobiological Screening and Tailored Intervention

If one acknowledges that current interventions have achieved only limited success and that treatment resources should be prioritized, then a rational decision would be to replace the commonly used "blanket" approach with a more targeted one, involving screening for existing neurobiological impairments and assessment of environmental risk factors that impact on neurodevelopment. How would one proceed in selecting children for intervention who are at risk for developing antisocial behavior later in life?

We already described in the sections on stress response systems how at-risk children could be identified and different subgroups could be assigned to more tailored forms of intervention. In addition, it is possible to screen children for risk status (e.g., high–low) based on a genetic screening procedure. For example, those having the short (s) allele in the 5-HT transporter gene linked polymorphic region (5-HTTLPR) have been found to show increased stress vulnerability and altered volumes and function of specific brain structures (Canli et al., 2005; Caspi et al., 2003; Hariri et al., 2002; Pezawas et al., 2005). Moreover, those with lower MAOA expression show reduced volumes in limbic brain regions, amygdala hyperreactivity, and diminished responses in the prefrontal cortex (Meyer-Lindenberg et al., 2006). These genetically identified children are considered to be at greater risk for developing behavioral problems, and therefore, could be prioritized to receive early intervention if it is known that they are being maltreated (otherwise you would be targeting ~35% of the population!). The intervention, depending on a proper assessment of environmental risk factors, could involve a program of frequent home visits, in which trained staff provides guidance and support, or focus specifically on fostering the development of secure attachment relationships between infant and mother (see Cicchetti, Rogosch, & Toth, 2006, for an example of an intervention involving 1-year-old infants from maltreated families). Research by Olds and colleagues (2002) and Cicchetti and colleagues (2006) support the positive effects of early interventions on maternal and child outcomes.

The causal mechanisms, how these effects occur and in whom they occur, remain, however, unclear. Active parenting can modify neurodevelopment and induce resilience to stress (Suomi, 2003). As such, parenting programs not only reduce psychopathology in children of the families that are treated, but may also disrupt epigenetic transmission of problem behavior to future generations. Specifically, the early environment can affect genetic programming by influencing the promoter region of the gene; maternal care changes gene expression and behavioral traits, and

these effects are maintained throughout the life span (Kaffman & Meaney, 2007). Thus, these early interventions could be effective in deflecting the path of the would-be life-course persistent offender.

At present, we do not know precisely how parenting enhances resilience in children, and future research on the moderating role of the caregiver on the developing brain systems of the child is badly needed. It is important that we find out what aspects of the caregiver–child relationship are significant in modifying genetic risk, how caretakers can help improve their children's resilience to stress, and what the critical period is for these functional consequences to occur. Elucidating these causal mechanisms should be one of the main goals of our future research efforts.

To summarize, we have argued that that some form of neurobiological screening could be done to replace the current "scattergun"-type approaches, and that the chances of enduring success will be greatest if interventions are offered when at-risk individuals are young because of the greater plasticity of the brain in early life. The implication is that we should prioritize resources to children and parents who have distinctive neurobiological risk profiles, in contrast to the approach of current programs such as Head Start (USA) or Sure Start (UK). Further research is particularly needed to investigate the mechanisms involved in this heightened sensitivity to stress, because this information could lead to interventions capable of reversing some of the deleterious consequences of maltreatment.

A Developmental Perspective

It is clear that the structure and function of the stress and neurotransmitter systems change over the course of development. We mentioned the existence of critical periods in development (i.e., prenatal, early postnatal, adolescence) and discussed early environmental factors that can influence the developing neurobiological systems. Although we are clearly beyond the stage of circumstantial evidence that links early experience to HPA reactivity, personality types or ability to cope with challenge, current evidence is primarily correlational in nature (Vasquez, 1998).

