

# Aggression in young children with concurrent callous-unemotional traits: can the neurosciences inform progress and innovation in treatment approaches?

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Parenting is the 'clean water' of healthy psychological development and parenting interventions remain the number one treatment at the individual and community levels for early-onset aggression and antisocial behaviour in children. However, recent progress in child psychopathology research is specifying a number of biological mechanisms that interact with environmental risk to influence pathways into aggression and antisocial behaviour. After a brief review of the parent training literature, we focus on child factors, especially callous-unemotional traits, that parse 'aggressive' children into more homogeneous groupings, and then review selected ideas about the origins of aggression coming from the neurosciences (such as neurobehavioural responsivity to emotional stimuli; hypothalamic-pituitary axis abnormalities influencing low cortisol and low serotonin production). We review human and, where relevant, animal models of neurobiological system changes with particular attention to developmental timing and interactions with environmental factors, especially parenting. Based on this innovative research, we then discuss a number of ideas that hold potential for interventions. We conclude that the future will see the development of interventions that aim for synergy between specific biological processes and psychological experiences as they unfold developmentally. The use of D-cycloserine in fear extinction and oxytocin in affiliative bonds is used as an example of these futuristic approaches.

Keywords: callous-unemotional; treatment; children

## 1. INTRODUCTION

Violence and antisocial behaviour (VAB) are a consistent and central feature of human history. Approaches to understanding their causes, manifestations and remediation cover all aspects of human endeavour: religious, sociological, medical, legal and ethological. The focus of this paper is the use of the emerging tools of neuroscience and psychology to present a speculative discussion of one particular type of VAB: the individualistic type that characterizes the life histories of a small but significant number of people, usually males, in all societies. By this we mean a chronic pattern of self-interested behaviour that offends against the rights of, and thus causes harm to, other people and society in general.

The natural history of this behavioural pattern is quite well known (Loeber & Farrington 2000); it usually begins early in life as repetitive oppositional behaviour, impulsivity and aggression in the child, with his environments typified by violence and instability. Across the years he progresses through a series of predictable milestones, such as school failure, drug use and criminal involvement, developing a pattern that

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once established is largely intractable to the efforts of our juvenile justice and psychiatric systems. Thanks to decades of research, we also know a lot about how to best identify and manage these problems, as a lot is known about how, when and why interventions work and do not work. The first section of this paper will briefly review evidence for the effectiveness of current interventions. As will be shown, there are wellcharacterized and evaluated interventions that can successfully remediate and prevent early pathways into VAB. We also have a wealth of information about when these interventions fail to produce change. This will lead us to a discussion, necessarily speculative, about whether the rapid progress being made in the neurobiology of VAB can help inform the development of new approaches to help us when the traditional interventions fail.

First to the successful treatments; put simply, parenting is the 'clean water' of mental health and parenting interventions are the clean water of child psychiatry. Early identification of VAB (viz. roughly before adolescence) that leads to effective engagement of the families of such children into best-practice services can and does lead to a positive change in a large proportion of cases (Serketich & Dumas 1996). There is little point in reviewing the literature in support of this claim here, as decades of research has led to several review papers and a number of meta-analyses. Overall,

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this literature shows that parenting interventions focused on teaching parents how to positively engage with their child and promote prosocial behaviour, and effectively reduce aggression and antisocial behaviour using non-violent, sensitive discipline strategies, which are the treatment of choice for the early emergence of VAB.

The science of these parenting interventions began in the 1960s when pioneers such as Gerry Patterson, John Reid, Robert Wahler and Rex Forehand applied operant learning theory to understand how parent's and children's behaviour shapes and maintains each other's aggressive versus prosocial behaviour. The idea of 'coercive family process' in which aggressive loops become self-sustaining (Patterson 1982) is arguably one of the great ideas of the 20th century in the behavioural sciences. Importantly, these researchers showed empirically that programmed changes in parental responding led to reliable and clinically significant changes in child behaviour. From the 1980s onward, programmes were packaged into readily disseminated modules that have spread all over the world and have considerable empirical support in efficacy and effectiveness trials, for example, The Incredible Years (Webster-Stratton 1998), Triple P (Sanders & Turner 2005) and Multisystemic Therapy (Henggeler 1999), just to name a few. It is difficult to overstate the conclusion, from research across all major continents of the world, that these interventions represent one of the major achievements of the mental health sciences.

