Stability and Change of Antisocial Behavior in Children and Adolescents: The Role of Neurobiological Factors

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Stabiliteit en Verandering van Antisociaal Gedrag bij Kinderen en Adolescenten: De Rol van Neurobiologische Factoren

(met een samenvatting in het Nederlands)

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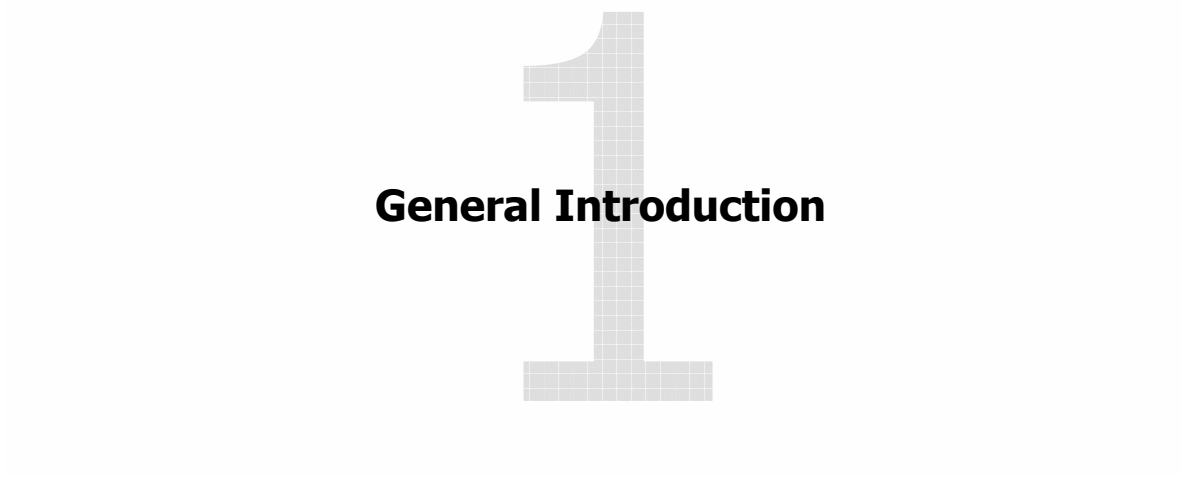

General Introduction

Aggression and antisocial behavior

Aggressive behavior has long been a major concern in our society. Recently, some extremely aggressive school incidents have become world news. On April 20, 1999, a shooting incident at Columbine High School in Littleton, Colorado, *'resulted in the deaths by homicide of 12 students and one teacher, and the suicides of the two teenage perpetrators'* (Brener et al 2002). On January 13, 2004, an incident at a school in the Netherlands shocked the Dutch nation. *'A student of the Terra College in The Hague shot his teacher in the head in the school cafeteria in full view of many of the students. The critically injured teacher was rushed to hospital but died later'* (Agence France-Presse).

In the above cases, the perpetrators obviously used some kind of *physical aggression*, which had a fatal outcome. *Aggression*, defined as behavior deliberately aimed at inflicting physical damage on persons or property (Vitiello and Stoff 1997) is often physical in nature. However, besides *physical aggression*, some other forms of aggression, such as *psychological* and *relational aggression*, are known to cause problems in society. *Psychological aggression* is aimed at inflicting psychological harm, e.g., humiliating others. *Relational aggression*, on the other hand, harms others through damage to their peer relationships or the threat of such damage (Crick and Grotpeter 1995). In addition, aggressive behaviors can also be classified into two types: *instrumental (or proactive) aggression* and *hostile (or reactive) aggression* (Dodge and Coie 1987; Moyer 1976). *Instrumental/proactive* aggression involves a relatively nonemotional display of aggressive behavior that is directed towards obtaining some goal. *Hostile/reactive aggression*, on the other hand, involves highly aroused impulsive aggressive behavior and often arises as a defensive reaction in response to some perceived frustration, insult, or provocation (Scarpa and Raine 1997).

Most studies do not differentiate between types of aggressive behaviors, and since aggression occurs in the context of other inappropriate behaviors, aggression is often aggregated with different forms of *antisocial behaviors* (Tremblay 2000). *Antisocial behavior*, defined as behavior by which people are being disadvantaged and basic norms and values are being violated, includes not only aggression but also a broad range of activities such as theft, vandalism, firesetting, lying, truancy, running away, and oppositional behaviors, i.e., negativistic, defiant, or disobedient behaviors towards authority figures. Many different terms denote antisocial behaviors including acting out, externalizing behaviors, disruptive behaviors, conduct disorder or conduct problems, and delinquency (Kazdin 1989). The aggregation of these types of aggressive and antisocial behaviors clearly creates an important problem for researchers who are trying to understand the origin and development of these behaviors (Tremblay 2000).

From time to time, most children show negativistic and disobedient behavior towards adults. Normally developing children also sometimes engage in lying, fighting, and badgering other children. However, when antisocial behaviors form a pattern that is beyond the realm of 'normal' functioning, with obvious unfavorable effects on the functioning of the child, a diagnosis of oppositional defiant disorder (ODD) or conduct disorder (CD) is given (DSM-IV,

American Psychiatric Association 1994). The term disruptive behavior disorder (DBD) covers both ODD and CD. DBD often co-occurs with attention-deficit hyperactivity disorder (ADHD; Lahey et al 1999). The prevalence of DBD is high; 2.0% for CD and 3.2% for ODD children (Lahey et al 1999). The problem behavior of children with these disorders is often quite stable and persistent (Offord et al 1992). Children with DBD are also at risk for a series of negative outcomes in adolescence and adulthood, such as dropping out of school, criminality, social isolation, unemployment, dependence on welfare, and almost all adult psychiatric disorders, including depression, anxiety disorder, and substance abuse (Maughan and Rutter 2001). The costs to society are high: these children cost at least ten times more than well developing children (Scott 2001).

Although adult antisocial behavior virtually requires childhood antisocial behavior, most antisocial children do not become antisocial adults (Robins 1978). On the one hand, there are studies examining the stability of DBD, and they report a moderate to high stability of antisocial behavior. In a study based on a community sample, 45% of the children with CD at age 4-12 years continued to have CD at follow-up 4 years later (Offord et al 1992). Moreover, Lahey et al (1995) found that half of the 65 referred boys who initially met the criteria for CD met the criteria again after one year, and 88% met the criteria for CD again at least once during the next 3 years. On the other hand, some studies investigated not only the stability in behavior, but also investigated changes in antisocial behaviors (e.g., Heijmens Visser et al 2003; Matthijssen et al 1999).

There is a growing consensus that DBD originates from the interaction of biologically based child characteristics with non-optimal characteristics of the child's environment. In this thesis, we investigate neurobiological correlates of aggression and their role in the stability of behavior and the changes in behavior. We do this by focusing on the relationship between aggression and cortisol, testosterone, and the autonomic nervous system (ANS) in a population-based sample as well as in a sample of referred DBD children. In addition, the role of some psychological and family characteristics in stability and change was examined, although these correlates occupy a very modest place in this thesis.

Neurobiological correlates of antisocial behavior

Hypothalamic-pituitary-adrenal axis

Stress is regulated primarily by the hypothalamic-pituitary-adrenal (HPA) axis. Physical and psychological stress activates the HPA axis, causing it to produce a series of hormones, which leads to the release of corticoids. Cortisol, the end product of this activation, is the major stress steroid in humans; it modulates several neurophysiological processes such as the termination of digestive activity, increase in heart rate, and the mobilization of glucose as an energy source in a 'flight or fight' type situation (De Kloet 1991; Johnson et al 1992). These processes have a survival function, preparing the animal for action. The HPA process begins when the paraventricular nucleus of the hypothalamus produces and secretes the corticotropin-releasing hormone (CRH), which in turn triggers the anterior pituitary to secrete

adrenocorticotropic hormone (ACTH). ACTH eventually activates the adrenal glands, causing them to release cortisol. In addition, cortisol is its own regulator; it activates feedback mechanisms whereby the HPA axis stops releasing activating hormones and consequently cortisol's own release. Furthermore, the HPA axis also has an intrinsic activity. It maintains a 24-hour cortisol rhythm that is independent of stress responses and is linked to the activity level (Lopez et al 2004). The rhythm generally has the following pattern: high levels in the early morning, which are decreasing during the day.

Cortisol and antisocial behavior

Stress-regulating mechanisms are important factors contributing to individual differences in antisocial behavior (Kerr et al 1997; McBurnett et al 2000; Mezzacappa et al 1997; Vanyukov et al 1993). Several investigations of antisocial adults have analyzed cortisol levels and have found the cortisol level to be inversely related to the magnitude of behavioral deviation (King et al 1990; Virkkunen 1985; Woodman et al 1978). Similar results have been obtained in children and adolescents; some studies using basal cortisol concentrations (e.g., McBurnett et al 2000; Pajer et al 2001; Vanyukov et al 1993), and others using cortisol levels under stress (e.g., Van Goozen et al 1998a and 2000). There are two theoretical points of view that attempt to explain the observed pattern of low HPA axis activity in antisocials, i.e., the fearlessness theory (Raine 1993 and 1997), and/or the stimulation-seeking theory (Eysenck 1997; Quay 1965; Raine et al 1997) (see *autonomic nervous system (ANS) and antisocial behavior*). Although the cause of these patterns of cortisol hypoactivity or hyporesponsivity is still unknown, it may be the result of differences in genetic makeup (Van Goozen et al 2000). In addition, as referred DBD children often have a history of negativistic and oppositional behaviors, resulting in poor parent-child relations, they might have experienced higher levels of stress over a longer period of time. This may lead to alterations in the setpoint of the HPA axis (Liu et al 1997). However, positive relationships between cortisol and antisocial behavior have also been found in some studies (e.g., Gerra et al 1997; McBurnett et al 1991; Susman et al 1997). Finally, some studies have found no relationship between cortisol and antisocial behavior (Azar et al 2004; Klimes-Dougan et al 2001; Kruesi et al 1989; Scerbo and Kolko 1994; Schultz et al 1997; Stoff et al 1992; Susman et al 1999).

Hypothalamic-pituitary-gonadal axis

The androgenic hormone testosterone is the most important male sex hormone. The production of testosterone is regulated by the hypothalamic-pituitary-gonads (HPG) axis (Tremblay et al 1997). In males, testosterone is produced mainly by the testes, whereas in females it is produced by the adrenal glands. However, no differences can be observed from the seventh month after birth until puberty. Differences between males and females reappear only at puberty (Forest 1989). It has been suggested that sex differences in testosterone levels during the months after birth play a role in hypothalamic sexual

differentiation, and could explain later sex differences in behavior (Tremblay et al 1997). During adrenarche, the period between age 7 to the onset of puberty, the adrenal glands start to produce higher levels of androgens, mainly dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). In addition, testosterone rises slightly in both males and females and has a predominant adrenal origin. With puberty, male levels of plasma testosterone increase 20- to 30-fold between age 12 and 18 years. The rise in testosterone levels during adolescence is highly correlated with pubertal development, characterized by bone growth, increase in muscle or body mass, growth of the genitalia, and the development of other secondary sexual characteristics (Forest 1989). In females, plasma testosterone levels also show an increase during puberty (Forest 1989), but the rise is much less dramatic. Finally, testosterone has a circadian rhythm in both sexes, highest and most variable in the morning, lower and more stable during the afternoon (Dabbs 1990).

Testosterone and antisocial behavior

Testosterone affects not only physical but also behavioral masculinization. In human adults, testosterone has been found to be related to delinquency, drug abuse (Dabbs and Morris 1990) and criminal violence (Dabbs et al 1995; Ehrenkranz et al 1974; Kreuz and Rose 1972; Strong and Dabbs Jr 2000), as well as to conduct problems in childhood (Dabbs and Morris 1990). However, Bain and colleagues found no difference in testosterone between men charged for aggressive crimes and those charged for non-aggressive crimes (Bain et al 1987). It is clear, therefore, that in humans the evidence is at best suggestive of a positive relationship (Archer 1991). There is a lack of information about the influence of testosterone on behavior in children and adolescents. Some studies have indeed found a positive relationship between testosterone and aggression (Chance et al 2000; Maras et al 2003; Olweus et al 1980 and 1988; Sánchez-Martín et al 2000; Scerbo and Kolko 1994). However, it is important to keep in mind that there are also quite a few studies that have found no relationship between aggression and testosterone in children or adolescents (Constantino et al 1993; Halpern et al 1993; Inoff-germain et al 1988; Mattsson et al 1980; Susman et al 1987; Van Goozen et al 1998b). Although most research has focused on aggression, there is also evidence from studies in nonhuman primates of a relatively strong association between testosterone and dominance (Mazur and Booth 1998; Paikoff and Brooks-Gunn 1990). Social dominance may or may not involve aggressive behavior and it is possible that a more direct relationship exists with dominance than with aggression (Albert et al 1993; Strong and Dabbs 2000). This line of reasoning was supported in a study by Schaal et al (1996) in which it was shown that testosterone levels were associated with social success rather than with physical aggression. Just as in the studies about cortisol and aggression, findings on testosterone and aggression have been mixed. These inconsistent findings may be explained by the fact that aggressive behavior was defined and operationalized in different ways in the studies, and that studies examining the testosterone -aggression relationship in children and adolescents obviously differed with regard to the age of the participants; ages varied from prepubertal to postpubertal, which may have affected the outcome of the relationship.

Autonomic nervous system

The autonomic nervous system (ANS) plays an essential role in regulating man's internal metabolism. It operates through the sympathetic and parasympathetic systems. The sympathetic system controls the 'fight or flight' reaction, whereas the parasympathetic system is responsible for 'rest and digest'. In a crisis situation the body is called upon to react to a sudden change in its external or internal environment. The resultant increase in HR, in body temperature and blood glucose, and pupillary dilation let the body respond rapidly to potentially disturbing external conditions. In contrast, the role of the parasympathetic system is to maintain basal HR, respiration, and metabolism under normal conditions (Dodd and Role 1991). In short, the ANS is involved in 'homeostasis' and is under both neural and hormonal control. Short-term responses are under neural control whereas long-term responses are under hormonal control. Neural control of autonomic function stems from multiple areas in the brain and spinal cord whereas hormonal control derives from both central (e.g., hypothalamus, pituitary) and peripheral (e.g., adrenal gland, gonads) sites (Pritchard and Alloway 1999).

Autonomic nervous system and antisocial behavior

Of the many psychophysiological processes that have been studied, low autonomic arousal is the one which has been most often related to antisocial, criminal, and violent behavior in both child and adult samples (Raine 2002a). In particular, skin conductance level (SCL) and heart rate (HR) are commonly used psychophysiological measures recorded from antisocial populations. SCL was found to be significantly lower in subjects who were rated as high on CD than in subjects rated low on CD (Venables 1989). In addition, in a 2-year follow-up of disruptive behavior disordered juveniles SCL was shown to predict institutionalization (Kruesi et al 1992). HR and several measures of electrodermal arousal (i.e., skin conductance response (SCR) half recovery times, non-specific SCRs, baseline level of SCL) were also found to be useful markers for predicting aggressive and criminal behavior over quite a long developmental period (Raine et al 1990 and 1995; Venables 1989). Furthermore, two studies at our Department found baseline levels of HR (Van Goozen et al 1998a and 2000) and SCL (Van Goozen et al 2000) to be lower in DBD children than in healthy controls. It has been suggested that low ANS activity (e.g., HR and SCL) is related to fearlessness. From the *fearlessness theory* it was argued that low levels of arousal during mildly stressful psychophysiological test sessions are markers of low levels of fear (Raine 1993 and 1997). The performance of antisocial and violent behavior requires a degree of fearlessness, and lack of fear of socializing punishment in early childhood may well contribute to poor fear conditioning and lack of conscience development (Raine 1993). On the other hand, according to the *stimulation-seeking theory*, low arousal represents an unpleasant physiological state; antisocial individuals seek stimulation in order to increase their arousal levels to an optimal or normal level (Eysenck 1997; Quay 1965; Raine et al 1997). Antisocial behavior is thus

seen as a form of stimulation seeking. For some individuals, committing a burglary, assault, or robbery can be stimulating.

Other correlates of antisocial behavior

ADHD comorbidity

Another factor that seems to play a role in predicting the outcome of children with DBD is the comorbidity of ADHD. The presence of ADHD seems to predict certain aspects of poor outcome for children with CD (Frick and Loney 1999). For instance, boys with DBD and hyperactivity were found to show more violent offending in adulthood than boys who had DBD but who were not hyperactive (Klinteberg et al 1993). Furthermore, hyperactivity was found to be a risk factor for impaired social adjustment, which includes the development of psychiatric disorders, irrespective of the existence of conduct problems (Taylor et al 1996).

Neuropsychological correlates

Findings regarding aggression and executive functioning provide evidence that neuropsychological deficits are linked to disruptive behavior (Séguin et al 1999). In this connection, constructs of interest are impulsivity and behavioral inhibition. Impulsivity was associated with the early onset (Tremblay et al 1994) and presence of antisocial behavior (White et al 1994), whereas behavioral inhibition was found to decrease the risk of later delinquency (Kerr et al 1997). Moreover, behavioral inhibition may be positively related to anxiety, which has been shown to moderate physical aggression, even among boys who are already disruptive (Harden et al 1995; Walker et al 1991). Another important correlate of antisocial behavior is the level of intelligence. Low intelligence is often considered to be a precursor of DBD, although Hogan (1999) suggested that this conclusion might be premature. It has been suggested that a higher verbal intelligence predicts a more positive outcome (Lahey et al 2002). In addition, a large discrepancy between verbal IQ (VIQ) and performance IQ (PIQ), with VIQ lower than PIQ, has been shown to play a role in the etiology of DBD (Hinshaw 1992; Moffitt 1993b). A study of a non-referred community sample, however, did not find intelligence to be a significant predictor of antisocial outcome over time (Nagin and Tremblay 2001).