From a neurobiological point of view, there is, in particular, an urgent need to understand both normal and altered mechanisms of brain development (Gunnar et al., 2006). There is also a need to identify the maturational changes in the vulnerability of the systems that are relevant for our understanding of developmental psychopathology in general, and serious antisocial behavior in particular (i.e., the HPA axis, the amygdala, the hippocampus, and the 5-HT system). Moreover, although it is difficult to extrapolate findings from nonhuman animal research in which development and neurobiology can be manipulated to humans with a constellation of neurobiological abnormalities and impairments, future studies should also investigate interactions between different systems, for example, the 5-HT and HPA axis systems. To address all of these goals, prospective longitudinal studies conducted in large cohorts of normal and at-risk children are required, which start early in life.

We also need to set up these studies from a psychological point of view. Given that concurrent data cannot distinguish between substantively different interpretations of the associations between family (including genetic) factors, neurobiological, cognitive, emotional, and behavioral functioning, a critical next step in building this area of research is to conduct prospective longitudinal studies that permit tests of the mediating and moderating factors that underlie early adverse influences on antisocial behavior in childhood. Collecting prospective data improves the confidence with which one can infer cause and effect relations because it provides an opportunity to examine changes in constructs over time, allows for tests of the influence of children's behavior on family adversity and vice versa, and makes it possible to control for a negative affectivity bias that might artifactually inflate zero-order associations between measures of cognitive, emotional, and behavioral functioning in childhood (Van Goozen et al., 2007). In addition, longitudinal research designs provide the opportunity to control for initial levels of behavioral disruption (e.g., aggression) so that the impact of such disruption on neurobiological, cognitive, and emotional functioning may be assessed over time. Longitudinal studies, however, cannot provide definitive support for a causal relation between constructs because of the

possibility that an unmeasured third variable could account for the associations, both concurrently and over time. Complementing longitudinal correlational studies with carefully designed and conducted experimental studies (a multimethod approach) serves as the "gold standard" by which future research in this area may be evaluated (Van Goozen et al., 2007).

The mediating role of neurobiological functioning

We have proposed that a combination of genetic factors, either directly influencing the development of different neurobiological systems, or in conjunction with early exposure to adversity, act to predispose the individual to more severe and persistent antisocial behavior (Van Goozen et al., 2007). We also proposed that an early deficit in HPA axis functioning and ANS system activity is particularly crucial in this developmental sequence, because it results in the individual becoming emotionally detached from his or her actions and unable to learn from what others might experience as negative events (e.g., punishment situations). If, as discussed above, the cortisol (HPA) and ANS responses to stress act as a form of "warning signal" to restrain ongoing behavior in situations of (psychological or physical) danger, then children who fail to activate these systems are likely to behave in a more disinhibited fashion. Again, this could arise because of genetic factors (such as polymorphisms in the gene encoding the glucocorticoid receptor, which confer increased sensitivity of HPA axis feedback mechanisms) or through exposure to uncontrollable stress or maltreatment in early childhood. Together, these factors permanently compromise HPA axis and ANS function.

We noted that it is not the case that antisocial children fail to realize they are in danger or face punishment; they have a "hostility bias," which leads them to appraise even ambiguous or innocuous situations as threatening (e.g., Milich & Dodge, 1984), and they experience more intense negative emotions than controls when stressed (Van Goozen et al., 2000). Rather, their appraisal of the situation is not accompanied by contextually appropriate patterns of emotional arousal, and does not lead to activation of autonomic or endocrine stress response systems. Moreover, children who, as a result of their risky or impulsive behavior, place themselves in threatening or dangerous situations might gradually become further desensitized to stress, because of habituation. This leads to a vicious circle in which the child becomes increasingly resistant to stress and therefore places him- or herself in increasingly threatening situations. As a result of this genetically based hypersensitivity of the HPA axis, together with the experience of negative life events and frequent exposure to situations that other children experience as stressful, antisocial individuals may become unable to initiate normal stress responses in conditions that typically evoke anger, fear, or embarrassment (Van Goozen et al., 2007).