There are three important riders to this conclusion. First is the issue of 'reach'. Many children and their families do not access these best-practice services (Turner & Sanders 2006). The reasons for this are many, including unavailability of local services and expertise, family alienation from the health care system and chaotic families that are not consistent in attendance and tend to dropout. Consequently, an important focus of current clinical research and service development is to maximize the extent to which high-risk children are afforded effective services. To date, there are several lineages of such research. Of particular note is the creative application of public health models of service delivery to these parenting interventions (Prinz & Sanders 2007). At the other extreme, even simple solutions such as telephoning parents to prompt their attendance at appointments can improve engagement rates in parents of VAB children (Watt et al. 2007).

The second rider is that families of children showing early signs of VAB are often beset with a range of other mental health and social problems. Reviews, such as Miller & Prinz (1990), have documented the common co-occurrence of interparental violence and discord, depression, substance abuse problems, social isolation and poverty that pose direct threats to our ability to engage and produce change in parent-child processes and outcomes. The main challenge, and one that the behavioural sciences has not shied from, is to integrate the parenting interventions into broader clinical approaches. The primary aim of these interventions is to address the multiple problems of many of these families without producing cluttered and cumbersome interventions that are impossible to implement except by the most skilled and motivated clinicians. Again

there are many examples of empirically supported programmes that specifically provide clinical strategies for managing complex systems of family problems associated with VAB in young children (e.g. Henggeler & Borduin 1990; Sanders & Turner 2005; Dadds & Hawes 2006).

The third rider is the one that has received relatively little attention and thus will be the main focus of this paper. While much effort is underway to parse the heterogeneous population of aggressive children into more sensible subgroupings, they are still treated as a unity with respect to best possible treatments. Given that parent training literature arose from within a social learning perspective, it is not surprising that the traits of the children themselves attracted little attention. However, recent evidence suggests that child factors are predictive of outcomes; further, there appears to a small proportion of children who do not appear to benefit from the receipt of our best available services.

For example, Hawes & Dadds (2005) recently showed that young oppositional boys with a 'cold' temperamental form of aggression (callous-unemotional, CU traits) did not benefit from improvements in parenting relative to their 'hot' peers. In this study, a sample of boys from 3 to 8 years of age were treated using a standardized parenting intervention and measures were taken pre-, post- and at six months follow-up. As a group, the parents and their sons showed a typical no-diagnosis rate of approximately 60% at the completion of treatment. Having high-CU traits was a unique predictor of poor response to treatment even after controlling for parenting and family characteristics, socioeconomic status, parent's implementation of the programme and other characteristics of the child. Direct observations of the parent-child interactions in the home showed that the only variable differentiating the high-CU group was their responsiveness to the 'timeout' procedure. When removed from ongoing interactions and placed in a quiet area due to aggression or antisocial behaviour, these children showed little emotion and their parents rated this particular procedure as less effective than did parents of the low-CU children.

This observation squares well with literature showing that high-CU children are generally less emotional, less influenced by parenting and more likely to have a genetic basis to both the CU traits and their aggressive/antisocial behaviour (Frick et al. 2003). More generally, it exemplifies that there are specific traits that characterize and differentiate children's problems into groups that may have very different aetiologies and thus require different treatment approaches. There can be no doubt that the future will see increasing differentiation of VAB children into meaningful subgroups, but at present the dichotomy of VAB children into high- versus low-CU traits is receiving considerable support for its predictive validity and will be used throughout the rest of this paper. Given the high genetic loading for VAB in the high-CU subgroup (Viding et al. 2005), it is probable that neurobiological markers may be more evident. In what follows, we will first ask what is it about high-CU traits that make them more immune to parenting. This will take us into the fascinating area of emotion

processing. We will also review animal models of early bioparenting interactions, and we will speculate about how specific patterns of disturbance might be targeted using combined or synergistic biological and behavioural procedures. Two examples of emerging work will be drawn upon to illustrate this potential: oxytocin (OT) in attachment processes and cycloserine in fear learning.

# 2. EMOTION PROCESSING AND CU TRAITS IN **CHILDREN**

Analysing how people respond to emotional faces has become a major tool in the neurosciences; the emotional face is a 'superstimulus' (e.g. Tinbergen 1951) that automatically sets off specific neural systems that are central to our emotional and interpersonal lives. There is increasing evidence that neural and behavioural responses to emotional stimuli, specifically emotional faces, differ between healthy people and those with various forms of psychopathology. There is also some evidence that specific responses to particular emotions (e.g. fear versus anger versus happiness) can differentiate between various forms of psychopathology such as bipolar disorder, depression, anxiety and aggression (e.g. Guyer et al. 2007; Leist & Dadds submitted).