Family and contextual correlates

Below we will review some family and contextual correlates of antisocial behavior, although the topic plays only a minor role in this thesis. Low socioeconomic status (SES) and poor parenting skills seem to affect the development of DBD. Some studies indicate that DBD is more prevalent among youths from families with low SES (Lahey et al 1999). Moreover,

inconsistent and negative parenting appears to play a mediating role between SES and conduct problems. If parents are socioeconomically disadvantaged they are less able to respond appropriately to their children, which in turn elicits increased problematic behavior in these children (McLoyd 1998). In addition, research into extremely harsh or abusive parenting behaviors, such as sexual and physical abuse, demonstrates that such behaviors significantly increase the risk of CD (e.g., Fergusson et al 1996a). Boys in a community sample who had a single parent were predicted to have higher levels of antisocial behavior over time (Pevalin et al 2003). In the latter sample parental depression was found to increase the likelihood of a child's antisocial behavior, although this was not found within a DBD sample (Lahey et al 2002). Furthermore, boys whose mothers smoked during pregnancy were found to have a higher chance of developing CD (Wakschlag et al 2002). Studies with rodents have shown that prenatal exposure to nicotine, even at relatively low levels, negatively affects the development of the noradrenergic system (Levin et al 1996), and, more specifically, interferes with neuronal development in the cerebellum, which in turn is implicated in inhibitory processes (Raine 2002a). Inhibition problems caused by smoking during pregnancy might therefore result in poor adolescent outcome. As to gender, it seems clear that boys are more likely than girls to meet the criteria for CD and to exhibit a higher frequency of CD symptoms (Lahey et al 1999). However, Zoccolillo (1993) found that ODD and CD diagnoses are relatively common in girls, especially in clinical settings. It is becoming evident that sex differences in disruptive behavior do not emerge until after the age of 6. From then onwards more boys than girls show overt forms of disruptive behavior (Keenan and Shaw 1997; Loeber and Hay 1997; Webster-Stratton 1996). There have also been studies of the predictive role of gender in the adolescent outcome of DBD children, but findings have been mixed (Fergusson et al 1996b; Pevalin et al 2003).

Population-based samples versus referred DBD samples

Some studies on disruptive behaviors and their correlates have been conducted in large longitudinal community-based samples. For instance, the Dunedin Multidisciplinary Health and Development Study of mental disorders and violence used a cohort of 1,037 children constituted when the children were 3 years of age; the children were born between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand (Caspi et al 1996; Feehan et al 1993; Moffitt 1990). In addition, in Montreal, Canada, a longitudinal study began in 1984, which followed all males from kindergarten classes in 53 schools in low socioeconomic areas of Montreal (n= 1,161; Tremblay et al 1994 and 1995). The children in this sample were studied on their externalizing behaviors as well as on their neurobiological (Schaal et al 1996), neuropsychological (Séguin et al 1995), and psychosocial (Nagin and Tremblay 2001) correlates. In contrast, some studies examined a subgroup of children whose problem behaviors were diverse and serious enough to meet diagnostic criteria for DBD, and compared them with healthy controls in terms of neurobiological or neuropsychological characteristics (e.g., Matthys et al 1998; McBurnett et al 2000; Van Goozen 1998a and 2000). In this thesis we examine some neurobiological correlates of aggression and their role

in the stability of and changes in behavior, both in a population-based sample and in a sample of referred DBD children.

Aims of the presented studies

The aim of this thesis is to investigate neurobiological correlates of aggression and their role in the stability of and changes in behavior by focusing on the relationship of aggression with cortisol and testosterone in a population-based sample, and on the relationship of aggression with cortisol and the ANS in a sample of referred DBD children. Also, some psychological and psychosocial family characteristics of aggression were examined.

The studies presented in this thesis build upon results previously found by our research group in the Department of Child and Adolescent Psychiatry, University Medical Center Utrecht. Van Goozen et al (1998a) initiated our line of research on the activity of the ANS and the HPA axis in DBD children by measuring HR, SCL, androgens, and cortisol. In chapters 2 and 3, we examine the relationship between antisocial behaviors and both cortisol and testosterone in a sample of boys selected from a large cohort (*n*= 1,161), followed from kindergarten in a Montreal longitudinal-experimental study of social development (see for more details Séguin et al 1995 and 1996; Tremblay et al 1994). From age 6 to 21 years, the boys' behavior had been assessed repeatedly by different informants, and saliva had been collected in order to determine cortisol and testosterone levels. We ourselves were not involved in the collection of these data. In chapter 2, variously defined aggressive subgroups are compared for differences in salivary cortisol, which was collected when subjects were aged 13. In chapter 3 we investigate the relationship between testosterone and aggression, dominance and delinquency over time, covering the period from early adolescence to adulthood. In chapters 4 to 6, on the other hand, we study a sample of severely disturbed DBD children who were referred to our Department for psychiatric treatment. In chapter 4, we describe the functioning of these DBD children as adolescents in terms of their disruptive behaviors, depression, institutionalization, police contacts, smoking behavior, substance use, and educational status. Next, in chapter 5, we explore the predictive value of neurobiological child characteristics (i.e., cortisol, heart rate, skin conductance level) on treatment outcome, and we examine the predictive value of some family, neuropsychological, and demographic characteristics for the effect of treatment. The final chapter (chapter 6) describes a similar kind of study. Here we explore the predictive influence of various family, psychological, demographic, and neurobiological characteristics on the persistence of antisocial behavior in adolescence.

2

Salivary Cortisol and Aggression in a Population-Based Longitudinal Study of Adolescent Males

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ABSTRACT

Background
Chronic antisocial behavior in youth has been associated with cortisol, a measure of stress reactivity. However, some studies have found low cortisol levels, while others have found elevated cortisol levels.

Methods
The present study compared variously defined aggressive subgroups for differences in salivary cortisol. A population-based sample of boys was followed longitudinally from childhood to adolescence. Assessments of different forms of antisocial behavior were obtained from various informants at several points in time, and cortisol was collected at age 13.

Results
Higher cortisol levels were found in boys with conduct disorder (CD) than in boys without CD. In addition, boys with an aggressive form of CD had higher cortisol levels than boys who showed a covert form of CD. Furthermore, reactive aggression was strongly correlated with elevated cortisol.

Conclusions
Adolescent boys with chronic reactive aggression and those who scored high on aggressive CD symptoms seem to have a more active hypothalamic-pituitary-adrenal system.

INTRODUCTION

Among the many factors that contribute to individual differences in antisocial behavior, stress-regulating mechanisms appear important (Kerr et al 1997; McBurnett et al 2000; Mezzacappa et al 1997; Vanyukov et al 1993). The hypothalamic-pituitary-adrenal (HPA) axis is sensitive to physical and psychological stressors. Activity of the HPA axis can be estimated using measures of its end products, glucocorticoids. The primary glucocorticoid in humans is cortisol, and it can be assessed in saliva (Dettling et al 1999).

Most psychobiological investigations of antisocial adults have observed an inverse relationship between the magnitude of behavioral deviation and cortisol level (King et al 1990; Virkkunen 1985; Woodman et al 1978). Similar results have been obtained in children and adolescents: Cortisol levels have been reported to be negatively related to hostility towards teachers (Tennes and Kreye 1985), to conduct problems (McBurnett et al 2000; Pajer et al 2001; Shoal et al 2003; Van Goozen et al 1998a and 2000; Vanyukov et al 1993), and to deviant behaviors in sons of fathers with a psychoactive substance use disorder (PSUD) (Moss et al 1995). As in adults, in these younger age groups low levels of HPA axis activity have been interpreted as indicators of stress hyporesponsivity or fearlessness (Van Goozen et al 1998a and 2000). Although the cause of these patterns of cortisol hypoactivity or hyporesponsivity is as yet unknown, it may be the result of differences in genetic makeup or early modifications of the developing brain following pre- or postnatal stressful conditions of life (Van Goozen et al 2000). However, the findings for children and adolescents are not as clear-cut as those for antisocial adults, in that positive relationships between cortisol and antisocial behavior have also been found in some studies. In normal healthy adolescents a positive relationship was found between aggression and cortisol response level during an experimentally induced aggression task (Gerra et al 1997) and during an emotion-arousing and painful procedure (Susman et al 1997). Moreover, McBurnett and colleagues (1991) reported higher levels of cortisol in conduct-disordered (CD) children, but only when they had a comorbid anxiety disorder. Finally, some studies have found no relationship between cortisol and antisocial behavior (Klimes-Dougan et al 2001; Kruesi et al 1989; Scerbo and Kolko 1994; Schultz et al 1997; Stoff et al 1992; Susman et al 1999).

The mixed cortisol findings for children and adolescents may be due to important methodological differences among these studies. First, the label 'antisocial' has been used for behaviors as different as physical aggression, running away from home, stealing, and drug use (Coie and Dodge 1998; Tremblay 2000 and 2003). Furthermore, studies, which specifically assess physical aggression, have generally not taken into account whether they are of the reactive or proactive type. Reactive and proactive aggression has been observed in children, adolescents and adults (Brendgen et al 2001; Dodge et al 1997; Pulkkinen and Tremblay 1992; Vitaro et al 1998). Reactive aggression is impulsive, often accompanied by disinhibition and affective instability, but not necessarily by antisocial tendencies; it is characterized by high levels of bodily arousal. On the other hand, proactive aggression is nonimpulsive and controlled, and occurs in the context of persistent antisocial behavior. Proactive aggressive individuals are less likely to have unstable affects, their aggression is goal-directed, and the level of arousal is usually low (Vitiello and Stoff 1997). Therefore, one

could predict theoretically that proactive aggression is more likely to be associated with low levels of cortisol whereas reactive aggression will co-occur with elevated levels of cortisol. Differences in assessments of cortisol may also explain the diversity of results. Some studies measured cortisol under resting conditions (Kruesi et al 1989; McBurnett et al 2000; Shoal et al 2003; Tennes and Kreye 1985), while other studies measured cortisol before the occurrence of an anticipated stressful event (Dawes et al 1999; Moss et al 1995), during an aggression provoking task (Gerra et al 1997), or under highly stressful conditions (Van Goozen et al 1998a and 2000). Moreover, the majority of studies on children's cortisol concentration involved measurements varying over the day, without controlling for the clear circadian rhythm in cortisol secretion or for the kinds of activity that participants had done before the start of the study (McBurnett et al 2000); only a few studies measured cortisol concentration at specific time points, having kept the conditions for all participants equal (Susman et al 1997; Van Goozen et al 1998a and 2000). Finally, some studies used clinical samples (McBurnett et al 2000; Scerbo and Kolko 1994), some compared clinical samples to non-clinical samples (Kruesi et al 1989; Pajer et al 2001; Stoff et al 1992; Van Goozen et al 1998a and 2000), while others used community samples (Gerra et al 1997; Klimes-Dougan et al 2001).

We report results of a study with a population-based sample of boys, followed over a 9-year period for the development of their aggressive behavior. The aim was to investigate whether variously defined aggressive subgroups would differ in salivary cortisol level. We examined this in four different ways. First, we compared participants with and without a CD diagnosis. In a second analysis, we distinguished between aggressive and covert CD symptoms and examined the effect of this classification on cortisol. Third, we classified all participants according to the frequency of their use of physical aggression as assessed from age 6 to age 15, and related that to cortisol. And in a last analysis, we took into account the boys' use of reactive and proactive aggression and related this to cortisol. We specifically predict that the more aggressive groups would have lower levels of cortisol. Like in most studies on cortisol we used a single saliva sample and considered this to be the participants' baseline or resting level.

To our knowledge this is the first study that has used longitudinal data from a population-based sample comparing cortisol levels of physically aggressive and non-aggressive cases.

METHODS

Participants

The participants involved in the present study (*n*= 194) were participating in a longitudinal study from kindergarten onwards (*n*= 1,161). The selection and reduction procedure of the larger sample had been described previously (Séguin et al 1995 and 1996; Tremblay et al 1991b and 1994). To obtain a high base rate of boys at risk for disruptive behavior, the 53 schools in an urban area with the lowest socioeconomic index were chosen. Teachers were asked to rate each boy in their classes. Ratings were returned by 87% of the teachers, and 1,161 boys had been rated. To control for cultural effects, boys were only included in the

study if both biological parents were born in Canada and were French speaking. To ensure that the sample would be from families of low socioeconomic background, we also eliminated boys when either of the parents had more than 14 years of schooling. The sample was reduced to 1,034 boys after applying these criteria and eliminating those who declined to participate and those who could not be located (Tremblay et al 1991b and 1994).

Physically aggressive behavior had been assessed at ages 6, 10, 11, and 12 years by means of the fighting subscale of the teacher form of the French Canadian version of the Social Behavior Questionnaire (SBQ; Tremblay et al 1991a). After eliminating the boys who withdrew their participation from the longitudinal project (n= 116) and those who had more than one missing value on physical aggression at follow-up (n= 28), we determined stability and severity of physical aggression for 893 boys from assessments at ages 6, 10, 11, and 12 (see also Séguin et al 1995 and 1996). Those who fell above the 70th percentile at age 6 and at least at two or more assessment points were classified as stable aggressive boys (19% of the sample). Nonaggressive boys had scores that fell below the 70th percentile at all assessment points (35% of the sample). Those who did not meet the above criteria were classified as unstable aggressive boys (46% of sample). Compared to another sample of boys (n= 882) representative of the whole province, physically aggressive behavior is over-represented in this urban community sample of low socioeconomic status (Séguin et al 1996).

For logistical reasons, we were able to invite approximately 200 13-year old boys to come to the laboratory for various observational and experimental procedures. Several overlapping criteria were used to select this subsample. Exclusion criteria (for purposes not particular to this study) were applied as follows: 234 boys who could not be classified as stable anxious or stable nonanxious were eliminated, as well as 326 boys who did not meet priority criteria such as (a) stability of physical aggression or nonaggression, (b) a history of going to the laboratory since age 6, or (c) a pattern of late onset physical aggressive or anxious behavior. Thus, some moderate or unstable anxious boys remained in the selected sample because they met some of these priority criteria (n= 138). Those who met priority criteria (b) or (c) but not (a) were classified as unstable aggressive boys. When all these criteria were applied, the selected sample consisted of 333 boys who were 13 years old at the time of our assessment. Of these, 203 boys agreed to come to the laboratory (Séguin et al 1995 and 1996). It turned out not to be possible to take a morning saliva sample in 9 boys, leaving us with a total subsample of 194 boys. We considered this subsample representative of the larger sample (n= 843), because when we compared our subsample of 194 boys to the remainder of the sample on a number of important variables (e.g., SES, physical aggression trajectory group (Nagin and Tremblay 1999), proactive and reactive aggression), no differences were observed with the exception of proactive aggression. The subsample was slightly more proactive aggressive (t= -2.23, p= .03).

Procedure and instruments

Assessments of Conduct Disorder (CD) and physical aggression at 14-16 years of age

The Diagnostic Interview Schedule for Children (DISC-2.25) (Shaffer et al 1991) was administered to the participants and their parents (mostly their mothers) when the boys were 14-16 years old. A letter followed up by telephone contacts served to solicit participation (Séguin et al 1999). The DISC could not be administered to 15 of the participants, and 7 participants had only a child or a parent report. A participant was attributed to the CD subgroup when he met three or more of the thirteen CD criteria based on combined reports of parent and child. In this way a CD subgroup consisting of 20 boys and a normal control (NC) subgroup of 159 boys were created. Additionally, and following McBurnett et al (2000), we divided the 13 diagnostic criteria for CD into items describing aggressive behavior (i.e., often initiates physical fights; has used a weapon; has been physically cruel to people; has been physically cruel to animals; has stolen while confronting a victim; has forced someone into sexual activity) and covert (non-aggressive) behavior (i.e., has set fires; has destroyed property; has broken into someone else's house, building or car; tells lies; has stolen; has run away from home overnight; is truant from school). Two subgroups were created on the basis of the number of items checked for aggression and/or non-aggression. A participant belonged to the aggressive subgroup (A) when he exhibited one or more of the 6 aggressive behaviors, regardless of whether he exhibited covert behaviors (n= 22), and to the covert subgroup (C) when he exhibited one or more of the 7 covert behaviors, but not any of the aggressive behaviors (n= 39).

Assessments of physical aggression trajectories from 6 to 15 years of age

The estimation of developmental trajectories for repeated measures of physical aggression from kindergarten to mid-adolescence is based on teacher reports. The boys' classroom teachers rated physical aggression in the spring of each year using a French Canadian version of the Social Behavior Questionnaire (Tremblay et al 1991a). This questionnaire was administered when the boys were age 6, 10, 11, 12, 13, 14, and 15 years. Physical aggression was assessed with three items; "kicks, bites, hits"; "fights"; and "bullies or intimidates other children". The range of possible values of the physical aggression score was 0 through 6. The internal consistency scores (Cronbach's alpha's) for the physical aggression scale ranged from .78 to .87 with a mean reliability score of .84 for assessments between 6 and 15 years.

Nagin and Tremblay (1999 and 2001) identified four distinct groups when they estimated the developmental trajectories of physical aggression for the total Montreal sample with a semiparametric, group-based method. When applied to our sub-sample the criteria led to the following four groups: a never physical aggression trajectory group (never agg, n= 40), a low level desister physical aggression trajectory group (low agg, n= 78), a high level near desister physical aggression trajectory group (n= 68), and a chronic physical aggression trajectory group (n= 8). Because the latter group was so small, we combined the high level near desister and chronic trajectory groups into one high physical aggression trajectory group (high agg, n= 76).

Assessments of reactive and proactive aggression from 12 to 15 years of age

In addition, when the boys were 12, 13, 14 and 15 years old, their teachers completed three reactive aggression, and three proactive aggression items (Dodge and Coie 1987). The reactive items were "when teased or threatened he gets angry easily and strikes back"; "when accidentally hurt by a peer he assumes that the peer meant to do it and then overreacts with anger and fighting"; and "always claims that other children are to blame in a fight and feels that they started the whole trouble". The proactive items were "uses (or threatens to use) physical force in order to dominate other children"; "threatens or bullies others in order to get his way"; and "gets other children to gang up on a peer he does not like". The 3-unit response scale for these items ranged from 0 "does not apply", and 1 "applies sometimes", to 2 "applies often" (Brendgen et al 2001). Cronbach's alpha's varied between .82 and .86. For each year a reactive and proactive aggression score was calculated by summing the scores of the three respective items, resulting in an annual reactive and proactive score ranging from 0 to 6. Next, these four annual scores were averaged to form a mean reactive and proactive score. Ten boys did not participate in the analyses, as they had missing values on reactive aggression in more than two years. On the basis of this information we created three subgroups of reactive aggressive boys; a boy belonged to the low reactive aggressive subgroup (LRA, n= 52) when this mean score over the four successive years was 0, he belonged to the moderate reactive aggressive subgroup (MRA, n= 92) when the mean score ranged from $0 < x \leq 2$, whereas boys who had a higher mean score (>2) belonged to the high reactive aggressive subgroup (HRA, n= 40).