These neurobiological consequences of genetically based hypersensitivity of the HPA axis, early exposure to chronic stress, and self-selection for exciting but often dangerous or punishing environments have predictive power in terms of discriminating between those who persist in antisocial behavior and those who desist from such activities (Van Goozen et al., 2007). Those individuals who are considered high risk because of the presence of early-life adversity, parental criminality, or antisocial personality disorder, but who exhibit preserved or even enhanced basal ANS or HPA axis activity or reactivity to stress, seem to be protected from engaging in antisocial behavior or exhibit desistence from such behavior (Brennan et al., 1997; Van de Wiel et al., 2004). It is of interest that this finding holds even in adolescents who were already engaging in antisocial behavior (Raine et al., 1995) or who were clinically diagnosed with CD in childhood (Van Bokhoven et al., 2005). Thus, normal HPA axis functioning and high autonomic reactivity both appear to serve as protective factors that permit the individual to exercise a greater degree of self-control over behavior. Raine et al. (1997) proposed that those who desist from antisocial behavior have a more open attentional stance to the environment, as opposed to the narrowly focused attention of the persistent offender. Because of their attentional openness, the desistor group is more responsive to new situations or new behavioral contingencies, and also more fearful and conscientious (see also, Babcock, Green, Webb, & Yerington, 2005).

Neuroethical Issues

Our recommendation to use neurobiological research in the screening and treatment of antisocial children raises a number of ethical concerns. Some of these are directly related to ethical aspects of the technologies involved, examples being brain stimulation, psychopharmacology, neurofeedback, and neuroimaging. Further, the attempt to localize antisocial or psychopathic behavior and explain this in terms of the pathological functioning of a specific part of the brain has significant moral implications. A third ethical concern is related to the power of neurobiological and physiological research to predict future psychopathology. As argued above, at present, the state of knowledge is relatively limited, and many interesting findings from the neurobiological domain await replication and extension. In addition, even well-established findings (such as low HR in antisocial populations) are only applicable at the group level; they are insufficiently selective or specific to be used in their own right as diagnostic tools. Despite these ethical problems, neurobiological research may well be used in the future to prevent, diagnose, and treat a variety of disorders and social problems. As Canli and Zamin (2002) put it: "These approaches could identify vulnerability factors for psychopathology such as structural abnormalities, dysfunctional metabolism, or activation patterns. Preventative interventions such as medication, cognitive therapy (like anger management therapy for antisocial individuals with prefrontal damage but not those with amygdala damage), or life style changes could be motivated by these data, and progression toward psychopathology could be monitored" (p. 428). We believe that future interventions and treatments would profit from this approach because it will enable us to identify subgroups of individuals in whom different causal processes initiate and maintain behavioral problems. This will ultimately result in a more optimal match between patient and treatment.

Conclusion

Antisocial behavior in children with CD is persistent and difficult to treat. Although behavioral interventions have been shown to be effective in mild forms of these disorders, their effectiveness in more seriously disturbed children is limited. This is partly because of the fact that we lack a comprehensive understanding of the cognitive and emotional problems of these children and the neurobiological causes of these difficulties.

At present, we do not know what causes the pattern of neurobiological impairments observed in CD children, although it is clear that genetic factors are involved (Caspi et al., 2002). An important line of research suggests that psychosocial adversity affects the development of the brain in early life. Knowing that many CD children have problematic backgrounds, it seems possible that they have been exposed to severe stress, and that these experiences have had neurodevelopmental effects. There is clearly a need for longitudinal research in high-risk children to shed more light on this issue.

If it is the case that CD children are characterized by neurobiological impairments, pharmacological interventions should be taken into consideration as a treatment option. It is also important to realize that the impairments in stress response system and neurotransmitter functioning described above may disrupt the types of cognitive or emotional processing that normally play a crucial role in therapeutic interventions. Thus, CD children with attenuated stress (re)activity may be more effectively treated using pharmacologically based therapies that reinstate normal HPA axis functioning, perhaps as a precursor or adjunct to psychological treatments. This is an important line for future research.

A final point is that the tendency to focus on persistence of antisocial behavior runs the risk of leading us to ignore the fact that a substantial proportion of children with CD do *not* grow up to be antisocial adults. A study of the neurobiological factors involved in antisocial behavior may also explain this observation: there are promising data from a small number of studies showing that neurobiological factors differ between antisocial children who persist in and desist from engaging in antisocial behavior (Brennan et al., 1997; Van de Wiel et al., 2004). Further research on this issue is also urgently needed.

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