Of particular interest to us is that the adult psychopaths, those with cold forms of VAB, and even children with psychopathic tendencies, are hyporesponsive to emotional faces, particularly those displaying fear (see Blair 2003 for a review). That is, they show deficits in recognizing fear on other's faces, as well as diminished behavioural and visceral responses to these stimuli. Recent studies with adult psychopaths have shown diminished responses in the amygdala to such stimuli using functional magnetic resonance imaging (fMRI) mapping (Deeley et al. 2006). Systems within the amygdala modulate attention and responsiveness to emotionally salient stimuli and form links between cues and salient outcomes. One of the most reliable ways for eliciting a response in the amygdala is to present a fearful face. While the amygdala is responsive to any emotionally salient cue, it is highly reactive to the configuration of widened eyes with the whites enlarged as seen in fear (Fox & Damjanovic 2006).

Why would psychopathy and indeed children with CU traits be associated with deficits in recognizing fear? Can this finding help inform how best to help these children? Adolphs et al. (2005) have conducted extensive work on the neural bases of fear blindness. In particular, they showed that fear blindness in an amygdala-damaged patient is due to neglect of the eye region; unlike healthy people, the patient fails to naturally attend to the most emotionally salient aspects of the environment; in this case, the eyes of other people. Interestingly, the patient also showed that this deficit could be overcome by asking the subject to look at the eyes of the target face; there was no problem recognizing fear once the relevant data were accessed.

Might fear recognition deficits in children with high psychopathy traits also be due to attentional problems? A recent study found that adolescent high-CU males showed the expected deficits in fear recognition, but that these disappeared when the participants were asked specifically to 'look at the eyes' of the stimulus faces (Dadds et al. 2006). When asked to 'look at the mouth' of the stimulus faces, their deficits in fear recognition returned. These findings suggest that children with high-CU traits have problems with the allocation of attention to critically salient aspects of the environment similar to those with fear blindness due to amygdala damage.

In a follow-up study, Dadds et al. (in press) used computerized eye tracking to measure gaze characteristics of young males while viewing a series of emotional faces. The results showed that the CU traits were associated with deficits in the attention given to salient emotional aspects of the environment; in this case, the eyes of other people. This deficit is one of the reasons that people with high psychopathy have trouble recognizing fear, the emotion that is uniquely associated with communication via the eyes. The study also shows that the deficit is present at least as early as adolescence.

The eyes of course can be regarded as 'superstimuli' (Tinbergen 1951) to humans and in healthy people sets off various automatic processes, perhaps the most basic of which is immediate attention. This automatic attention to the eyes of other people occurs very early in the newborn child and is intricately involved in attachment processes and the development of many human qualities such as the development of empathy and theory of mind (e.g. see Skuse 2003). What happens when a child lacks the automatic tendency to focus on the eyes of others? The answer is not fully known but there are good reasons to believe that the deficit will interfere with parent-child bonding, depriving the child of the building blocks for the development of empathic concern, and specifically, all but only the most superficial information about the consequences of his/her behaviour towards other people.

Blair (2003) has presented a number of models of how deficits in fear recognition may signal a failure of violence inhibition mechanisms. That is, mammals will generally inhibit aggression once a conspecific demonstrates submission. If one cannot recognize submission or distress, it is probable that the aggression will arise and continue unmodulated. We feel that the explanatory strength of this model will increase when couched in a developmentally precise context. That is, as well as representing a failure to inhibit aggression, failure to attend to critical emotional cues will compromise the development of more complex human systems that require emotion recognition as a building block. Typical examples of this would be the development of attachment bonds, empathy, moral conscience and theory of mind. Most of these building blocks are laid down in infancy.

Our knowledge of early attentional processes, neural function and parent-child interactions is quite limited for the human; however, there is a lot to be learned by some of the exciting work currently being done using animal models. Specifically, these models show that there are critical periods, very early in life, in which the interactions between parenting and biological processes in the young animal are synergistic and productive of lifelong changes in the biological and behavioural propensities of the mammal. To fully appreciate this work we need to

first introduce two neurobiological systems that are known to play a role in VAB. As we will see, there is emerging evidence that the cortisol and serotonergic systems may function differently in emotionally reactive versus high-CU children with VAB.