Assessment of anxiety trajectories from 6 to 15 years of age

Because anxiety is expected to have a stimulating effect on the activity of the HPA axis in general, and the secretion of cortisol in particular, we used an assessment of anxiety as a control variable. Using the Nagin and Tremblay approach (Nagin and Tremblay 1999), the developmental trajectories of anxiety were identified based on school teacher's ratings from 6 to 15 years of age. An annual score was obtained through the aggregation of three items from the teacher rated Social Behavior Questionnaire (Tremblay et al 1991a; "worries"; "tends to be fearful"; and "easily cries"). Two participants had missing data. The possible scores for the annual assessments ranged from 0 to 6. Crohnbach's aloha varied between .63 and .73 with a mean reliability score of .68. The three developmental trajectories identified led to the following subgroups: a low level (low anx, n= 101), moderate level (mod anx, n= 33) and a high level (high anx, n= 58) subgroup.

An overview of the sample sizes of different subgroup classifications is given in Table 1.

Table 1. *Classifications of aggression subgroups and their sample sizes.*

Conduct disorder symptoms	*normal control (NC)* *n*= 159	*conduct disorder (CD)* *n*= 20	
Covert vs. aggressive CD symptoms	*covert (C)* *n*= 39	*aggressive (A)* *n*= 22	
Reactive aggression	*low (LRA)* *n*= 52	*moderate (MRA)* *n*= 92	*high (HRA)* *n*= 40
Physical aggression trajectories	*never agg* *n*= 40	*low agg* *n*= 78	*high agg* *n*= 76
Anxiety trajectories	*low anx* *n*= 101	*mod anx* *n*= 33	*high anx* *n*= 58

NC: < 3 CD symptoms, CD: ≥ 3 CD symptoms; C: ≥ 1 covert CD symptoms but no aggressive CD symptoms; A: ≥ 1 aggressive CD symptoms; LRA: mean reactive aggression score ≤ 0; MRA: mean reactive aggression score 0 < x ≤ 2; HRA: mean reactive aggression score > 2

Cortisol measurement

Cortisol level was assayed from a saliva sample, collected during the boys' one-day visit to the laboratory at 13 years of age. During that day, all boys were administered an extensive neuropsychological test battery and participated in different games (see for details Séguin et al 2002). For all participants the cortisol sample was collected immediately upon arrival at the laboratory at approximately 9h00 A.M., with the arrival time ranging from 8h45 A.M. to 9h55 A.M. (Mean ± SD: 9h09 ± 0h16). Although cortisol had a low inverse correlation with time of assessment (r= -.14, p= .05), the size of the correlation made us decide not to enter collection time as covariate. Participants were requested to donate saliva on paper strips (Stahl and Dorner 1982). Salivary cortisol concentrations were determined using an adapted version of a commercially available radioimmunoassay kit (Coat-A-Count; Diagnostic Products Corp., Los Angeles, California). The interassay coefficients of variation were 5.2% and 6.4% respectively at 0.33 and 3.6 µg/dL. The Coat-a-Count Cortisol antiserum is highly specific for cortisol, with an extremely low crossreactivity to other naturally occurring steroids. Collection of saliva for cortisol determination is a stress-free approach that avoids potential confounds produced by venipuncture. Saliva cortisol levels have been shown to correlate highly with serum cortisol concentrations, and are thought to reflect the unbound fractions of circulation cortisol (Laudat et al 1988).

Data analysis

Single isolated outlier values, with an outlier defined as an individual value more than 2.5 SD's above the mean value of the group, were removed from the analyses. One-factor

analyses of variance (ANOVAs) were used to test for differences in cortisol levels between the various aggression groups. In case of significant group differences between more than two groups, post-hoc Bonferroni tests for multiple comparisons were conducted. Values are expressed as means (± SD). When scores or groups were unevenly distributed non-parametric tests were used.

In case there was a significant correlation between cortisol level and anxiety score at age 13, we controlled for anxiety. With respect to the teacher reported reactive and proactive aggression scores, correlations were calculated between these scores.

Finally, a continuous variable stepwise approach using multiple regression was applied to predict cortisol levels from assessments of aggressive behavior. Continuous scores of proactive- and reactive aggression, the probability score (see Nagin and Tremblay 2001) of being in the high physical aggression trajectory group, and aggressive and covert CD symptoms (as dichotomous variables) were used as predictors. Variables were entered if correlations between them were lower than r= .90 (multicollinearity assumption).

RESULTS

First of all, we assessed whether anxiety had to be taken into account in any subsequent analyses on the relation between cortisol and aggression. Since no significant correlation was found between cortisol level and anxiety score at age 13 (r= .08, p= .29), we decided there was no need to control for anxiety.

A significant difference was found in cortisol between the CD and the NC group, with the CD group having a higher level of cortisol (Mean ± SD: NC= 0.95 ± 0.64 µg/dl, CD= 1.26 ± 0.71 µg/dl, F(1,170)= 3.85, p= .05; see also Figure 1).

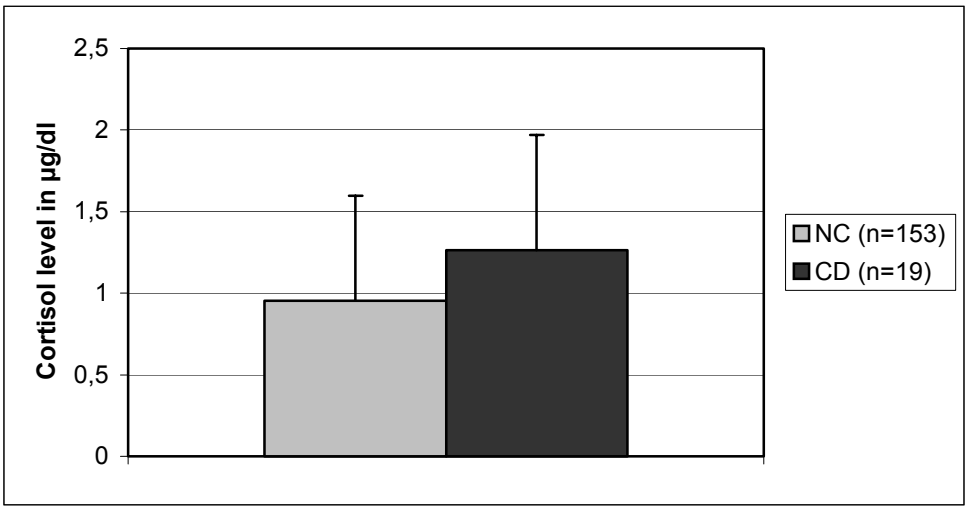

Figure 1. *Differences in cortisol concentration between normal control (NC, n= 153) and conduct disorder (CD, n= 19) subgroups (F(1,170)= 3.85, p= .05).*

In a further analysis, involving the covert (C) and aggressive (A) CD subgroups only, it was established that these subgroups differed significantly in cortisol (Mann Whitney U test; Z= -2.31, *p*= .02; Figure 2).

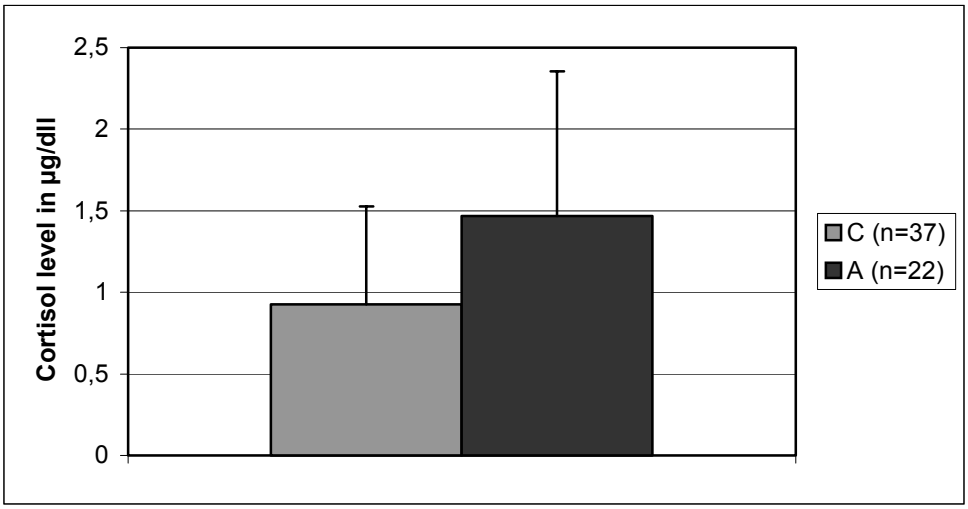

Figure 2. *Differences in cortisol concentration between covert (C, n= 37), and aggressive (A, n= 22) subgroups (Z= -2.31, p= .02), with the A subgroup having higher cortisol levels than the C subgroup.*

Next we tested whether boys in the three teacher rated physical aggression trajectory groups differed in cortisol. Only a marginally significant difference in cortisol was found (Chi-square= 5.12, *p*= .08; see Figure 3). Because, for the purposes of the present paper, we combined the high level near desister (*n*= 68) and the chronic trajectory subgroups (*n*= 8) into the high physical aggression trajectory group, we also examined whether these two subgroups differed in cortisol. This turned out not to be the case (Mann Whitney U test*; Z*= -.71, *p*= .48).

Next we analyzed whether cortisol levels differed between the low reactive aggressive (LRA), the moderate reactive aggressive (MRA), and the high reactive aggressive (HRA) subgroups. A significant difference in cortisol was found between these three subgroups (Mean ± SD: LRA= 0.83 ± 0.59 µg/dl, MRA= 0.94 ± 0.62 µg/dl, HRA= 1.31 ± 0.78 µg/dl, *F*(2,175)= 6.36, *p*< .01; see also Figure 4). Post hoc Bonferroni tests indicated that the difference in cortisol was mainly due to a significant difference between the HRA and both the MRA and LRA subgroups, with the HRA subgroup having higher levels of cortisol.

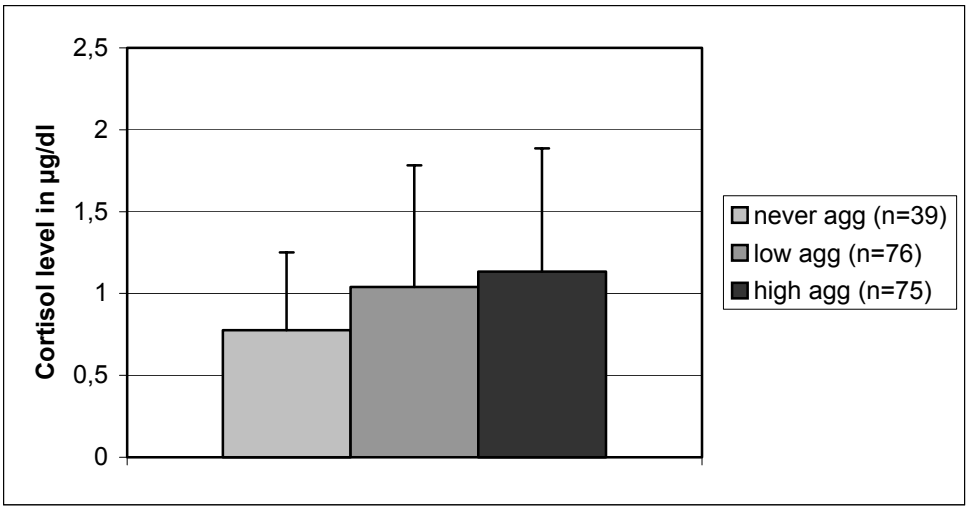

Figure 3. *Differences in cortisol concentration between never (never agg, n= 39), low (low agg, n= 76), and high (high agg, n= 75) physical aggression trajectory subgroups (Chi-square= 5.12, p= .08).*

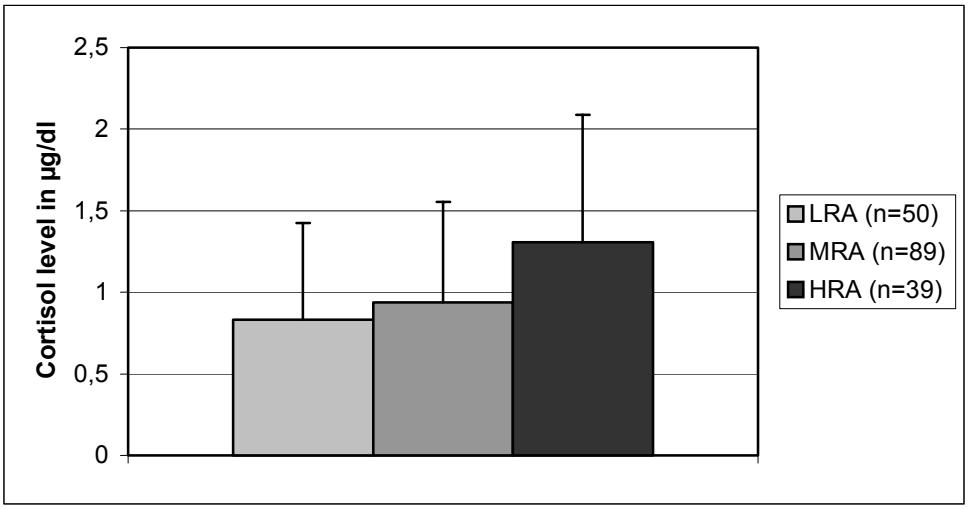

Figure 4. *Differences in cortisol concentration between low (LRA, n= 50), moderate (MRA, n= 89), and high reactive aggression (HRA, n= 39) subgroups (F(2,175)= 6.36, p< .01), with HRA having higher cortisol levels than both the MRA and LRA subgroups (LRA=MRA<HRA).*

We did not find a difference in cortisol between the low, moderate, and high anxiety trajectory subgroups (ANOVA; $F(2,184)= 0.75$, $p= .48$; see Figure 5). Because some previous studies observed an interaction between CD and anxiety (e.g., McBurnett et al 1991), we similarly calculated whether there was an interaction between the anxiety and

aggression trajectory groups on cortisol. No significant interaction effect was found (F(4,183)= 0.45, *p*= .77).

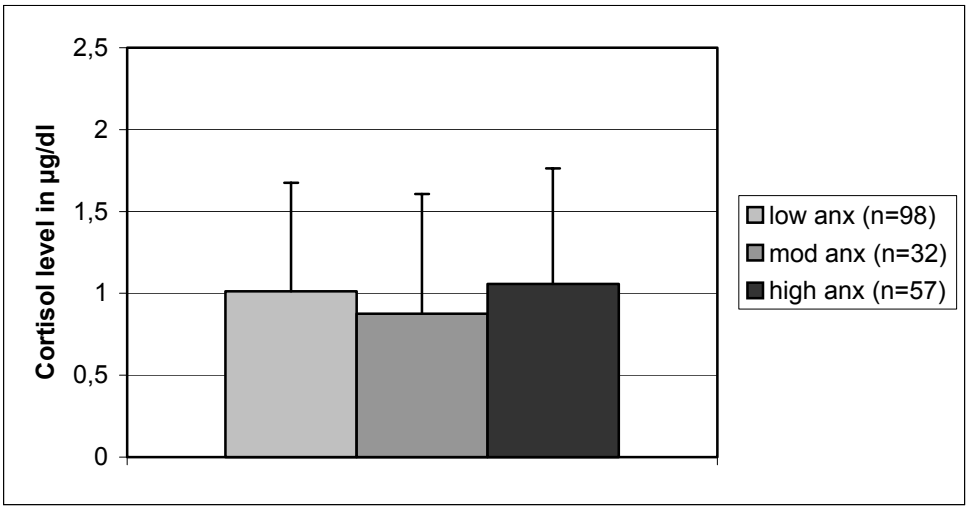

Figure 5. *Differences in cortisol concentration between low (low anx, n= 98), moderate (mod anx, n= 32), and high (high anx, n= 57) anxiety trajectory subgroups (F(2,184)= 0.75, p= .48).*

Finally, we used a stepwise multiple regression analysis to identify the aggression assessment that best predicted salivary cortisol level when controlling for each of the other assessments. We found that aggressive CD symptoms, together with reactive aggression score, best predicted cortisol level, accounting for 8.5% of the variance (with *beta*= 0.21, *p*< .01 and *beta*= 0.16, *p*= .05, respectively, *F*(2,165)= 7.62, *p*< .01). Once aggressive CD symptoms and reactive aggression had been entered into the equation, covert CD symptoms, proactive aggression, and the aggression trajectory variables did not add significantly to the prediction.

DISCUSSION

The aim of the present study was to investigate in early adolescent boys the relationship between cortisol and different types of aggressive and antisocial behavior. In contrast to our prediction, the results suggest that teenage boys who have a history of relatively high levels of antisocial behavior have higher levels of cortisol than similarly aged boys with less behavioral problems, and therefore could have a more active hypothalamic-pituitary-adrenal (HPA) axis. However, when different forms of antisocial behavior were taken into account, the results indicated that it were specifically the boys who scored relatively high on aggressive CD symptoms that were the ones who had higher levels of cortisol (see Figure 2). Moreover, high cortisol levels were also found to be related to reactive forms of

aggression (see Figure 4). These results confirm some previous findings that an association between cortisol with antisocial behavior is most evident for aggression (McBurnett et al 2000). Still, our pattern of findings is inconsistent with the results of some earlier studies which showed that antisocial children have lower levels of cortisol (McBurnett et al 2000; Pajer et al 2001; Van Goozen et al 1998a and 2000).

This potentially important difference could be related to differences in the types of participants used in the studies. Previous studies, which observed lower levels of cortisol in antisocial children often assessed clinical cases whereas the current sample was drawn from a large population-based sample followed prospectively from kindergarten to adolescence. Thus, within clinical samples, participants with the highest levels of aggressive behavior appear to have lower HPA axis activity; whereas in population samples the results suggest that the more aggressive individuals have elevated HPA axis activity. This phenomenon could be explained by the fact that there is not only a restriction of range in clinical samples, but also that the more severely aggressive cases are most likely to be found in clinical rather than population samples. Moreover, because our results with a population-based sample show that the aggression - cortisol association in particular concerns reactive aggression, clinically aggressive boys with low cortisol levels would theoretically be expected to engage more in proactive aggression. To our knowledge, studies addressing the cortisol - aggression relationship in clinical samples have not yet differentiated between proactive and reactive aggression. The previously established inverse association between cortisol and aggression in clinical samples could thus be dependent on the type of aggression measure used as well as the mix of proactively and reactively aggressive participants. Although the results of the present study indicate that in a community sample of early adolescent boys, those who tend to use reactive physical aggression may more frequently have a more active HPA axis, we could not determine with the available data whether this is a cause or a consequence of their chronic aggressive behavior.