# 3. HYPOTHALAMIC-PITUITARY AXIS FUNCTION DIFFERENTIATES SUBTYPES OF VAB AND IS RESPONSIVE TO EARLY PARENTING

Information about the role of the hypothalamic-pituitary axis (HPA) in mental health is primitive yet promising and there is clear evidence that the system plays a role in the development and expression of VAB (Van Goozen et al. 2007). Further, its role is intimately linked with the history and quality of parenting the child has received and its specific patterns of disturbance may help us understand the hot versus cold expressions of VAB in young children. The following focuses on two key aspects of HPA functioning: the cortisol and serotonergic systems and their relationship with early parenting experiences.

Cortisol is a hormone involved in stress response modulation and is a rough marker of stress reactivity in humans and rats (as corticosteroids). In people who have suffered acute stress (trauma sufferers) and those who are highly reactive to challenges (high anxious people), cortisol levels are generally elevated. Of interest, low cortisol is a marker of people with high and chronic levels of VAB, especially the cold or high-CU traits subset. This has been found in adult perpetrators of violent crimes and 'psychopaths' (see Van Goozen et al. 2007), and children with 'psychopathic' traits (Loney et al. 2006). This finding is typically interpreted within a broad understanding that psychopaths are fearless and not perturbed by the outcomes of their behaviour and effects on other people. However, recent animal models indicate that there is a lot more to be learned about cortisol in early learning about threat and the interpersonal attachment systems in which this learning occurs.

The first example comes from the innovative work of Sullivan et al. (e.g. Moriceau & Sullivan 2005): all young mammals will naturally seek out and remain centred around the nest and the mother. Pairing the smells of the mother/nest with an aversive stimulus produces radically different effects depending on the age of the pup. After approximately 9-12 days of age, a pup that associates the nest with discomfort will show avoidance; before that time, the opposite occurs. Strong associations between the nest odours and discomfort will ironically lead to increased preference for the nest. Around this time, the amygdala of the pup undergoes rapid growth and this change is dependent on activation of corticosterone (or cortisol in humans) in the system at that time. Thus, with sufficient cortisol, amygdala functioning emerges and is associated with learning to recognize and avoid aversive stimuli in the environment. Dysfunction of the cortisol systems associated with hypo-amygdala responsiveness leads to an organism that exhibits diminished registration and avoidance of aversive stimuli. Taken together, this shows remarkable parallels to the characteristics of the low-CU or psychopathy subset of VAB.

Other works have shown more directly the important role of serotonin and cortisol in the development of 'normal' versus cold aggression. Haller et al. (2005) found that in rats, there is an inverse relationship between activation of serotonergic systems (5-HT neurons in the dorsal raphe nucleus) and attacks on non-vulnerable targets (offensive or normal aggression), which is consistent with an inhibitory influence of serotonin on aggression. By contrast, serotonergic systems appear unrelated to attacks on vulnerable targets (abnormal predatory aggression). Similarly, lesions of various serotonergic systems modulate offensive, but not predatory, aggression (de Bruin et al. 1983). In humans, it is well known that serotonergic medication can be used to reduce 'emotional' or hot aggression in certain personality disorders, but has little or no effect on aggression in chronic offenders. Haller et al. (2005) suggested that the reduced influence of serotonergic system (5-HT) in cold aggression could be due to the overriding effects of central amygdala activation or changes in prefrontal cortical functioning. Alternatively, it is possible that low glucocorticoid secretion impairs the functioning of the 5-HT system, which explains the low efficacy of serotonergic system (raphe neurons) in controlling aggression under these circumstances.

Various authors have argued that serotonergic 5-HT stabilizes information processing in various neural systems, resulting in controlled behavioural, affective and cognitive output. Spoont (1992) argues that high levels of 5-HT lead to excessive restraint, cognitive inflexibility and anxiety, whereas low levels lead to disinhibition and distractibility. Coccaro *et al.* (1997) proposed that the threshold for aggressive reactions is modulated by overall 5-HT system function. Low serotonergic function may disinhibit aggression (to self and others) by lowering thresholds to stimuli that elicit irritation and aggression and blunting sensitivity to cues that signal punishment (Spoont 1992).

Of particular interest to this paper is that there is emerging data to show that serotonin manipulations may directly influence the facial emotion processing. As noted, it is well known that serotonergic agents can stabilize mood and thus reduce irritable aggression in people with various forms of mood and personality problems. Merens et al. (2007) reviewed empirical evidence that the effects of serotonin on mood are mediated by specific changes in the emotional information processing. They presented clear evidence that even short-term manipulations of serotonin levels produce reliable changes in responses to emotional faces, including recognition skills, and that these are particularly evident for fear faces. The specific direction of change was predicted by the pre-existing levels of psychopathology in the subjects, their baseline skills in emotion recognition, and whether the serotonin effects were measured immediately or over longer courses of treatment. This work is important in showing that common mood stabilizers might in part work by changing basic emotion recognition processes. While provocative, the review reported no such research with children and no focus on aggression.

While the exact determinants of various forms of aggression are likely to involve multiple interacting biological and behavioural systems, the above examples show that differentiating cold versus hot aggression by serotonergic versus cortisol systems has support across multiple research methods and species. The main advantage of Sullivan et al.'s (see Moriceau & Sullivan 2005) and Haller et al.'s (2005) animal models is that they show that experimentally induced changes in these systems lead directly to the changes in stimulus preferences and aggression, respectively. Therefore, these changes are more than just correlational artefacts of an overwhelmingly complex system. In natural development, complex interactions of various systems are likely to be the rule. For example, serotonergic function interacts with testosterone through puberty. Keleta et al. (2007) assessed the interactive effects of chronic anabolic-androgenic steroid (T) exposure and brain serotonin (5-HT) depletion on aggression in pubertal male rats. Serotonin depletion resulted in significantly decreased locomotor activity and increased irritability, but had no effect on sexual behaviour, partner preference or aggression. T alone had no effect on locomotion, irritability or sexual behaviour, but increased partner preference and aggression. The most striking effect of combining T with serotonin depletion was a significant increase in attack frequency as well as a significant decrease in the latency to attack, particularly following physical provocation. Similarly, in humans, Popma et al. (2007) showed that cortisol moderates the relationship between testosterone and aggression in VAB boys such that low cortisol amplifies the relationship of testosterone with overt aggression through this critical period.

So can these models be related back to parenting and the young child at risk for VAB? Baby rhesus monkeys suffering high rates of maternal rejection and abuse in their first month of life often produce less serotonin and these effects can come to characterize families through generations. In a study conducted by Maestripieri et al. (2006), the effects of maternal behaviour on brain serotonin in the offspring were observed in both infants who were reared by their genetic mothers and those reared by foster mothers. Infants who became abusive as adults had approximately 10-20 per cent less serotonin than did infants who did not become abusive as parents or infants who were not exposed to maternal abuse.

It is interesting that in most of the animal models, the age at which the effects are brought about is critical; however, once established, the effects remain remarkably constant throughout adulthood (e.g. Maestripieri et al. 2006; Kaffman & Meaney 2007). However, through childhood, variations in the system of interest may be the rule. Given that our treatments are generally aimed at preventing the problem from becoming a permanent feature, understanding of its early course is a priority. In one of the few longitudinal studies of serotonergic function, Auerbach et al. (1999) categorized children according to their polymorphisms of the serotonin transporter promoter gene (5-HTTLPR) and assessed emotional reactivity through the first year of life. At two months of age, infants possessing the short/short (s/s) alleles of 5-HTTLPR (low serotonin) received higher scores on the negative emotionality and distress to limitations scales than those infants possessing the short/long (s/l) or long/long (l/l) alleles. At 12 months, the association

reversed; infants with the s/s alleles did not show more negative emotionality and actually scored significantly lower on measured behaviours such as intensity of facial fear, intensity of escape behaviour and active escape manoeuvres. The authors speculate that these changes are probably due to complex bioenvironmental interactions in which early emotionality may elicit more concern and attention from their carers, which in turn helped these infants to become able to best regulate their own behavioural arousal or distress.

While this is speculative, it is consistent with the finding of developmental change in behavioural characteristics associated with high vagal tone. High vagal tone in early infancy is related to higher distress and negative reactivity, whereas by 14 months, high vagal tone can reverse and be associated with positive outcomes of sociability and ease of approach (Calkins & Fox 1992). Similarly, Sullivan's (see Moriceau & Sullivan 2005) demonstration of critical period reversal in cortisoldependent associative learning in the rat pup again alerts us that timing is crucial in understanding the important interactions between biological development and the parenting environment.

One of the dramatic demonstrations of the effects of parenting on lifelong changes in biological vulnerability comes from Meany's work on the nurturance and the epigenetics of brain development (e.g. see Kaffman & Meaney 2007). His initial work showed that natural variations in the degree to which mother rats lick and groom their offspring varies naturally and produces important changes in the behaviour of pups. Over the years, his impressive body of literature has expanded to where we now know that: environmental adversity results in chained patterns of parent-offspring interactions; and low levels of nurturance (licking and grooming) increase stress reactivity in the pup through sustained effects on gene expression in brain regions known to regulate behavioural, endocrine and autonomic responses to stress. While such effects might be adaptive, the associated cost involves an increased risk for stressrelated illness (see Parent et al. 2005 for a review).