Limitations

The present study had also some methodological limitations. First, the population-based sample was limited to young Caucasian males from lower socioeconomic areas in a large North American city. It will be important to replicate these results with other population-based samples. Second, like the majority of studies on cortisol (McBurnett et al 1991 and 2000; Scerbo and Kolko 1994; Shoal et al 2003; Vanyukov et al 1993), this study aimed to measure baseline cortisol concentration, and we therefore only took one sample which was collected on the participants' entrance to the laboratory. However, it has become clear that in order to be sure to measure the individual's baseline or resting cortisol level it is advisable to take more than one sample of saliva while keeping the participant in a relaxed state. Third, we collected salivary cortisol in 1991, using the filter paper method of Stahl and Dorner (1982), which is now considered to be a less optimal method. This might be an explanation for the rather high cortisol levels that we observed. Future research should use other collection methods, such as the salivette sampling device (Sarstedt Inc., Rommelsdorf, Germany). Fourth, since no special dietary restrictions were placed on the boys the night

before the laboratory visits in 1991, we were not able to examine the effect of possible stimulants on the relationship between cortisol and aggression. Fifth, another issue that is potentially important and that the current study could not address, is that it is unclear which cortisol parameter has the most reliable relationship with aggression. At present, it is not clear whether differences between aggressive and non-aggressive groups exist for baseline cortisol levels or for changes in cortisol reactivity during stress. Only a few aggression - cortisol studies have measured changes in cortisol due to stress (Gerra et al 1997; Klimes-Dougan et al 2001; Moss et al 1995; Susman et al 1997; Van Goozen et al 1998a and 2000). Clearly, future studies should within each individual take repeated measurements of cortisol under varying conditions, while keeping the timing for all participants equal. Moreover, because of its strong diurnal rhythm with lower afternoon values, the influence of external stimulation on cortisol can be more reliably assessed in the afternoon. Also, it is clear that studies need to assess antisocial behavior and aggression in ways that would be comparable (Tremblay 2000 and 2003). Finally, future studies should examine assessments of proactive and reactive aggression from different sources of information.

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3

Salivary Testosterone and Aggression, Delinquency, and Social Dominance in a Population-Based Longitudinal Study of Adolescent Males

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ABSTRACT

Background
Testosterone (T) has been found to have a stimulating effect on aggressive behavior in a wide range of vertebrate species. There is also some evidence of a positive relationship in humans, albeit less consistently.

Methods
In the present study we investigated the relationship between T and aggression, dominance and delinquency over time, covering a period from early adolescence to adulthood. From a large population-based sample (*n*= 1,161) a subgroup of 96 boys was selected whose behavior had been assessed repeatedly by different informants from age 6 to 21 years, and who had provided multiple T samples over these years of assessment.

Results
On the whole, a decrease in aggressive and delinquent behavior was observed in a period in which T rises dramatically. Boys who developed a criminal record, had higher T levels at age 16. In addition, positive associations were observed between T and proactive and reactive aggression and self-reported delinquent behavior.

Conclusions
Over the pubertal years different forms of aggression and antisocial behavior were positively related to T, which may indicate that specific positive links are dependent on the social setting in which this relationship is assessed.

INTRODUCTION

Testosterone (T), which is the most important male sex hormone, affects not only physical but also behavioral masculinization. For example, T has been found to increase aggressive behavior in a wide range of vertebrate species (Archer 1988). Studies in male rodents show that competitive or intermale aggression increases at puberty, a time in which T levels dramatically rise. Also, administration of T results in an increase in aggression (Brain 1979), whereas it is reduced by (chemical) castration (see Van Goozen et al 1995 for results in humans).

In human adults, T has been found to be related to delinquency, drug abuse (Dabbs and Morris 1990) and criminal violence (Dabbs et al 1995; Ehrenkranz et al 1974; Kreuz and Rose 1972; Strong and Dabbs Jr 2000), as well as to conduct problems in childhood (Dabbs and Morris 1990). However, Bain and colleagues (Bain et al 1987) found no difference in T between men charged for aggressive or non-aggressive crimes. It is clear, therefore, that in humans the evidence is at best suggestive of a positive relationship (Archer 1991).

Little information exists about the influence of T on behavior in children and adolescents, although one could argue that if one wants to study this relationship it can better be done at a younger age because socializing processes start early. Some studies have indeed found a positive relationship between T and aggression. For example, associations were found between heightened levels of T and physical and verbal aggression (Olweus et al 1980 and 1988), persistent externalizing behavior (Maras et al 2003), and age-graded norm-violating behaviors (Udry 1990) within a sample of (early) adolescent males. Scerbo and Kolko (1994) studied pre- and early adolescent clinical cases and found that T was related to increased staff-rated aggression. Likewise, disruptive children, especially boys approaching puberty, seem to have higher T levels as compared to normal controls (Chance et al 2000). Sánchez-Martín and colleagues (Sánchez-Martín et al 2000) found a positive relation between T and the frequency of engaging in aggressive interactions in four-year-old boys. However, it is also important to keep in mind that there are also quite a few studies that have found no relationship between aggression and T in children or adolescents (Constantino et al 1993; Halpern et al 1993; Inoff-Germain et al 1988; Mattsson et al 1980; Susman et al 1987; Van Goozen et al 1998b). Moreover, one study, using a multitrait, multimethod procedure, found a relationship between T and disruptive behavior in girls, but not in boys (Granger et al 2003). In a study by Schaal and colleagues (Schaal et al 1996) boys with a history of high levels of physical aggression between age 6 and age 12 had even lower T levels at age 13 than boys without such a history.

These mixed findings in studies on children and adolescents may be due to important methodological differences between the studies. First, some studies have used a clinical sample of children referred for disruptive behavior disorders (Chance et al 2000; Constantino et al 1993; Scerbo and Kolko 1994; Van Goozen et al 1998b), while others examined the T-aggression relationship in a population-based sample of boys (Olweus et al 1980; Schaal et al 1996; Udry 1990). Second, most studies only used a single measurement of T (e.g., Constantino et al 1993; Scerbo and Kolko 1994; Strong and Dabbs, 2000), taken from blood or saliva, whereas only a few studies assayed T levels from multiple (saliva) samples

(Granger et al 2003; Sánchez-Martín et al 2000; Schaal et al 1996). Third, most studies (Constantino et al 1993; Sánchez-Martín et al 2000; Scerbo and Kolko 1994) have made use of small sample sizes, which affects the power of the study as well as the generalizability of the results. Fourth, different instruments have been used to investigate this relationship, and therefore a mixture of information on various forms of antisocial behaviors (disruptive, assertive, or physically aggressive behaviors) has been collected (Tremblay et al 1998). Studies that assess aggression have generally not taken into account different types of aggression, e.g., whether it is reactive or proactive in nature. Reactive and proactive aggression have been observed in children, adolescents and adults (Brendgen et al 2001; Dodge et al 1997; Pulkkinen and Tremblay 1992; Vitaro et al 1998). Reactive aggression is impulsive and often accompanied by disinhibition, affective instability, and high levels of bodily arousal, but it is not necessarily characterized by antisocial tendencies. On the other hand, proactive aggression is nonimpulsive and controlled, and occurs in the context of persistent antisocial behavior. Proactive aggressive individuals are less likely to have unstable affects, their aggression is goal-directed, and the level of arousal is usually low (Vitiello and Stoff 1997). And fifth, studies examining the T-aggression relationship in children and adolescents obviously differed in the age of the participants, varying from prepubertal to postpubertal ages, which affects the outcome of the relationship. We already mentioned that Schaal et al (1996) showed that boys who were physically aggressive between age 6 and 12 years had, at age 13, a lower mean T level compared to those who had never been physically aggressive. However, when the same boys were followed up, the T levels of the physically aggressive boys were found to be higher at age 16; thus a group by time interaction was observed (Tremblay et al 1997).

Although the focus of most research has been on aggression, there is also evidence from studies in nonhuman primates of a relatively strong association between testosterone and dominance (Mazur and Booth 1998; Paikoff and Brooks-Gunn 1990). Social dominance may or may not involve aggressive behavior and it is possible that a more direct relationship exists with dominance than with aggression (Albert et al 1993; Strong and Dabbs 2000). This line of reasoning has been supported in humans (Rowe et al 2004; Schaal et al 1996), in which it was shown that testosterone levels were associated with social success rather than with physical aggression.

In the present study we explored the relationship between testosterone and antisocial behavior in a period covering early adolescence and adulthood. Puberty is a period in which T levels progressively rise from extremely low to mature levels, and it is also - in most cultures - a period of psychological development characterized by increases in antisocial behavior (Moffitt 1993a; Weisfeld and Berger 1983). Therefore, one would expect that longitudinal studies from childhood to adolescence and adulthood could provide crucial data on the influence of hormones on behavior (Archer 1991). To this end we based ourselves partly on data reported by Schaal et al (1996), but extended the measurement period to adulthood and used a larger number of behavioral assessments. Our first aim was to examine whether, in concert with a rise in T, different types of antisocial behavior increased from early adolescence into adulthood. Secondly, we wanted to investigate whether physical

aggression, social dominance and/or delinquent behavior, as shown from childhood to adulthood, had a positive relationship with (changing) T levels. We expected to find an overall increase in antisocial behavior, together with a rise in T, in our assessment period. Moreover, when examining T levels in separate years, we expected to find positive relationships between T and physical aggressive, social dominant, and/or delinquent behaviors.

METHOD

Participants

The participants involved in the present study (*n*= 96) were part of a longitudinal study that started in 1984, when teachers of kindergarten classes in 53 schools in an urban area in Montreal were asked to rate the behavior of each boy in their classroom (Tremblay et al 1994). Eighty-seven percent of the teachers agreed to participate, and 1,161 boys were rated. To minimize social and cultural effects, the boys were recruited according to the following criteria; 1) attending school in low socioeconomic areas of Montreal; 2) born from Caucasian, French-speaking parents themselves born in Canada; and 3) living with parents having medium to low educational status. The sample was reduced to 1,037 boys after applying these criteria and eliminating those who declined to participate and those who could not be located (Tremblay et al 1994 and 1995).

Physically aggressive behavior was assessed at ages 6, 10, 11, and 12 years by means of the fighting subscale of the teacher form of the French Canadian version of the Social Behavior Questionnaire (SBQ; Tremblay et al 1991a). Physical aggression could be determined for 893 boys, after boys who withdrew from the longitudinal project (*n*= 116) and boys who had more than one missing value (*n*= 28) had been eliminated (see also Séguin et al 1995 and 1996). Stable highly aggressive boys were defined as those who fell above the 70th percentile at age 6 and on two or more assessment points on the physical aggression scale (19% of the sample). Nonaggressive boys had scores that fell below the 70th percentile at all assessment points (35% of the sample). Those who did not meet the above criteria were classified as unstable aggressive boys (46% of sample). Compared to another sample of boys (*n*= 882) representative of the whole province, physically aggressive behavior is over-represented in this urban community sample of low socioeconomic status (SES; Séguin et al 1996).

For logistical reasons, we were able to invite approximately 200 13-year old boys to come to the laboratory for various observational and experimental procedures. Several overlapping criteria were used to select this subsample. Exclusion criteria (for purposes not particular to this study) were applied as follows: 234 boys who could not be classified as stable anxious or stable nonanxious were eliminated, as well as 326 boys who did not meet priority criteria such as (a) stability of physical aggression or nonaggression, (b) a history of going to the laboratory since age 6, or (c) a pattern of late onset physical aggressive or anxious behavior. Thus, some moderate or unstable anxious boys remained in the selected sample because they met some of these priority criteria (*n*= 138). Those who met priority criteria (b) or (c)

but not (a) were classified as unstable aggressive boys. When all these criteria were applied, the selected sample consisted of 333 boys. At age 13, 203 of these boys agreed to come to the laboratory (Séguin et al 1995 and 1996). Only data of those participants were used in subsequent analyses when information on their T level was available when they had been 13, 16 and 21 years old. This resulted in a sample of 96 males. This subsample did not differ from the larger sample (*n*= 941) on a number of important characteristics such as SES, physical aggression trajectory group (Nagin and Tremblay 1999), and/or reactive or proactive aggression. We considered this subsample therefore to be representative of the sample at large.

Procedure and instruments

Initial examination of the data revealed that correlation coefficients (*r*) between annual scores for reactive and proactive aggression (as assessed at age 12, 13, 14, and 15), and for toughness and leadership (as assessed at age 13, 14, and 15) were relatively high (*r* varied from .21 to .67 for successive years), indicating a relatively high stability of individual aggression rank over time (see Table 1). Also, a relatively high *r* was found for scores on delinquency (as assessed at age 13, 15 and 20; *r* varied from .30 to .41, see Table 2). Therefore, these behavioral measures were assumed to be more trait-like, and we decided to create high and low aggressive and delinquent subgroups based on the means calculated over these years. Moreover, because correlation coefficients between T levels at age 13, 16, and 21 were low (*r* varied from .02 to .19, see Table 3), we decided not to calculate a mean T value over time, but to use annual T data instead.

Table 1. *Correlation coefficients (r) for annual aggression- and social dominance scores at age 12, 13, 14, and 15.*

		Respective aggressive behavior		
		age 13	age 14	age 15
Leadership	age 13	-	.21*	.19
	age 14	-	-	.46**
Toughness	age 13	-	.37*	.27*
	age 14	-	-	.42*
Proactive aggression	age 12	.58**	.51**	.25*
	age 13	-	.40**	.33**
	age 14	-	-	.51**
Reactive aggression	age 12	.56**	.46**	.32**
	age 13	-	.49**	.46**
	age 14	-	-	.67**

* $p < .05$

** $p < .01$

Table 2. *Correlation coefficients (r) for annual delinquency scores at age 13, 15, and 20.*

		age 15	age 20
Delinquency	age 13	41**	.10
	age 15	-	.30**

* $p < .05$
** $p < .01$

Table 3. *Correlation coefficients (r) for annual T levels at age 13, 16, and 21.*

		age 16	age 21
Testosterone	age 13	.19	.05
	age 16	-	.02

* $p < .05$
** $p < .01$

Peer rating assessments at 13 to 15 years of age

During the laboratory visit, once a year at age 13 to 15 years, ratings of toughness and leadership were obtained from individual interviews during which every subject from a peer group was asked to nominate the leader ('Who would you choose as leader?') and identify the toughest boy ('Who was the toughest?'). The interviews were done at approximately 10:30 AM, three hours after the boys had been picked up at home and driven together (in groups of 3 to 5) to the laboratory in a van, had been assessed individually on personality, cognitive functioning, and had taken part in a competitive group task to provide an opportunity to observe social interaction. Each subject received a toughness and a leadership score ranging from 0 to 5 depending on the number of nominations he received (including self-nominations). Average scores were computed over age 13 to 15, and we created a low tough (LT, $n = 49$) and a high tough (HT, $n = 47$) subgroup, using the median score. In a different analysis we created a low leader (LL, $n = 49$) and a high leader (HL, $n = 47$) subgroup. Thereafter, and following Schaal et al (1996), these subgroups were combined, resulting in a low tough-low leader (LT-LL, $n = 31$), a low tough-high leader (LT-HL, $n = 18$), a high tough-low leader (HT-LL, $n = 18$), and a high tough-high leader (HT-HL, $n = 29$) subgroup.

Assessments of reactive and proactive aggression from 12 to 15 years of age

In addition, when the boys were 12, 13, 14 and 15 years old, their teachers completed three reactive aggression, and three proactive aggression items (Dodge and Coie 1987) The reactive items were "when teased or threatened he gets angry easily and strikes back"; "when accidentally hurt by a peer he assumes that the peer meant to do it and then overreacts with anger and fighting"; and "always claims that other children are to blame in a fight and feels that they started the whole trouble". The proactive items were "uses (or

threatens to use) physical force in order to dominate other children"; "threatens or bullies others in order to get his way"; and "gets other children to gang up on a peer he does not like". The 3-unit response scale for these items ranged from 0 "does not apply", and 1 "applies sometimes", to 2 "applies often" (Brendgen et al 2001). Cronbach's alpha's varied between .82 and .86. For each year a reactive and proactive aggression score was calculated by summing the scores of the three respective items, resulting in an annual reactive and proactive score ranging from 0 to 6. Five boys did not participate in the analyses, as they had missing values on reactive or proactive aggression in more than two years. Based on the average scores at age 12 to 15 years, we created a low reactive aggressive (LRA, *n*= 47) and a high reactive aggressive (HRA, *n*= 44) subgroup, using the median score. In a different analysis we created a low proactive aggressive (LPA, *n*= 50) and a high proactive (HPA, *n*= 41) subgroup.

Assessments of delinquency at 13, 15, and 20 years of age

A 27-item delinquency questionnaire was administered to the boys when they were 13 and 15 years old (Tremblay et al 1994). A revised and for this age group adjusted version was administered at age 20. This questionnaire was reduced to 23 items ([1] items are overlapping, and [2] items are added at age 20). The items, which were rated on a 4-point scale (never, once or twice, a number of times, very often), included: 'steal objects worth more than $10 in school[1]', 'steal from store[1]', 'take psychostimulants/hallucinogenics[2]', 'take opiates[2]', 'steal objects worth more than $100[1]', 'take money from home', 'keep object worth less than $10', 'keep objects worth between $10 and $100[1]', 'steal a bicycle[1]', 'steal a car[2]', 'sell stolen goods', 'enter without paying[1]', breaking and entering[1]', 'trespassing[1]', 'take marijuana[1]', 'take alcohol', 'get drunk', 'destroy school material[1]', 'destroy other material[1]', 'vandalism at school[1]', 'destroy objects at home', 'vandalism of cars[1]', 'set a fire[1]', 'strong-arm[1]', 'gang-fights[1]', 'use weapon in a fight', 'fist fight', 'force someone into sexual activity[2]', 'beat up someone[1]', 'carry a weapon[1]', 'throw objects at persons[1]'. Three boys did not participate in the analyses, as they had missing values in more than one year. The total number of items generates a total delinquency score (Cronbach's alpha at age 13, 15, and 20 ranges from .82 to .93). The total scores were transformed into Z-scores within each year to correct for variation in number of items. Next, average Z-scores were calculated for ages 13 to 20, and based on these scores we created a low (LD, *n*= 47) and a high delinquency (HD, *n*= 46) subgroup, using the median score.