In conclusion, we have seen in this section that the neurobiology of VAB varies according to the type of aggression; the distinction between hot and cold (or CU in humans?) maps nicely onto distinctions between serotonergic and cortisol-dependent functions. Put simply, in both humans and animals, there is clear evidence that serotonergic dysregulation appears to be related to decreased thresholds for explosive violence, whereas low cortisol appears to be associated with colder more predatory violence associated with low capacity for fear, aversive conditioning (or punishment insensitivity; see Dadds & Salmon 2003) and is probably associated with diminished amygdala involvement in attention to and responsiveness to emotionally salient stimuli. These relationships are unlikely to be linear; rather, complex interrelationships between hormonal and neurobiological agents (for example, testosterone and 5-HT) that occur at critical and sensitive periods for critical epigenetic and neural transcription (e.g. early nurturance and epigenetic changes to hippocampal development; testosterone and 5-HT transporter at puberty; cortisol and amygdala development in aversive attachment conditioning during days 6–12 in rat pups) will be the rule.

By way of linking this section on the biological underpinnings of hot versus cold aggression back to the earlier section on emotion recognition, recent research has linked genetics, serotonergic function and emotion recognition using fMRI methods. As noted, adults with psychopathy show reduced amygdala activation when presented with fear faces and this is consistent with most theories of psychopathy as involving a core deficit in emotional responsiveness. While not 'psychopathic', men who have suffered early childhood abuse and violence and have the short polymorphisms of the monoamine oxidase A gene associated with low serotonergic function are at risk for chronic antisocial behaviour (Caspi et al. 2002). However, these men show hyperresponsiveness of the amygdala to fear faces in fMRI studies (see Meyer-Lindenberg & Zink 2007). These findings bring current findings about the genetics of VAB into the equation relating responsiveness of the amygdala as a marker of cold and hot forms of VAB.

It should be noted that the above discussion does not lead us to the obvious corollary that interventions that directly modify serotonergic and cortisol function may help with VAB. Unfortunately, medications for diminished serotonergic and cortisol function are intensive and intrusive in that they require long-term daily use and are characterized by variable side effects, and there is little evidence to suggest that they reduce aggressive behaviour in antisocial populations. While serotonergic drugs are used in adolescents, and sometimes in children, primarily for depression and behavioural problems related to mood instability, they offer little in the way of a general intervention for the early development of VAB except for extreme cases of explosive aggression. However, more potential might be realized should we learn more about the conditions, both behavioural and biological, that are associated with healthy serotonergic and cortisol function.

# 4. IMPLICATIONS FOR THE DEVELOPMENT OF INNOVATIVE INTERVENTIONS

The above discussion leads us back to the question of whether interventions can produce positive changes in children's attention to and understanding of the emotional environment directly through the HPA and neural systems that support these functions, and the environment that shapes their expression. There are several promising indications.

In terms of behavioural interventions, it has been shown that simply directing people's attention to emotionally significant stimuli does alter their registration and understanding of these stimuli (Dadds *et al.* 2006); however, it is unlikely that this could lead to any long-term gains without some other powerful changes in place. When adults with autism are trained to attend to and interpret emotional faces, their accuracy levels increase and compensatory changes in neural activity, measured via fMRI, are observed (Bölte *et al.* 2006). Thus, in the short term at least, there is evidence that targeted training in reading emotions does lead to change.

With children, it is probable that such changes would have the best impact if timed to coincide with relevant development changes and placed in the context of ongoing parent-child interactions. Recent work on emotion talk between children and their attachment figures has shown that children's understanding of the emotional world and their own emotions can be enhanced by training parents to regularly engage their offspring in conversational reviews of day-to-day emotional events. The impact of these interventions have so far been demonstrated in healthy (Reese & Newcombe 2007) and clinically referred children (Salmon *et al.* submitted), but data on the impact of the interventions on mental health are yet to be gathered.

Emotional attention and understanding can also be altered biochemically. Animal research has shown that the neuropeptide OT enhances social recognition and approach behaviour, while decreasing social avoidance and aggression (Lim & Young 2006). These findings have led some (Bartz & Hollander 2006) to suggest that OT may have a role in the enhancement and treatment of relationships (i.e. parent-child bonds, couple distress), and the amelioration of disorders characterized by social deficits (i.e. autism, schizophrenia). Emerging research with humans has shown that OT nasal administration (24-27 IU) enhances trust (Kosfeld et al. 2005), identification of emotions from the eyes of others (Domes et al. 2007), the benefits of social support during social stress tasks (Heinrichs et al. 2003) and reduced responsiveness to social threat stimuli (Kirsch et al. 2005). For example, in Domes et al. (2007), 30 males received OT (24 IU) or a placebo before tests of one's ability to read subtle facial cues of internal emotion states. OT participants were better able to infer the emotion state of the actors and effects were stronger for faces rated difficult to read. Domes et al. (2007) argued that one possible mechanism underlying this effect was OT enhancement of eyegaze during face perception. Of relevance is that face perception is a basic process in interpersonal communication (Haxby et al. 2002). Critical information is taken from the eyes, and to a lesser extent the mouth, where individuals assess the degree of interest, threat and emotion of another (Haxby et al. 2002; Domes et al. 2007). In fact, amount of eye-gaze has been found to be predictive of one's ability to interpret the intentions of others and the meaning of social situations (Klin et al. 2002; Garrett et al. 2004; Spezio et al. 2007).

A recent study suggests that eye-gaze enhancement is one mechanism that may be associated with improved face perception and interpersonal communication from OT administration. Disorders characterized by deficits in communication and emotion perception, such as autism (Baron-Cohen et al. 2001; Klin et al. 2002; Dalton et al. 2005), schizophrenia (Loughland et al. 2002) and fragile X syndrome (Garrett et al. 2004), and of particular interest, psychopathic traits in young people (Dadds et al. 2006) are associated with deficits in face perception and eye-gaze. OT may have therapeutic value in the treatment of these disorders. Interestingly, the direction to focus attention towards the eyes in disordered populations ameliorates some emotion perception deficits (Dadds et al. 2006). Clearly, OT has the potential to be used in interventions that aim to alleviate social attachment and communication deficits.

The missing part of this research is the consideration of possible synergies between biochemical and behavioural interventions. Emotional training improves attention to and understanding of the emotional world, as does OT administration. What would result from carefully targeted interactions between the two? If OT improves some aspects of autism, what would happen if it was administered during training on emotion recognition tasks or, better, during intensive interactions with a loving carer? We argue that a key direction of this research should be to explore how such interventions can be integrated into caregiving relationships at sensitive developmental periods for children with specified deficits in emotion processing, such as the aforementioned children with CU traits and VAB.

There are precious few examples of the targeted use of bioagents to enhance specific psychological experiences. We are unaware of any synergistic biobehavioural interventions currently available for VAB in young people. Thus we will draw an example from another area: one of the more exciting developments of recent years has been the potential of biobehavioural synergy as exemplified by the use of D-cycloserine (DCS) in fear learning. While we are not claiming that this has direct relevance to the treatment of VAB, we conclude by putting this forward as a positive example of this emerging line of thinking.

# 5. INTERACTING BIOLOGICAL AND BEHA-**VIOURAL SYSTEMS: THE EXAMPLE OF DCS**

Pavlovian conditioning studies have shown that the partial N-methyl-D-aspartate agonist DCS facilitates the extinction of learned fear in animals when administered immediately before or even shortly after extinction training (Ledgerwood et al. 2003). It appears that DCS strengthens extinction memories, so they may be more easily retrieved during subsequent exposures to fear-relevant cues. When DCS is administered chronically to patients over weeks and months, it has no effect on symptoms of anxiety (Heresco-Levy et al. 2002). However, when administered acutely in combination with psychological extinction-based procedures, DCS may enhance treatment outcome in height-phobic (Ressler et al. 2004), social-phobic (Hofmann et al. 2006; Guastella et al. 2008, in press) and obsessive-compulsive (Kushner et al. 2007) patients (cf. two negative results with non-clinic subjects; Guastella et al. 2007a,b).

Overall, this research supports a radical new approach to the treatment of psychological disorders that enhances the adaptive learning that occurs in therapy via medication. That is, the DCS has effects that are specific to emotionally significant learning experiences. This represents one of the first demonstrations of targeted biological-behavioural interactions in the remediation of behavioural disorders. It is not a huge leap to imagine that the future will see the development of more of these synergistic interventions. That is, medications are used in short bursts during prescribed psychological experiences. What would happen if OT was administered to children who then experienced a targeted period of intense love and attachment with a responsive carer? How might the acute normalization

of cortisol functioning affect a child who was undergoing a prescribed series of positive experiences with emotionally significant scenarios?