Assessments of Conduct Disorder (CD) and physical aggression at age 15

The Diagnostic Interview Schedule for Children (DISC-2.25) (Shaffer et al 1991) was administered to the participants and their parents (mostly their mothers) when the boys were approximately 15 years old. A letter followed up by telephone contact served to solicit participation (Séguin et al 1999). The DISC could not be administered to 5 of the participants, and 2 participants had only a child or a parent report. A participant was attributed to the CD subgroup when he met two or more of the thirteen CD criteria based on combined reports of parent and child. In this way a CD subgroup consisting of 10 boys and a normal control (NC) subgroup of 81 boys were created.

Official criminal records as an adult

We created subgroups based on the information of whether boys did or did not have an official crime record as an adult (18 to 20 years of age). We have been given access to this information by The Royal Canadian Mounted Police (RCMP). We could not get criminal record information for 18 of the participants. A 'no official record' (NOR, *n*= 71) and an 'official record' (OR, *n*= 7) subgroup was composed.

Assessments of physical aggression trajectories from 6 to 15 years of age

The estimation of developmental trajectories for repeated measures of physical aggression from kindergarten to mid-adolescence is based on teacher reports. The boys' classroom teachers rated physical aggression in the spring of each year using the Social Behavior Questionnaire (Tremblay et al 1991a). This questionnaire was administered when the boys were age 6, 10, 11, 12, 13, 14, and 15 years. Physical aggression was assessed with three items; "kicks, bites, hits"; "fights"; and "bullies or intimidates other children". The range of possible values of the physical aggression score was 0 through 6. The internal consistency scores (Cronbach's alpha's) for the physical aggression scale ranged from .78 to .87 with a mean reliability score of .84 for assessments between 6 and 15 years.

Nagin and Tremblay (Nagin and Tremblay 1999 and 2001) identified four distinct groups when they estimated the developmental trajectories of physical aggression for the total Montreal sample with a semiparametric, group-based method. When applied to our sub-sample the criteria led to the following four groups: a low physical aggression trajectory group (LOW, *n*= 21), a moderate physical aggression trajectory group (MOD, *n*= 37), a high physical aggression trajectory group (*n*= 35), and a chronic physical aggression trajectory group (*n*= 3). Because the latter group was so small, we combined the high and chronic trajectory groups into one high physical aggression trajectory group (HIGH, *n*= 38).

Assessments of pubertal status at 13 and 16 years of age

Pubertal status was self-assessed at age 13 and 16 using the Pubertal Development Scale (Petersen et al 1988). This scale of pubertal status assessment integrates self-report of growth spurt, body and facial hair development, and skin and voice changes on 4-point scales. Pubertal status could not be assessed for 10 of the participants. Classification into one of the five pubertal status categories (pre-, early, mid-, late, and postpubertal) is based on the level of development of the three most salient indices of pubertal change (i.e., body hair, facial hair, and voice alterations. Because most boys were either in the early pubertal or midpubertal status categories at age 13, and in the midpubertal or late pubertal status categories at age 16, we decided to transform this variable into a dichotomous variable.

Testosterone measurements

T levels were assayed from multiple saliva samples collected during a visit to the laboratory in 1991 (at approximately 8:30 AM, 10:00 AM, 11:30 AM, and 3:30 PM), in 1994 (at approximately 9:25 AM, 10:30 AM, 12:00 AM, and 2:00 PM), and in 1999 (at approximately 9:00 AM, 10:00 AM, and 11:00 AM). A mean level of T was calculated for each year in order to get more reliable values. Participants were requested to donate saliva into sterile vials,

which were immediately frozen (-20°C) until radioimmunoassay. The assays were performed blindly. The procedure was a variant of that established by Vittek et al (1984) with T-assay kits purchased from ICN Biomedicals Inc. (Montreal). Once centrifugated, 500 µL of saliva was pipetted and extracted with 2 mL of ether. One milliliter of the organic phase was taken and evaporated to dryness. The residue was incubated at 37°C for 120 minutes with 50 µL of steroid diluent. After incubation, 100 µL of sex-hormone-binding-globulin inhibito, 400 µL of ^{125}I-testosterone, and 400 µL of anti-T were added and incubated overnight. A separation antibody was then added and allowed to incubate for 90 minutes at 37°C. After 15 minutes of centrifugation, the supernatant was discarded and the tube was counted in a gamma counter. Precision of the analytical procedure was improved by extraction of the standard curve. Intraassay and interassay coefficients of variation were 6.3% and 12.3%, respectively. Regarding the specificity of the assay, no significant cross-reactions of the antibody were measured, except for 5-α-dihydrotestosterone (3.4%). In 1999, we used a commercially available radioimmunoassay kit (Coat-A-Count Total Testosterone Determinations in Saliva; Diagnostic Products Corp., Los Angeles, California). The intraassay coefficients of variation were 13.92% and 6.66% respectively at 43.29 pg/ml and 154.92 pg/ml. The interassay coefficients of variation were 19.95% and 10.81% respectively at 43.29 pg/ml and 154.92 pg/ml. Regarding the specificity of the assay, very little crossreactivity was measured, except for dihydrotestosterone, which was less than 5%. The titration of T from saliva was preferred to any other way of obtaining similar data for practical and theoretical reasons. Its application being unobtrusive, it does not interfere with stress-elicited alterations of T. In addition, the handling of saliva is uncomplicated in comparison with the handling of blood or urine. Salivary T level, being highly correlated with the unbound fraction of circulating T, is assumed to be a precise indicant of the behaviorally active fraction of T (Riad-Fahmy et al 1982; Wang et al 1981).

T trajectory groups

Based on their T levels in 1991, 1994, and 1999, participants were divided into a low (LT), a moderate (MT), or a high (HT) testosterone group. For someone to be assigned to the LT group he had to have T values in the lower 33% of at least two of the 3 years of assessment. In a similar way boys were classified as belonging to the MT or HT group. In this way, 15 boys were classified as LT, 26 as MT, and 18 boys as HT.

Data analyses

In order to examine whether aggressive and delinquent behaviors, as well as T levels, changed over time, analyses of variance (ANOVA's) with repeated measures were used. Moreover, Pearson correlations between T levels and pubertal stage were calculated. In case of high positive correlations pubertal stage was entered as covariate in further analyses. AN(C)OVA's with group as independent and T level at age 13, 16, and 21 as dependent variable were conducted to find out whether there were differences in salivary T between low and high antisocial groups. Values are expressed as means (± SD). In case of significant group differences between more than two groups, post-hoc Bonferroni tests for multiple comparisons were conducted. When scores or groups were unevenly distributed non-

parametric tests were used. Single isolated outlier values, with an outlier defined as an individual value more than 2.5 SD's above the mean value of the group, were replaced by the group averages. In addition, an ANOVA with T trajectory groups as between subject factor and aggression scores as dependent variables was used to examine whether T trajectory groups differed in their antisocial, aggressive, or delinquent behavior scores. In case the dependent variables were dichotomous, we conducted a Pearson chi-square test.

Finally, a continuous variable stepwise approach using multiple regressions was applied to establish whether the various assessments of aggressive and delinquent behavior from childhood to adulthood had a predictive relationship with T at age 21. With respect to the teacher reported reactive and proactive aggression scores, correlations were calculated between these scores, and on the basis of these results, proactive and/or reactive aggression scores were entered in the regression analysis. Continuous scores for proactive- and reactive aggression (mean scores over ages 12 to 15), for toughness and leadership (mean scores over ages 13 to 15), and for delinquency (mean scores over age 13, 15, and 20), dummy scores for CD group and crime record group, and the probability score of being in the high physical aggression trajectory group (see Nagin and Tremblay 1999 and 2001) were used as predictors, whereas T level at age 21 was entered as dependent variable.

RESULTS

Behavioral and T changes in the pubertal period

Figures 1 and 2 show the patterns of mean T levels at age 13, 16, and 21 (Figure 1) and behavioral assessments from early adolescence to adulthood (Figure 2). As expected, T levels increased significantly in this time period ($F(2,94)= 160.4$, $p< .01$). However, contrary to expectation, significant main effects of time were found reflecting an overall decrease in scores on teacher rated proactive- ($F(3,66)= 4.6$, $p< .01$) and reactive aggression ($F(3,66)= 10.7$, $p< .01$). With respect to self-reported delinquency we also found a significant curve linear effect of time ($F(2,74)= 46.4$, $p< .01$).

T levels in aggressive and antisocial subgroups

Next, separate AN(C)OVA's were conducted to find out whether there was a relationship between T and antisocial or aggressive behavior at age 13, 16, and 21 years (see Table 4).

At age 13 T correlated moderately strong with pubertal status ($r= .30$, $p< .01$) but at age 16 the size of the correlation was much lower ($r= .12$, ns). Pubertal status at age 13 was therefore entered as a covariate in the analyses for that particular year. When examining the differences between high and low aggressive or antisocial subgroups in T level at age 13, we did not find any significant differences (see Table 4).

At age 16, boys with an official crime record were found to have significantly higher T levels compared to boys without such a record (Mann Whitney U test; $Z= -2.14$, $p= .03$). Moreover, at age 16 T was higher in high proactive aggressive (HPA) boys than in low proactive aggressive (LPA) boys (Mean $\pm$ SD: LPA= 38.3 $\pm$ 19.0 pg/ml, HPA= 53.4 $\pm$ 22.6 pg/ml, $F(1,89)= 11.89$, $p< .01$), and higher in the high reactive aggressive (HRA) subgroup

than in the low reactive aggressive (LRA) subgroup (Mean ± SD: LPA= 39.5 ± 19.3 pg/ml, HPA= 51.1 ± 23.1 pg/ml, $F(1,89)= 6.83$, $p= .01$). No T differences were found at age 16 between high and low dominant groups, high and low physically aggressive groups, groups with and without CD, or between self-reported delinquent subgroups (see Table 4).

At age 21, high delinquent males (HD, $n= 46$) had higher T levels than low delinquent males (LD, $n= 47$; $F(1,91)= 11.1$, $p< .01$). No meaningful differences in T were found between the other antisocial or aggressive subgroups.

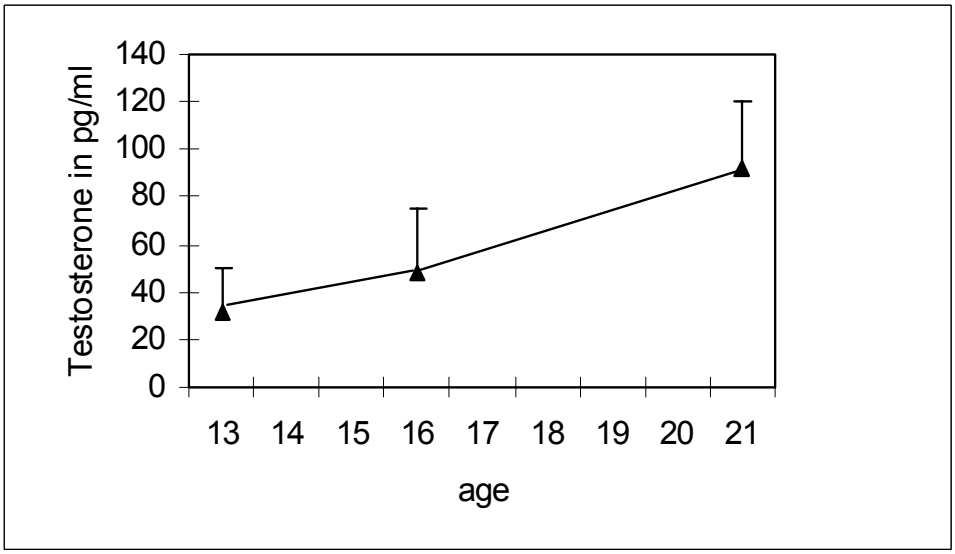

Figure 1. *Changes in mean T over the day from early adolescence to adulthood.*

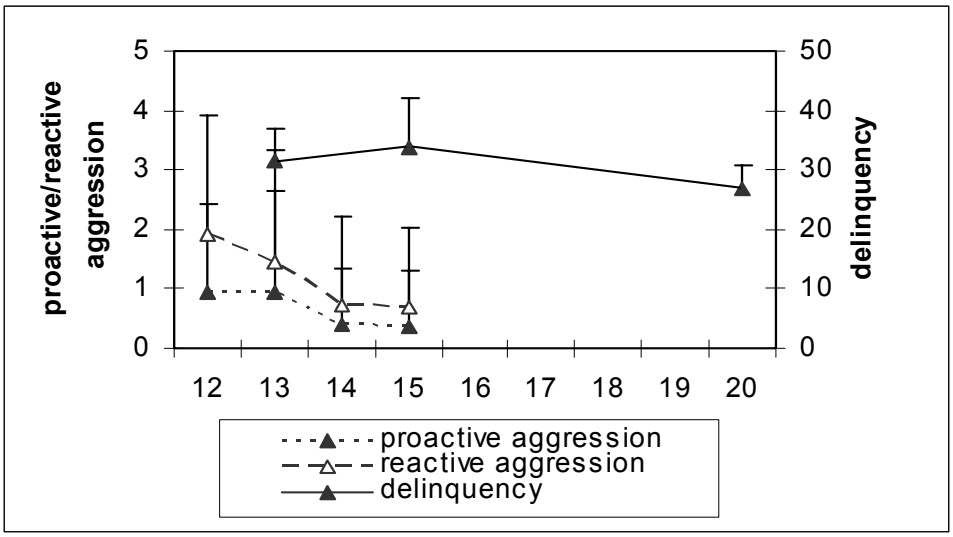

Figure 2. *Changes in scores for (proactive and reactive) aggression and delinquent behavior from early adolescence to adulthood.*

Table 4. Differences in T level between aggression- and antisocial subgroups at age 13, 16, and 21.

	Age 13 (ANCOVA)			*Age 16 (ANOVA)*			*Age 21 (ANOVA)*		
Independent variables	*df*	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
Toughness	1,83	0.59	.45	1,94	0.06	.81	1,94	0.04	.84
Leadership	1,83	3.50	.07	1,94	0.46	.50	1,94	0.29	.59
Proactive Aggression	1,80	0.33	.57	1,89	11.89	.00	1,89	0.17	.68
Reactive Aggression	1,80	0.01	.94	1,89	6.83	.01	1,89	0.01	.95
Aggression trajectory	2,82	0.11	.89	2,93	2.16	.12	2,93	1.16	.32
Delinquency	1,83	0.09	.76	1,91	0.34	.56	1,91	11.11	.00
Interactions									
Toughness x leadership	3,81	1.00	.40	3,92	0.26	.85	3,92	0.30	.82

T trajectories

Additional analyses were conducted to examine whether T trajectory groups differed in scores for antisocial behavior. We found that of the 5 boys who had a criminal record no one belonged to the LT group, one belonged to the MT group, and the remaining four boys belonged to the HT group (Pearson chi-square= 6.21, p= .05).

Finally, a (linear) stepwise multiple regression analysis identified the behavioral assessment that best predicted T at age 21 when controlling for each of the other assessments. Although a high correlation was found between the mean reactive and proactive aggression scores (r= .79, p< .01) this score was not sufficiently high enough (the criterion being r > .90) to treat these variables as essentially the same. Both variables were therefore entered into the analysis. It turned out that the mean Z-score on self-reported delinquency between age 13-20 years best predicted T level at age 21, accounting for 5.5% of the variance (with Beta = .24, F(1,69)= 4.02, p= .05). Once the delinquency score had been entered into the equation, the other antisocial or aggression variables did not add significantly to the prediction.

DISCUSSION

So far, very few studies (Drigotas and Udry 1993; Granger et al 2003; Tremblay et al 1997) have examined the aggression – testosterone (T) relationship by taking repeated samples of T over time and by assessing this relationship longitudinally with a multi method/multi informant procedure. In the present study, we first aimed to explore whether aggressive and/or delinquent behaviors increased from early adolescence to adulthood due to the concurrently rising levels of T. Secondly, we investigated whether physical aggression, social dominance and/or delinquent behavior, as observed from childhood to adulthood, had a positive relationship with (changing) T levels. To that end, we examined a population-based

sample of boys (n= 96) who were followed from kindergarten up to age 21. As expected, T levels increased significantly during pubertal development. However, contrary to prediction we found that in the same period, boys did not display an increase in either teacher-rated aggressive behavior or self-reported delinquency; we even observed a decreasing pattern in these types of behavior. These findings are in line with earlier results (Susman et al 1987), in which T levels were found to rise with pubertal stage and age, but no significant positive relationship was found between aggression and age. These results clearly pose problems for accounts of an activational influence of T on aggressive behavior. Thus, the evidence for a direct, activating or stimulating effect of T on aggression during adolescence remains therefore at best controversial (Eichelman 1992; Reiss and Roth 1993).

However, a further and closer examination of the data showed that at different annual time points there were clear and positive associations between T, on the one hand, and aggressive, antisocial, and/or delinquent behavior, on the other. We found that boys who turned out to have an official crime record as an adult (so-called criminals-to-be), had higher T levels at age 16, compared to boys without such a record. Moreover, we found that high proactive and high reactive aggressive boys also had higher T levels at age 16 than the low aggressive subgroups. At age 21, T levels were higher in boys who were highly delinquent from age 13 to age 20, compared to the low delinquent subgroup. In a linear stepwise regression analysis, we also showed that the mean self-reported delinquency score from age 13 to 20 was the only and therefore best predictor of T level at age 21. In contrast to earlier findings by Schaal et al (1996), no relationship was found between T at age 13 and either nominations of toughness or leadership. This is surprising given that the Schaal et al study and the present one at least in part shared the same data set. An important difference between these two studies, however, is that we decided to use in the present statistical analyses the mean T level as calculated over several samples collected on one day, whereas Schaal et al (1996) examined the pattern of T concentration over the day. In addition, from a further set of analyses in which we created T trajectory groups, it became clear that the boys who consistently have the highest levels of T over the years are the ones who later have an elevated risk of becoming delinquent convicts. Thus, although there is some positive association between T and dominant, antisocial or delinquent behavior over the years of assessment, different variables turn out to have a significantly positive relation with T at different ages, while it is the general impression that T is most closely related to delinquent behavior. At present it is not clear why this is the case. One explanation is that we used a sample that was restricted to boys from low socioeconomic families. SES is known to correlate inversely with externalizing problems, such that lower SES boys show higher average levels (e.g., Nagin and Tremblay 2001). Thus, the present sample is composed of adolescents who could be expected to be at the higher end of the continuum of externalizing behavior, and this restriction of variance may influence the likelihood of detecting relations among the variables. In addition, Mazur and Booth (1998) suggested that dependent on the social setting T could be related to dominance, aggressive behavior, or antisocial behavior, such as norm breaking. Within settings in which the behavior of subordinates is required to conform to rigid norms or laws (e.g., such as in schools), high T in dominant boys could

encourage types of behavior which are regarded as rebellious, antisocial, or even criminal (Mazur and Booth 1998). We examined in our study boys over a period of important physical, emotional and social change and thus depending on the precise timing of the measurements and the circumstances of the boys T could be related to different types of antisocial, aggressive or dominant behavior.

Limitations

The present study also had some methodological limitations. First, the population-based sample was limited to young Caucasian males from lower socioeconomic areas in a large North American city. It will be important to replicate these results with other population-based samples. Second, it is clear that future studies even more than we did now need to assess antisocial behavior and aggression in ways that are comparable (Tremblay 2000; Tremblay 2003). Third, future studies could examine assessments of proactive and reactive aggression from different sources of information. And finally, although we examined the aggression – T link longitudinally by measuring T and antisocial behavior repeatedly over time, future studies should assess T, antisocial behavior, and measures of social context simultaneously.

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4

Adolescent Outcome of Disruptive Behavior Disorder in Children who were treated in In-Patient and Day-Treatment Settings

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ABSTRACT

Background
Although several studies have been conducted on the longitudinal course of childhood disruptive behaviors in community samples and in general psychiatric samples, little is known about adolescent adjustment in psychiatrically treated DBD children.

Methods
We examined a sample of adolescents (*n*= 47) who had been treated as children in an in-patient and/or day-treatment setting because of their severely disruptive behavior.

Results
At follow-up, we found that half of the adolescents had a DBD diagnosis, and on average higher numbers of participants ever used soft drugs, have ever been in court, were not attending school when this was mandatory, and were smoking on a daily basis, as compared to comparison groups. There was, however, a large variance among the adolescents of our sample. When outcome was defined in terms of DBD diagnosis, living status, delinquency, school attendance, and smoking behavior, 38% had a positive outcome and 34% had a poor outcome.

Conclusions
For clinical purposes it is important to recognize that there are large individual differences in outcome.

INTRODUCTION

Children who engage in oppositional, aggressive, or multiple antisocial behaviors that affect diverse domains of their functioning are said to have an oppositional defiant disorder (ODD) or a conduct disorder (CD; DSM IV American Psychiatric Association 1994). The term disruptive behavior disorder (DBD) covers both ODD and CD. The prevalence of these disorders is high; 3.2% for ODD and 2.0% for CD (Lahey et al 1999). In addition, their behavior is highly costly to society: these children cost at least ten times more than well developing children (Scott et al 2001). The aim of the present study was to describe the adolescent functioning of a psychiatrically treated DBD sample.

Although several studies have been conducted on the longitudinal course of childhood antisocial behavior in community samples and in general child and adolescent psychiatric samples, (e.g., Haapasalo and Tremblay 1994; Nagin and Tremblay 1999; Pulkkinen and Tremblay 1992), little is known about the adolescent or adult adjustment of DBD children who had been treated psychiatrically. Below, we will review studies on the adolescent outcome of children with severe behavioral problems.

Stability of antisocial behavior

Among the few studies that had been conducted on the persistence of disruptive behaviors in clinic-referred DBD children, there is a substantial stability in measures of antisocial behaviors (42% - 88%) at 2 to 7-year follow-ups (Grizenko 1997; Kazdin 1989; Lahey et al 1995 and 2002; Sourander and Piha 1998). For example, in a study of Lahey et al (1995), it was found that 88% of the boys who met criteria for CD met criteria again during the next 3 years. Moreover, it was shown that most boys with a childhood CD diagnosis continued to engage in significant numbers of CD behaviors up to the age of 18, although there were marked individual differences in the course of CD during adolescence (Lahey et al 2002). Kazdin (1989) showed that among hospitalized children with antisocial behaviors, those with CD were functioning more poorly at home and at school over the course of follow-up, compared to those without CD (but having ADHD, depression, adjustment disorders, anxiety disorders, or other mental disorders). Indeed, two years after intervention, 72% of the CD children were still in the borderline or clinical range according to the Child Behavior Checklist (CBCL; Achenbach 1991a). In another study in children with behavioral and emotional disorders, 45% of the children were functioning within the clinical range at three-year follow-up on the basis of parental (CBCL) ratings, whereas 44% fell within this range on the basis of teacher (TRF) ratings (Sourander and Piha 1998). In addition, some prospective studies determined how much of the variance in outcome could be explained by certain predictors. In the study by Grizenko (1997) it was shown that 42.2% of the variance in behavioral functioning of children at 5-year follow-up was explained by initial externalizing behaviors.

Adolescent and adult delinquency

With respect to delinquent outcome in DBD children, Robins (1966) found that two-thirds of the boys and half of the girls who were referred for their antisocial behaviors became officially delinquent in youth. Moreover, 71% of the male and 40% of the female participants

had been arrested as adults for a non-traffic offence (Robins 1966). In addition, in a study of hospitalized girls with CD, it was shown that 24% had been arrested by the police or had contact with the juvenile justice system at the time of follow-up (Zoccolillo and Rogers 1991). Other studies of adult outcome in antisocial women (e.g., Robins 1986; Robins and Price 1991) found that women are less likely than men to engage in adult criminal offences but have diffusely poor outcomes, including non-antisocial psychiatric disorders, serious difficulties with interpersonal relationships, use of social services, and early pregnancy. In a study of non-referred hyperactive boys (Satterfield and Schell 1997), among whom were boys with conduct problems, 53% of the hyperactive boys with conduct problems, compared to 13% of the hyperactive boys without conduct problems, were found to become a single or multiple adolescent offender. In addition, 26% of the hyperactive boys with conduct problems whereas none of the hyperactive boys without conduct problems became offenders in adulthood. This suggests that the risk of becoming an adult offender is associated with conduct problems in childhood and serious antisocial behavior in adolescence (Satterfield and Schell 1997).

Adolescent and adult substance use

In a prospective longitudinal cohort it was found that 39% of the adults with substance use disorder had a prior childhood DBD (Kim-Cohen et al 2003). Furthermore, a study on cigarette smoking showed that the presence of psychiatric comorbidity, especially in the form of disruptive behavior disorders, is common in adolescent cigarette smokers. Moreover, cigarette smoking in adolescence appeared to be a strong marker for future psychopathology (Upadhyaya et al 2002). In addition, cigarette smoking was found to be more prevalent in lower educated men than in men with higher education (e.g., Cavelaars et al 2000), however this was not the case in every country.

Depression

On the basis of retrospective data from a longitudinal, population-based sample of 2926 male and 1929 female adult twin subjects, prior psychiatric disorders (among which CD) were found to be significant risk factors for the development of major depressive disorders (Hettema et al 2003). In addition, the study by Kim-Cohen et al (2003), showed that 24% of the adults with depressive disorders had a prior childhood DBD.

School attendance

In the study by Zoccolillo and Rogers (1991), 26% of the 55 adolescent girls with CD were still in high school, 14% had graduated, 41% had dropped out permanently, 10% had dropped out but had returned, and 8% had been expelled and did not return at the time of follow-up. A comparison with national figures indicates that the outcome for these girls is worse than expected and that these differences are unlikely to be due to sampling error (Zoccolillo and Rogers 1991).

Personality characteristics underlying delinquency

The reason why delinquent behavior is present more often in clinic-referred DBD children than in a normally functioning population, may be connected with certain personality characteristics, such as high sensation-seeking behavior. In a study among 12 to 15 years old DBD boys, elevations on the sensation-seeking scale correlated marginally with delinquent behavior, suggesting a relationship between high sensation-seeking tendencies and antisocial or disruptive behavioral disorder (Gabel et al 1994).

In the present study, we examined a sample of adolescents (*n*= 47; mean age: 16.9 years) who had been treated as children (mean age: 10.1 years) in an in-patient and/or day-treatment setting because of their severely disruptive behaviors. The participants in our sample received an up-to-date treatment consisting of behavioral therapy in combination with pharmacotherapy, which is known to be effective, at least in the short-term (Brestan and Eyberg 1998; Kutcher et al 2004). The aim of the present study was to describe the functioning of these DBD children as adolescents in terms of their disruptive behaviors, institutionalization, smoking behavior, substance use, police contacts, educational level and educational status.

METHODS

Participants

Our study population consisted of 5 girls and 42 boys. At the time of follow-up the mean age of the participants was 16.9 (± 0.8) years, which was on average 5.1 (± 1.0) years after discharge from our Department. When participants were on average 10.1 (± 1.2) years, they had received in-patient or day-treatment at our Department, in units that are specialized in treating DBD children. Only children with a DSM-IV (American Psychiatric Association 1994) diagnosis of DBD and an IQ of at least 80 are admitted to these units. The clinical diagnosis of the participants was based on the information obtained from multiple informants. During a period of observation participants were observed intensively by childcare workers and teachers, and they were also examined psychiatrically and (neuro-) psychologically. Because the hospital is a teaching hospital, psychiatrists and residents provided feedback every 2 weeks on the diagnoses, made on the basis of discussions of accumulated case information. After the period of observation, a consensus on the diagnoses was reached between child psychiatrists and residents. According to the Child Behavior Checklist/ 4-18 (CBCL; Achenbach 1991a; Verhulst et al 1996), which was administered to the caregiver of 37 participants in the first months of treatment (pre-CBCL), the average of participants' externalizing problems (mean T-score ± SD: 75.4 ± 8.1) was in the clinical range (T-score > 63). To be included in this study, participants had to be aged sixteen to eighteen at follow-up.

Treatment

The treatment involved a standardized package, which was given in the context of either in-patient or day-treatment patients. This package consisted of a comprehensive and integrated programme based on cognitive behavioral and operant procedures, i.e., social problem-solving skills training, contingency management, parent management training, and special education at the school allied to the treatment units, in combination with pharmacotherapy for the treatment of ADHD, severe aggression, and depression (Matthys 1997; Van de Wiel et al 2002). Some children received in-patient treatment (*n*= 29), some received day-treatment (*n*= 10), and some children received both kinds of treatment (*n*= 8). The duration of the treatment ranged from 0.7 to 2.8 years (mean duration: 1.7 $\pm$ 0.5).

Procedure and instruments

Follow-up procedure

We included formerly treated in-patient or day-treatment patients, who were aged 16 to 18 years at the time of follow-up. All adolescents included could be located and were approached. Of all the adolescents (*n*= 52) and their caregivers who were asked (by telephone) to participate in our study, 87% (*n*= 45) of the adolescents, and 90% (*n*= 47) of the caregivers agreed. Next, an appointment was made to visit the adolescent and caregiver at home, on a separate occasion. At that time, 70% of the participants were living with (one of) his/her biological or adoptive parents. The other participants were living either with their grandparents (4%) or with foster parents (2%), or were living independently (2%), independently but under professional supervision (6%), or were institutionalized (15%). We visited them in their particular living environment. During the home-visit, several questionnaires were administered to the participants, and they were interviewed concerning substance use, police contacts, and educational status (see below).

SELF-REPORT DATA

No self-report data were available for two participants about whom we collected data. The internal consistencies mentioned below (Crohnbach's alphas) refer to the present sample.

Youth Self-Report. The participants completed the Youth Self-Report (YSR; Achenbach 1991b; Verhulst et al 1997), which includes 112 items, each rated on a 0- to 2-point scale, covering multiple symptom areas. The externalizing behavior (broadband) scale was used, reflecting outward directed problems (aggression and delinquency) during the past six months. The internalizing behavior (broadband) scale, on the other hand, reflects inward directed problems (e.g., anxiety, depression). Among the internalizing behaviors, we were particularly interested in depression, and therefore we decided to use only the anxiety/depression syndrome score.

Sensation Seeking Scale. The Dutch version of the Zuckerman Sensation Seeking Scale (SSS; Feij & Van Zuilen 1984) includes 67 items, rated on a 5-point scale (1= totally agree, 2= more or less agree, 3= don't know, 4= more or less disagree, 5= totally disagree), and consists of the following four subscales. *Thrill and adventure seeking* (TAS; range 12-60; α=

.80) refers to the need to participate in sports and other activities with strong accent on rapidity and danger. *Experience seeking* (ES; range 14-70; α= .53) refers to seeking of new sensory and psychic experiences and to an unconventional lifestyle. *Boredom susceptibility* (BS; range 13-65; α= .72) refers to the adverse reaction to the repetition of experiences, routine work, predictable boring people, and restlessness in the case of monotony. *Disinhibition* (DIS; range 12-60; α= .74) refers to the need for social disinhibition, for example by drinking, partying, and an extensive variety of sexual experience. Together, these scales constitute the *general sensation-seeking scale* (GS; range 4-20; α= .68). Comparison samples were available in the user's manual of the SSS. These were two male (SSS-S_1; *n*= 174 and SSS_2; *n*= 116) (university) student samples.

In addition, the SSS contains one item concerning the number of cigarettes that the participants were used to smoke each day. A study called 'Health Behavior in School-age Children' (HBSC), which was conducted by the Trimbos Institute in The Netherlands (2002), provided some comparison data of a sample, representative for Dutch 16- to 17-year old students, attending regular schools.

Beck Depression Inventory. The Beck Depression Inventory (BDI; Beck et al 1979; Dutch version: Bouman et al 1985) includes 21 items, rated on a 4-point scale for severity of depression, and consists of a total score (range 21-84, α= .75) corresponding to symptoms like mood, pessimism and suicidal intentions. The BDI is an internally consistent and valid measuring instrument (Beck et al 1988; CoTAN 2000). Random sample surveys were available from the user's manual of the BDI. There were two samples; a (university) student sample (BDI-S_1; *n*= 156), and a sample of psychiatric patients (BDI-S_2; *n*= 106). In both samples, females were overrepresented.

Interview

Questions were taken from the 'Standard Survey Offenders' (SSO; Advies- en Onderzoeksgroep Beke 2004). Participants were asked how many times in the past year they had been so drunk that they almost could not walk; they were asked whether they had ever used soft drugs and/or hard drugs, whether they had ever had an alternative punishment for their first or second offence, which is given only in cases of relatively mild offences such as vandalism, graffiti, or shoplifting, whether they had ever been in court, and whether they had been convicted. A sample that was representative for a general Dutch population of 12 to 17 year olds was available (*n*= 8,938), consisting of adolescents from 3 police districts in the Netherlands. We selected a subsample of participants (*n*= 743) who had answered all the questions on the SSO questionnaire mentioned above, except for the last question, (namely whether they had been convicted) and they were matched to our sample with respect to age (≥ 16 years) and gender (referred to as SSO-I sample). Furthermore, two questions were based on an interview called the 'Questionnaire Data Juveniles' (QDJ; Vreugdenhil et al 1999), in which participants were asked about their educational level and whether they were still attending school. A report of the Ministry of Education, Culture, and Science (ITS/Sardes 2002), which described the school attendance of a sample of Dutch school age pupils who were registered on 1st October, 2000 (MECS sample), was available

as a comparison group. In cases where no self-report data were available, we submitted the above-mentioned questions to the parents or caregiver, except for questions concerning substance use.

PARENT-REPORT DATA

In the case of 12 participants, someone other than the parent (e.g., childcare worker, foster parent, guardian) completed the questionnaire and was interviewed. No data were available for two participants.

Child Behavior Checklist. The Child Behavior Checklist (CBCL; Achenbach 1991a; Verhulst et al 1996) includes 118 items, each rated on a 0- to 2-point scale, and covers multiple symptom areas. As in the YSR, the externalizing scale was used.

Diagnostic Interview Schedule for Children, Version IV. The ODD and CD module of the Diagnostic Interview Schedule for Children, Version IV (DISC-IV; Shaffer et al 2000) was administered to the parents. No DISC data were available for two participants.

Comparison group

In order to interpret scores on the present questionnaires, one would need matched control groups. Although comparison groups were available in some cases, most of them were not matched to our sample with respect to age, sex, or educational level.

Statistical analysis

We used an ANOVA in order to examine whether there were differences on pre-CBCL scores between adolescents who agreed to participate at the time of follow-up and those who did not. Further, an ANOVA was used to examine whether participants who had only received treatment in an in-patient setting and those who had only received treatment in a day-treatment setting differed with respect to pre-CBCL, and to CBCL and YSR externalizing problems (T-scores) at follow-up. If there were no differences, the sample was considered as one single group. In order to compare the present sample to random sample surveys on questionnaire scores, we used a random sample *t*-test based on the mean, the SD, and the sample size; this provided us with a *t* value and a Cohen's *d,* which is a measure of the effect size. In addition, when data were available, we used a logistic regression analysis in order to compute odds ratios (ORs).

RESULTS

On pre-CBCL externalizing problem scores no differences were found between the participants who agreed to participate (PART; n= 36) and those who did not (N-PART; n= 6; Mean $\pm$ SD: pre-$CBCL_{PART}$= 75.3 $\pm$ 8.2, pre-$CBCL_{N\text{-}PART}$= 79.3 $\pm$ 5.1, $F(1,40)$= 1.35, p= .25). We subsequently examined whether there was a difference between participants who had only received treatment in an in-patient setting (IN) and those who had only received

treatment in a day-treatment setting (DAY) with respect to pre-CBCL externalizing problems (T-scores), and to CBCL and YSR externalizing problems at follow-up. We did not find any significant difference here either (Mean ± SD: pre-$CBCL_{IN}$ = 77.1 ± 4.8, pre-$CBCL_{DAY}$= 74.4 ± 11.0, $F(1,27)= 0.83$, $p= .37$; $CBCL_{IN}$ = 68.1 ± 9.7, $CBCL_{DAY}$= 65.3 ± 9.3, $F(1,37)= 0.65$, $p= .43$; YSR_{IN} = 55.2 ± 9.3, YSR_{DAY}= 57.8 ± 7.8, $F(1,35)= 0.63$, $p= .43$). Therefore, in the remainder of the analyses these participants were considered to be one single group ($n= 47$).

Child Behavior Checklist and Youth Self Report

According to the caregivers, 26% of the participants were in the non-clinical range (T-score < 60), 4% in the borderline range (T-score 60-63), and 70% were in the clinical range (T-score > 63) on CBCL externalizing problems at follow-up. According to the adolescents themselves, 71% of the participants were in the non-clinical range, 9% in the borderline range, and 20% were in the clinical range on YSR externalizing problems. Although parent-rated (CBCL) scores differed significantly from self-rated (YSR) externalizing problem scores (Mean ± SD: CBCL= 66.9 ± 10.0, YSR= 55.4 ± 8.6, $t=7.49$, $p< .01$), CBCL and YSR externalizing problems scores were significantly correlated ($r= .40$, $p< .01$). In addition, with respect to YSR anxious/depressive problems, 84% of the participants were in the non-clinical range (T-score < 67), 4% in the borderline range (T-score 67-69), and 11% were in the clinical range (T-score > 69), as rated by the adolescents themselves.