These imagined interventions raise many questions, not the least of which are aesthetic and ethical, as do all fruitful innovations in science. For instance, how could we work to improve attachment bonds with parents who are absent, emotionally disturbed, or abusive? How palatable is it to society, let alone the specific parents and children, to be directly modifying the mechanics of attachment? Ultimately, the value of these will probably lie in the psychological context in which they are applied. That is, the use of medications for directly stopping VAB is ethically odious, even forgetting its low acceptability and thus low impact value. However, it is a different matter if medications could be applied acutely to enhance experiences that we know instinctively and scientifically to be 'good', i.e. psychologically healthy. Examples of this are facing and overcoming fears, communicating affection and understanding with loved ones and trusted carers, and learning to understand and care about the emotions of other people.

# 6. IMPLICATIONS FOR SPECIFIC PARENTING **STRATEGIES**

We would like to end by discussing the above with reference to the specific parenting strategies that are the centrepiece of available parenting interventions for early signs of VAB. As noted, these interventions fall into two broad categories: positive parent-child engagement and reward strategies in which parents are helped to establish positive engagement with their child and deliberately reward prosocial behaviour; and a non-violent discipline strategy for responding to instances of child VAB. The most common strategy used for the latter is 'timeout' in child instances of VAB, resulting in the child being temporarily removed from any reward for the aggression. Traditionally, these techniques were developed and continue to be interpreted within operant theory. That is, rewards are used to increase prosocial behaviour and timeout to reduce problem behaviour. However, the operant aspects of these procedures are only the tip of the iceberg, and many writers now invoke ideas from attachment and self-regulation theories to better characterize their implementation (e.g. Dadds & Hawes 2006). Clearly, any move to better understand the specific nature of the patterns of disturbance seen for problem children can lead to a rethinking of how these strategies can be best employed.

In this regard, we have been particularly interested in how these strategies work with hot versus cold variants of VAB. Our research has shown first that reward strategies are rated as effective with both variants (Hawes & Dadds 2005). However, timeout appears to be less effective with cold children (Hawes & Dadds 2005; see also Dadds & Salmon 2003 for a review of the idea of 'punishment insensitivity'). As noted above, these children are insensitive to emotional stimuli and tend to be less outwardly perturbed by timeout (Hawes et al. 2005). On the other hand, hot children become outwardly very emotional during discipline.

Our clinical work and the findings referred to above led us to propose the following corollaries for the use of the timeout technique. Hot children may be particularly sensitive to threat cues, and the reason for implementing timeout is often interpersonal in nature (an argument); allowing the emotion to escalate before implementing timeout is problematic. More specifically, during the instructions for the child to go to timeout, close and direct eye contact with the parent can lead to acutely elevated stress responses and result in escalation and aggression from the child. We are careful with these children to advise parents to avoid 'getting in the child's face' too much, and especially to avoid aggressive facial emotion and eye contact.

On the other hand, cold children are more likely to come into conflict due to inappropriate reward seeking behaviour, and are unlikely to attend to the salient emotional aspects of the timeout procedure. Taken together, this literature indicates that increasing emotional salience and indeed close eye contact should increase the chances of a positive outcome for these children. We find that getting very close to the child and calmly attempting to make direct eye contact actually has the positive and opposite effect of focusing the cold child on what should be the salient aspect of the situation, rather than the inappropriate reward they are so often seeking at the expense of others.

This is one simple example of how more precise delineation of the child's pattern of disturbance can lead to new ways of thinking about even our most well-established strategies. We expect that the next several years will see increasing precision brought to the specific strategies that can be used to help children and parents learn alternatives to aggression.

In summary, this paper has started with the empirically supported idea that parenting interventions offer the best clinical and public health solution to early-onset aggression and antisocial behaviour in children. Unfortunately, there are systemic-, family-, and child-level factors that are associated with poorer outcomes for these children. We focused on the least well researched of these, viz. characteristics of children that predict chronic antisocial behaviour and poor treatment responses. We argued that rapid progress is being made in the developmental neurosciences of aggression and we reviewed a number of examples of human and animal models that help us think more precisely about the development of aggression and its treatment. Hopefully this paper may help inspire growth in the cross-fertilization between burgeoning neurosciences of violent and antisocial behaviour and the clinical sciences responsible for working with these children.

All research described in this paper and conducted by the authors was approved by the institutional ethics review boards of the University of New South Wales and Griffith University.

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