Diagnostic Interview Schedule, version IV (DISC-IV) diagnosis

On the basis of the parent-version of the DISC-IV, at follow-up 21 (47%) participants no longer had an ODD or a CD diagnosis, whereas 24 (53%) participants were rediagnosed as having either ODD ($n= 8$) or CD ($n= 16$).

Sensation Seeking Scale (SSS)

No differences were found on the GS score between the DBD group and either the $SSS\text{-}S_1$ or the $SSS\text{-}S_2$ groups. However, the DBD sample and the $SSS\text{-}S_1$ were found to differ in their scores for 'thrill and adventure seeking' (TAS) and in their scores for 'experience seeking' (ES), in that the DBD sample had higher TAS scores ($t_1= -2.51$, $p_1= .01$), and lower ES scores ($t_1= 5.09$, $p_1< .01$) compared to one of the student ($SSS\text{-}S_1$) samples.

Beck Depression Inventory (BDI)

No differences were found on the BDI scores between the DBD sample and the (university) student sample ($BDI\text{-}S_1$). However, the DBD sample had significantly lower BDI scores than the psychiatric patient ($BDI\text{-}S_2$) sample ($t_2= 7.60$, $p_2< .01$). In addition, 11% of the participants were found to score in the clinical range on anxiety/depression problems according to the YSR, whereas only 2% of the norm group scored in the clinical range (Achenbach, 1991b).

Substance use

As is shown in Table 1, a higher number of the participants in DBD sample (71%), compared to the number of participants in the HBSC sample (34%), smoked cigarettes on a daily basis (t= -3.64, p< .01), the average number for DBD participants being 18 a day. In addition, we found that 58% of the DBD participants versus 42% of the youth from the SSO-I sample had been 'so drunk that he/she could not walk any more'. However, for the comparison of the DBD sample with the SSO-I sample it should be specified that within the SSO-I sample, instead of the question being asked with regard to the past year, the question was asked with regard to the past three months. Furthermore, 64% of the participants in our sample compared to 39% of those in the SSO-I sample had used soft drugs (e.g., marijuana), resulting in a 2.9 higher chance (95% CI 1.5 – 5.4) of using soft drugs within the DBD sample. With respect to hard drug use, 18% of the DBD sample, compared to 19% of the SSO-I sample, had used hard drugs, which means that the DBD sample had a 0.9 higher chance (95% CI 0.4 - 2.0) of using hard drugs.

Table 1. *Outcome with respect to substance use and delinquency in a DBD sample versus a comparison sample.*

Characteristic variables	**DBD sample (*n*= 47)**		**SSO-I sample (*n*= 743)**		**HBSC sample (*n*= 635)**	
	%	*n*	%	*n*	%	*n*
Daily tobacco use	71%	32			34%	635
Drunk in the past year (DBD) or in the last 3 months (SSO-I)	58%	26	42%	310		
Had used marijuana at least once	64%	29	39%	286		
Hard drug use	18%	8	19%	141		
Police contacts						
Never	70%	33	71%	524		
Alternative punishment	22%	10	27%	197		
In court	17%	8	7%	54		

Delinquency

As to delinquency, 22% of the DBD sample compared to 27% of the SSO-I sample had been given an alternative punishment, resulting in a 0.8 higher chance (95% CI 0.4 – 1.6) of receiving an alternative punishment within the DBD sample. In addition, 17% of our sample, as compared to 7% of the SSO-I sample, had received an alternative punishment, and had also appeared in court, which means that the DBD sample had a 2.6 higher chance (95% CI 1.2 – 5.9) of being in court than the SSO-I sample.

School level and attendance

Of all, school attendance was mandatory for 16 participants, and every one of them was attending school. However, of the 19 participants for whom school attendance was mandatory but only on a part-time basis, 42% as compared to 7% within the MECS sample, were not attending school. Of the 12 participants for whom school attendance was no longer mandatory, 50% were attending school yet, and of those who were not, 33% had graduated and 17% had not. Furthermore, 91% of the participants were (or had been) attending school at the level of 'VMBO' (preparation for vocational training), and the remaining 9% were (or had been) attending school at the level of either 'HAVO' or 'VWO' (preparation for higher education).

Composite outcome

By means of a composite score, we examined a negative outcome in terms of 1) having a DBD diagnosis at follow-up, 2) living under professional supervision or being institutionalized, 3) have received an alternative punishment or have appeared in court, 4) not attending school when this was mandatory (or not graduated when not mandatory), and 5) smoking. Four participants had missing data in the case of 1 criterion. Twenty-one percent of the participants met none of the criteria for a negative outcome, 17% met 1 criteria, 28% met 2 criteria, 17% met 3 criteria, 17% met 4 of the criteria, and 0% met 5 of the criteria for a negative outcome. Thirty-four percent of the participants had a poor outcome, defined as meeting at least 3 of the negative criteria. On the other hand, if a positive outcome is defined as meeting 1 or none of the criteria, 38% of the participants had a positive outcome.

DISCUSSION

In the present investigation we studied a sample of DBD children who had been treated previously in an in-patient and/or a day-treatment setting for their severe behavioral problems, and we followed them up in adolescence. We aimed to describe the functioning of these children as adolescents in terms of their disruptive behavior, sensation seeking behavior, smoking behavior, depression, institutionalization, substance use, police contacts, and school attendance. Whenever possible, we compared the present DBD sample with a general population sample in order to examine to what extent previously treated DBD children deviated from a normal population in adolescence.

First, we examined to what extent disruptive behavior problems in childhood persist into adolescence. At pre-treatment, all children were diagnosed as having a DBD, according to the child psychiatrist. At the follow-up assessment, half of the participants (53%) were rediagnosed as DBD, on the basis of the parent version of the DISC-IV. In addition, 70% of the participants were found to score in the clinical range (above the 90th percentile of the norm group) with respect to parent-rated CBCL externalizing problems, whereas 20% of the participants were found to do so with respect to self-rated YSR externalizing problems. This discrepancy between parent-rated and self-rated scores on externalizing behavior could be due either to an underestimation of the adolescent or to an overestimation of the caregiver

because of a negative bias arising from a long history of negative parent-child interactions. Discrepancies between informants do not necessarily indicate that information from one or both is invalid (Achenbach et al 1987). As in other studies (e.g., Offord et al 1992; Tremblay et al 1992), the findings suggest a substantial stability of conduct problems, although a visible variance in antisocial behavior remains present.

Before discussing the other results, we need to consider some limitations of the present study. The study lacks a matched control group. As mentioned earlier, however, the user's manual of applicable questionnaires contained normative scores within some representative samples, and with respect to the other data, some comparison samples were available, although most of these were not matched with respect to age, gender or educational level. Therefore, we should be cautions about drawing conclusions.

In contrast to expectations, no differences were found on the 'general sensation-seeking scale' between DBD sample and the two male (university) student samples. However, we found that the DBD sample scored higher on the 'thrill and adventure' subscale and lower on the 'experience seeking' subscale of the SSS, compared to one of the student samples. Apparently, the need for sensation-seeking within the present DBD sample was limited to the need to expose oneself to activities with strong accents on rapidity and danger; this may be due to the relatively low educational level within the DBD sample (with 91% of the participants at the lowest level).

There is abundant evidence that antisocial behavior in middle childhood and later is strongly associated with an increased risk of substance abuse (Rutter 2002). In line with these findings, we found that almost three-quarters of the DBD sample smoked cigarettes on a daily basis, which is more than within a sample representing the general Dutch population of 16- to 17 year-olds. However, since smoking behavior is known to be related to educational level (e.g., Cavelaars et al 2000), it is not very surprising that high numbers of daily smokers were found in a low educated DBD sample. Furthermore, higher numbers of participants were found to have used soft drugs, whereas no differences were found in the use of hard drugs. As far as alcohol abuse is concerned, we observed that more DBD participants (58%) as compared to participants of the SSO-I sample (42%) had been seriously drunk. However, since in the latter sample the question was asked with regard to the past three months, instead of the question being asked with regard to the past year, the DBD sample seems not to be different from what is usual in a normal population.

With regard to delinquency, no differences were found between the DBD and the comparison (SSO-I) sample with respect to the number of participants who had received an alternative punishment of a first or second relatively mild offence, such as vandalism, graffiti, or shoplifting. Higher numbers of participants of the DBD sample, however, had been in court after committing a serious offence or a crime such as blackmail, threatening people in order to get money, or attempting manslaughter. The latter finding corresponds to the findings of Robins (1966).

With respect to depression, we found that BDI scores did not differ from a (university) student sample, and were significantly lower than the scores for the sample of psychiatric patients. However, 11% of the participants were found to score in the clinical range on

anxiety/depression problems according to the YSR; this result is higher than the prevalence of depression in a normal population (Achenbach 1991b).

Within our sample, none of the participants for whom school attendance was mandatory had dropped out of school so far. On the other hand, 42% of the participants for whom school attendance was mandatory but only on a part-time basis, were not attending school, which is a much higher number than in the MECS sample.

In sum, we found that half of the participants had a DBD diagnosis at follow-up, and on average higher numbers of adolescents ever used soft drugs, have ever been in court, were dropped out of school when school attendance was mandatory on a part-time basis, and were smoking on a daily basis, as compared to comparison groups. There was, however, a large variance among the adolescents of our sample. When outcome was defined in terms of DBD diagnosis, living status, delinquency, school attendance, and smoking behavior, 38% had a positive outcome and 34% had a poor outcome. When child psychiatrists discuss the outcome of DBD with parents of the child, with a view to possible treatment, they should emphasize that there are often large individual differences in outcome.

5

Prediction of Treatment Outcome in Children with Disruptive Behavior Disorders: An Exploratory Study

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ABSTRACT

Background
Although the short-term effectiveness of various behavioral intervention strategies with disruptive behavior disordered (DBD) children has been demonstrated, it is clear that some children benefit more than others.

Methods
In this study we explored the predictive value of family characteristics, psychological and demographic child characteristics, and neurobiological child characteristics, on treatment outcome. Existing data on child characteristics were combined with case-records concerning family characteristics in a sample of 52 DBD children who received cognitive behavioral therapy in combination with pharmacotherapy. Child Behavior Checklist externalizing problem scores served as outcome measure. We used linear regression analyses to examine the predictors of post-treatment externalizing problems, adjusted for pre-treatment problems.

Results
A larger discrepancy between verbal IQ (VIQ) and performance IQ (PIQ), with VIQ being lower than PIQ, and a lower skin conductance level (SCL) were found to predict a less favorable treatment outcome.

Conclusions
Only two factors (SCL and VIQ-PIQ) were found to have a predictive influence on the effect of treatment. These results support the fearlessness theory according to which low activity of the autonomic nervous system, as manifested in low skin conductance, is related to the effectiveness of conditioning and accordingly to poor treatment outcome.

INTRODUCTION

Recently, considerable progress has been made in behaviorally oriented approaches to treatment of disruptive behavior disordered (DBD) children (Kazdin 1997). Various behavioral intervention strategies (e.g., parent management training and cognitive behavioral therapy) have proved effective, at least on the short-term (Brestan and Eyberg 1998). However, it has become clear that some children benefit more than others. Obviously, if we could identify the individual and environmental factors that influence the effectiveness of the available treatment options we could direct children towards those treatments from which they are likely to derive the greatest benefit (Kazdin and Crowley 1997).

In risk and resilience research, several child and family characteristics have been shown to be related to an increased risk of developing problem behaviors (e.g., Verhulst and Van der Ende 1997), but little is known about the predictive value of aspects of behavioral change once problem behavior exists (Mathijssen et al 1999). Although some studies have considered child and family factors as predictors of treatment effect in DBD children, to our knowledge no studies to date have examined biological factors as predictors of treatment outcome. In the present study we explored the extent to which various family characteristics, psychological and demographic child characteristics, and neurobiological child characteristics could predict the effect of treatment in DBD children. We will first review the literature on these characteristics.

Predictive family characteristics

There are some aspects of family functioning, known from studies on DBD children, that have proven to be valuable predictors of the severity of behavioral problems after intervention. Some studies (Dumas and Wahler 1983; Kazdin and Crowley 1997; Webster-Stratton 1985), but not all (Conduct Problems Prevention Research Group (CPPRG) 2002; Hartman et al 2003), found that various indicators of family socioeconomic disadvantage (e.g., low family income, low educational and occupational attainment, or a construct representing a cluster of these variables) predicted poorer treatment outcome in conduct problem youth. Another indicator of socioeconomic disadvantage that seemed to be most strongly associated with poor treatment effect was coming from a single parent family (Webster-Stratton 1985; Webster-Stratton and Hammond 1990). However, this result has not been replicated by other intervention studies (CPPRG 2002; Kazdin and Crowley 1997). Furthermore, studies with conduct disordered children (e.g., Dumas and Albin 1986; Kazdin 1995; Kazdin and Crowley 1997; Webster-Stratton and Hammond 1990), revealed a modest association between parental psychopathology (e.g., depression, history of antisocial behavior) and a less favorable intervention outcome, although others did not reveal any such (e.g., Dumas 1986; Webster-Stratton 1985). In addition, one study found that parental cooperation with the therapist was the best predictor of positive outcome of day treatment (Grizenko 1997). Next to these treatment studies on family characteristics there are also some other factors that might be considered as candidates for the prediction of intervention outcome. For example, youth whose mothers smoked during pregnancy were found to be

more likely to develop severe antisocial behavior (Wakschlag et al 2002). Studies on rodents have shown that prenatal nicotine exposure, even at relatively low levels, negatively affects the development of the noradrenergic system (Levin et al 1996), and, more specifically, interferes with neuronal development in the cerebellum, which in turn is implicated in inhibitory processes (Raine 2002a). Difficulties in inhibition caused by smoking during pregnancy thus might lessen the effect of treatment.

Predictive psychological and demographic child characteristics

With respect to the child characteristics, earlier intervention studies on conduct disordered children showed that outcome behavior can be predicted by the severity of the children's initial behavioral problems (Ruma et al 1996). In addition, a number of other child characteristics have been found to contribute to variations in intervention responsivity; in some cases these were found to be even more predictive than initial problem severity (Vance et al 2002). Particularly, some specific cognitive features of the child, such as lower IQ, a lower verbal IQ, and lower reading achievement, were found to be predictive of a less favorable outcome in children with conduct problems (e.g., CPPRG 2002; Kazdin and Crowley 1997, Lahey et al 2002). In addition, a large discrepancy between verbal IQ (VIQ) and performance IQ (PIQ), with VIQ lower than PIQ, could be a predictor of poor treatment outcome as this factor has been shown to play a role in the etiology of DBD (Hinshaw 1992; Moffitt 1993b). Since we know that cognitively based treatments draw quite heavily on verbal abilities and strategies and that these are better developed in older children, it is not surprising that some studies report that older children respond better to cognitively based behavioral treatment than do younger children (Dush et al 1989; Kazdin and Crowley 1997). In addition, children's gender has sometimes been found to play a predictive role in intervention outcome, although the findings are mixed. In an effect study with DBD children, girls were found to do better at the end of treatment (Kazdin and Crowley 1997), whereas in other studies gender did not play a role in behavioral outcome (CPPRG 2002; Webster-Stratton 1996).

Predictive neurobiological characteristics

As far as we know, no study to date has been conducted on the predictive role played by biological factors in treatment effect. There are, however, some likely candidates. Raine (1993) suggested that low autonomic nervous system (ANS) activity (e.g., heart rate (HR) and skin conductance level (SCL)) is related to fearlessness. A lack of fear could predispose children to antisocial and violent behavior because low fear of socializing punishment in children would reduce the effectiveness of conditioning. In line with this theory, SCL was found to be significantly lower in subjects who were rated as high on CD than in subjects rated low on CD (Venables 1989). In addition, other measures of electrodermal arousal (i.e., skin conductance response (SCR) half recovery times, non-specific SCRs) were found to be useful markers for predicting aggressive and criminal behavior over quite a long developmental period (Raine et al 1990; Venables 1989). Two studies by Van Goozen and colleagues also found baseline levels of HR (Van Goozen et al 1998a and 2000) and SCL (Van Goozen et al 2000) to be lower in DBD children than in control children. In addition, a

decreased functioning of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in individuals with antisocial behavior (e.g., Vanyukov et al 1993). Van Goozen et al (1998a and 2000) found that when DBD children were exposed to frustration and provocation they had lower cortisol levels than normal participants. Snoek et al (in press) showed that children with DBD, with or without comorbid attention-deficit/hyperactivity disorder (ADHD), also had a significantly weaker cortisol response than children with ADHD alone. According to these authors, the result indicates that a pattern of lower HPA axis responsivity during stress probably does not characterize the spectrum of externalizing behaviors as a whole, but is only specifically present in children with DBD, with or without comorbid ADHD. Furthermore, Van de Wiel and colleagues (in press) found that DBD children without a cortisol response during stress had more problem behaviors after treatment than DBD children with a clear cortisol stress response. Although it is not yet clear how the findings regarding decreased cortisol reactivity should be interpreted, they fit in with existing evidence on ANS functioning (HR and SCL), and taken together could be considered consistent with the hypothesis of fearlessness. Since our research group has already conducted some studies concerning these (Snoek et al in press; Van Goozen et al 1998a and 2000), and other neurobiological characteristics (Matthys et al 1998 and in press; Van Goozen et al 2004) of DBD children, we have combined the data from these studies in order to examine the relationship between these characteristics and the effect of treatment. Because social conditioning plays a central role in behavioral therapy, we expect to find that HR, SCL, and cortisol reactivity play a predictive role in treatment effect, and more specifically, that a relatively low baseline HR, SCL, and cortisol level and/or a low cortisol reactivity are predictors of a less favorable treatment outcome.

Response perseveration, i.e., the tendency to continue a response set for reward despite punishment (McCleary 1966), might also be considered as candidate for the prediction of treatment effect. Children who have more difficulty in stopping their ongoing behavior would be less likely to profit from intervention. Specifically, oversensitivity to reward or insensitivity to punishment may lead to difficulties in the use of feedback given by peers and adults. Several studies have shown that children with conduct disorders evidence more response perseveration than normal healthy controls (e.g., Daugherty and Quay 1991; Fonseca and Yule 1995; Matthys et al 1998 and in press; Van Goozen et al 2004). Response perseveration has been studied with card playing and door-opening tasks (DOT). In these tasks, an initial high rate of reward is used to establish a dominant response set that participants need to alter as the response becomes more often punished than rewarded. At present it remains unclear whether response perseveration in DBD children is due to an increased sensitivity to reward or a decreased sensitivity to punishment (Matthys et al in press; Van Goozen et al 2004). In the present study we investigated whether higher response perseveration, higher impulsivity, oversensitivity to reward and insensitivity to punishment would be predictors of poor treatment outcome.

In addition, ADHD, when co-occurring with early behavioral problems, has been demonstrated to be a risk factor for poor outcome (Maughan and Rutter, 2001). Specifically, it has been reported that higher rates of special education involvement are predicted by

higher baseline hyperactivity in DBD children (CPPRG 2002), and therefore we expect attention problems to have a deleterious influence on the treatment outcome.

In this study, we involved a sample of seriously disordered DBD children (*n*= 52) who had been referred for long-term psychiatric in-patient treatment or day-treatment. Due to ethical reasons, we did not include either a comparison treatment or a no-treatment control group. We explored the predictive value of various child and family factors on treatment outcome in a sample of DBD children who were treated in specialized in-patient and day-treatment units. To that end, we included well-known predictive family characteristics. From the case-records, data on family characteristics were scored specifically for this study. In addition, we included routinely collected demographic and psychological data. We also studied neurobiological data that had been collected previously in this sample in the course of former studies in our Department (Matthys et al 1998; Snoek et al in press; Van Goozen et al 2000), and explored whether these characteristics also have a predictive influence on the effect of treatment.

METHODS

Participants

The participants were solicited from in-patient and day-treatment units of the Department of Child and Adolescent Psychiatry, specialized in the treatment of DBD children. Only children with a DSM-IV (American Psychiatric Association 1994) diagnosis of DBD and an IQ of at least 80 are admitted to these units. In this study, 48 boys and 4 girls participated, ranging at intake from six to twelve years of age (mean age: 10.0 $\pm$ 1.5). The clinical diagnosis of the participants was based on extensive diagnostic assessment: psychiatric interviews; psychological assessment of the child; interviews with the parents, including discussion of the developmental history; and standardized information from the child's teacher. On the basis of the information from these various informants, a board-certified child psychiatrist gave the clinical diagnosis. This clinical diagnosis was checked with Version 2.3 or Version IV of the Diagnostic Interview Schedule for Children (DISC-2.3; Fischer et al 1992, or DISC-IV; Shaffer et al 2000, respectively), depending on the time of administration, and was administered by a research assistant. DISC diagnoses were not available for 11 of the 52 children. In order to compare the results of the DISC-2.3 (which generates DSM-III-R scores; American Psychiatric Association 1987) with the clinical diagnoses, based on the currently used DSM-IV psychiatric classification, a conversion was made in the scoring results of the DISC. When the clinical diagnosis was compared with the (converted) DISC diagnosis, 87.8% of the clinical diagnoses were confirmed by a DISC diagnosis with respect to DBD, and 69.0% of the clinical diagnoses were confirmed with respect to ADHD.

Treatment

The treatment involved a standardized package, which was given in the context of either in-patient or day-treatment. This package consisted of a comprehensive and integrated

programme based on cognitive behavioral and operant procedures, i.e., social-problem-solving skills training, contingency management, and parent management training, in combination with pharmacotherapy for the treatment of ADHD and severe aggression (Matthys 1997; Van de Wiel et al 2002). Eleven children received this combination of cognitive behavioral therapy and pharmacotherapy in an in-patient setting, twenty-six children in a day-treatment setting, and fifteen children in both kinds of settings (11 first in an in-patient setting, then in day-treatment, 4 children first in day-treatment, and then in an in-patient setting). The duration of the treatment ranged from 0.7 to 3.2 years (mean duration: 1.5 ± 0.9).

Procedure and instruments

The Child Behavior Checklist/ 4-18 (CBCL) (Achenbach 1991a; Verhulst et al 1996) was administered to all parents (in two cases the child care worker, and in two other cases the grandparents completed the CBCL) before and after treatment. Since the problem behavior of our sample was in the externalizing spectrum, we decided to use the externalizing broad band grouping scale (including delinquent and aggressive syndromes) as the outcome measure.

Data on neurobiological measures and the DOT were collected during a procedure of stress exposure and have been reported in earlier studies (Matthys et al 1998; Snoek et al in press; Van Goozen et al 1998a and 2000).

Stress exposure procedure

Soon after treatment had started, each individual patient participated in a stressful experiment that consisted of a baseline measurement phase and a stress phase. During the stress phase, stress was induced for 80 minutes, and involved the exposure to frustration, provocation and aggression in a general setting of competition between the real participant and a videotaped opponent, who competed with the participant for best performance over the session (see for more details, Van Goozen et al 2000).

Saliva cortisol collection

Six saliva samples were collected: one sample was taken during the non-stress phase, and the other five samples represented the stress phase. As independent variables we used both the basal level of cortisol (sample 1), and the cortisol reactivity level (both in nmol/L), calculated by subtracting the cortisol level at baseline (sample 1) from the mean cortisol response during stress (sample 2 to 6) (for more details, see Van Goozen et al 2000).

SCL and HR registration

For the present purposes, data on HR and SCL in the non-stress phase were used. The first two samples relate to the non-stress phase. As we were interested in baseline levels of HR and SCL, we used the average HR (in BPM) and SCL (in µsiemens) of these two samples as predictor variables (for more details, see Van Goozen et al 2000).

Door-opening task

The door-opening task consists of a series of 110 doors presented sequentially on a MacIntosh computer in a preprogrammed order of 'winning' and 'losing' doors (Daugherty and Quay 1991). In this task, the participant chooses either to open the next door or to stop playing. When the child opens the door either a happy face appears on the monitor and the child receives a financial reward i.e., a dime or a sad face appears and the child has to give the money back. The independent measures were: 1) the total number of doors opened before the subject quits (range 0-110), as a response perseveration measure, 2) the number of premature responses as an index of impulsivity, 3) the mean time (in seconds) after punishment (TAP), as a punishment sensitivity measure, 4) the mean time (in seconds) after reward (TAR), as a reward sensitivity measure (for more details, see Matthys et al 1998).

WISC-R

Intelligence was assessed by means of the Dutch version of the Wechsler Intelligence Scale for Children - Revised (WISC-R; Wechsler 1974), the WISC-RN (Vandersteene et al 1986). The test yields three IQs: a total IQ (TIQ), a verbal IQ (VIQ), and a performance IQ (PIQ). In addition to these three variables, we also included the score obtained by subtracting PIQ from VIQ.

Case-Records

Upon first contact, the child psychiatrist collected information about the patient as part of a general assessment procedure; all this information was registered in case-records. From these records, data on child and family factors, and environmental factors were collected as part of this study. Specifically, 3 raters were trained to review the case-records and code the Time 1 (T1) information in a standardized way. After training, 10 records were used to establish cross-rater agreement. Raters' scores agreed with consensus scores (mean agreement 89%), ranging from 57-100% for 19 different variables. In the various variables, the reliability of the obtained information was maintained or, where possible, further increased by continuous supervision during the actual coding process. Case-records were scored on different continuous (e.g., age at intake) and dichotomous variables (e.g., gender, family composition). Family characteristics regarding the situation or circumstances before intake (parental psychopathology, family composition, smoking during pregnancy, physical abuse, sexual abuse, neglect) were used as variables predicting change.

Length of treatment

As was mentioned, duration of the treatment ranged from 0.7 to 3.2 years. In order to examine whether this variable had a predicting influence on outcome, we included length of treatment as independent variable in the analysis.

Statistical analysis

First of all, *t*-tests were used to examine whether participants only receiving treatment at an in-patient setting (IN, n= 11) differed from those only receiving treatment at a day-treatment setting (DAY, n= 26) on pre- and post-treatment externalizing problem scores.

Next, we applied a paired *t*-test with pre- and post-treatment externalizing problems as paired variables in order to find out whether there was an effect of treatment. We then used linear regression analyses in order to examine the predictors of post-treatment CBCL externalizing problems. Since the variables TAP, basal cortisol, and premature responses were highly skewed (skewness > 2), they were log-transformed. The regression analyses were accomplished in two steps. First, we examined the predictive influence of each of the independent variables separately (see Table 1), adjusted for pre-treatment problems. Given the number of participants, we limited ourselves to the predictor variables, which have strongest values of standardized regression coefficient (SRC). Second, the independent variables that had a high absolute SRC in the separate analyses were simultaneously entered into the final regression analysis (see Table 2).

RESULTS

Change over the course of treatment

First we checked whether there was a difference between the participants who only received treatment at an in-patient setting (IN, n= 11) and those who received treatment at a day-treatment setting (DAY, n= 26) with regard to pre-treatment (PRE) and post-treatment (POST) CBCL externalizing problems (T-scores). We did not find any significant differences (Mean ± SD: IN-PRE= 77.5 ± 10.7, DAY-PRE= 76.6 ± 8.7, t(1,35)= -0.26, p= .79; IN-POST= 65.4 ± 8.9, DAY-POST= 67.3 ± 8.2, t(1,35)= 0.64, p= .53). Therefore, in the remainder of the analyses they were considered to be one single group (n= 52). Our sample of children improved significantly as far as their externalizing behavioral problems were concerned (Mean ± SD: PRE= 77.6 ± 8.3, POST= 67.2 ± 7.8, t(1,51)= 7.5, p< .01). Before intervention, 2 participants were in the non-clinical range (T-score < 60), 1 in the borderline (T-score 60-63), and 49 in the clinical range (T-score > 63), whereas after intervention, 8 participants were in the non-clinical range, 7 were in the borderline range, and 37 participants were in the clinical range.

Predictors of change

Table 1 shows the standardized regression coefficient (SRC) for the 27 child and family characteristics predicting post-treatment CBCL externalizing problems, adjusted for pre-treatment problems.

Next, we entered the variables basal SCL, TAR, VIQ-PIQ, sexual abuse, and the log-transformed variable TAP into a linear regression analysis, controlled for pre-treatment externalizing problem scores (Table 2). When these variables were simultaneously entered in the analysis, this model turned out to be significant (F(6,41)= 4.29, p< .01) and 38.6% of the variance could be explained.

Children with a higher discrepancy between VIQ and PIQ, with a lower VIQ than PIQ (VIQ<PIQ), benefited less from treatment than those who had VIQ>PIQ. Furthermore, when children had not only a large discrepancy (VIQ<PIQ), but also lower basal SCL, they were predicted to benefit even less from treatment.

Table 1. *Standardized Regression Coefficients (SRC) for independent variables and their relation to parent-rated externalizing problems at post-treatment, controlled for parent-rated externalizing problems at pre-treatment.*

Independent variables	**SRC**	***p***
Parent-rated externalizing CBCL score at pre-treatment	.234	.10
Demographic		
Gender	.123	.38
Age at intake (in yrs)	.063	.66
Neurobiological		
Basal SCL (in µsiemens)	-.303	.03
Basal HR (in bpm)	-.018	.90
Basal cortisol level (in nmol/L) (log-transformed)	.205	.14
Cortisol reactivity level (in nmol/L)	.026	.85
Attention problems	-.051	.75
Nb of doors	-.098	.49
Nb of premature responses (log-transformed)	.195	.17
TAP (in s) (log-transformed)	-.299	.06
TAR (in s)	-.298	.03
Neuropsychological		
PIQ	.171	.22
VIQ	-.100	.48
TIQ	.040	.78
VIQ-PIQ	-.226	.11
Family		
SES mother	.018	.90
SES father	-.093	.54
Psychopathology mother	.137	.33
Psychopathology father	.077	.58
Smoking during pregnancy	.132	.37
Physical abuse	-.061	.67
Sexual abuse	-.249	.07
Neglect	-.019	.89
Family composition	-.185	.18
Parental cooperation	.096	.49
Treatment		
Length of treatment	.067	.63

Notes. Higher scores on all family characteristics, parental SES, and kind of treatment reflect greater dysfunction. A score of 0 corresponds to a boy, and a 1 corresponds to a girl.

Table 2. *Linear multiple regression analysis for parent-rated externalizing problems at post-treatment.*

Characteristics	**SRC**	***p***
Pre-treatment externalizing problems	.365	.03
Basal SCL (in μsiemens)	-.290	.03
Log-TAP	.085	.68
TAR	-.353	.06
VIQ-PIQ	-.385	.01
Sexual abuse	-.185	.15

The time children waited after reward (TAR) constituted a marginally significant prediction of outcome, in that children who were more reward sensitive profited less from intervention. Although sexual abuse and TAP had a relatively strong SRC in separate analyses, they did not make a unique significant prediction of outcome when entered simultaneously.

Contrary to expectations, none of the other neurobiological variables (i.e., HR, cortisol, response perseveration) and none of the other child and family characteristics had a predictive relationship to treatment outcome.

DISCUSSION

In this study we investigated the predictive influence of various family and child factors, among which some neurobiological characteristics, on the effect of treatment in a sample of seriously disordered DBD children who were receiving a long-term and intensive combination of cognitive behavioral therapy and pharmacotherapy in in-patient and/or day-treatment settings.

When looking at the externalizing behaviors during the course of treatment, we found that, according to the parents' judgements, the problem behaviors of the children decreased significantly over time. As expected, some children profited more than others. In the present study no family characteristics were found to predict treatment outcome. Among the psychological and demographic factors, only the discrepancy between participants' VIQ and PIQ showed to have an influence on the outcome, in that a large discrepancy between VIQ and PIQ, with VIQ<PIQ, was a predictor of a less favorable treatment outcome. No relationship was found between outcome and participants' VIQ, PIQ, or TIQ. In this study, it is only when VIQ is related to PIQ that it has a predictive influence on outcome. This in contrast to the results of Lahey et al (2002), who concluded that a poor outcome was

predicted by lower verbal IQ, whereas Vance et al (2002) concluded that it was predicted by a low general IQ.

Among the four psychophysiological factors (basal SCL, HR, cortisol, and cortisol reactivity) only SCL appeared to be a predictor. It was demonstrated that low basal SCL in children was a predictor of a smaller decrease in externalizing behavioral problems. This result is in line with the theory that low ANS activity as manifested by low SCL is a marker of a low level of fear. According to the fearlessness theory lack of fear reduces the effectiveness of social conditioning (Raine 1993), which is a central mechanism in behavioral treatment. No significant correlation was found between post-treatment externalizing behavioral problems and basal HR, basal cortisol or cortisol responsivity. SCL may be a better measure of fearlessness than HR, since HR reflects both sympathetic and parasympathetic nervous system activity, whereas SCL reflects sympathetic processes only.

Among the many variables of interest, only two factors were found to have a predictive influence on the effect of treatment. This may be due to the fact that some characteristics of DBD children (e.g., low cortisol responsivity, high response perseveration) did not vary much within a DBD sample, although they were found to be clearly different from those of normal controls. Therefore, it is not very surprising that, once the problem behaviors existed, these factors did not have a predictive influence on outcome.

Limitations

Some limitations of the present study need to be considered. In a strict sense, this is not a treatment effect study, since no comparison group was included, but a study on predictors of change over time. However, Angold et al (2000) demonstrated that children who were going to receive treatment in the future were already on a more deteriorating trajectory than were children who, although significantly symptomatic or psychiatrically impaired, never presented for treatment (Angold et al 2000). Therefore, it is unlikely that the decrease in symptoms in the severely disturbed DBD children from the present study is only caused by maturation. In other words, these children's behavior will probably not improve unless they receive treatment. Another possible criticism is that neurobiological and psychological measures were collected routinely in the assessment phase, whereas the data on family characteristics prior to treatment were collected later by a review of case-records. The quality of the latter measures (e.g., psychopathology of the parents, neglect) was lower than the quality of the neurobiological and psychological measures. Indeed, in contrast to the neurobiological and psychological child factors, which were measured as continuous variables, some family characteristics such as depression in the mother were designated as dichotomous variables, although they were continuous by nature. Since the latter fact could result in a loss of information, we were not in any position to judge the relative importance of the predictive value of neurobiological and psychological child factors versus family factors. Therefore, future studies should measure child and family characteristics prospectively in a way in which they would be more comparable.

Clinical implications

The results of this study indicate that, next to some factors that were known from literature to influence treatment outcome (e.g., parental co-operation, IQ), there are some other factors, i.e., neurobiological characteristics, which were found to have some influence on the effectiveness of treatment. Although it is still unclear how to adapt this knowledge to future treatment programs, one should realize that the effectiveness of treatment not only is dependent on environmental or psychological characteristics, but also on neurobiological characteristics.

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Prediction of Adolescent Outcome in Children with Disruptive Behavior Disorders: A Study of Neurobiological, Psychological and Family Factors

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Short running title: Predictors of Persistence of Antisocial Behavior in Adolescence

Conditionally accepted

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ABSTRACT

Background
In this preliminary study we explored the predictive influence of various family, psychological, demographic, and neurobiological characteristics on the persistence of antisocial behavior in adolescence.

Methods
Existing data were combined with case-records in a sample of 47 disruptive behavior disordered (DBD) children who had been treated in in-patient and/or day-treatment units when they were between 7 to 12 years old. Parent-rated and self-rated externalizing problem scores and the presence of a DBD diagnosis served as the outcome measures in adolescence. We used linear regression analyses to examine the predictors of adolescent outcome.

Results
A lower basal skin conductance level (SCL) was repeatedly found to predict poor adolescent outcome, either when rated by parents or by participants themselves. In addition, comorbid attention-deficit hyperactivity disorder, one aspect of performance on the door-opening task, and a mother of low socio-economic status also predicted that a child would have more antisocial problems in adolescence, depending on the type of outcome measure.

Conclusions
Results of this study support the fearlessness theory, according to which low activity of the autonomous nervous system, as manifested by low SCL, is related to the effectiveness of socializing punishment and accordingly to poor socialization and adolescent outcome.

INTRODUCTION

Children and adolescents with disruptive behavior disorders (DBD), a term that covers both oppositional defiant disorder (ODD) and conduct disorder (CD), have significant impairments in their social, emotional, and educational functioning (Frick and O'Brien 1995; Lahey et al 1994). In addition, their behavior is very costly to society (Frick and Loney 1999), and is often quite stable and persistent (Offord et al 1992). Furthermore, DBD in childhood predicts not only adolescent and adult antisocial behavior but also depression and substance abuse (Maughan and Rutter 2001).

So far, little is known about the factors associated with persistence and change. Although in risk and resilience research several child and family characteristics have been shown to be related to an increased risk of developing problem behavior (Fergusson and Lynskey 1996; Rutter 1992), less is known about the predictive value of aspects of behavioral change once problem behavior exists (Matthijssen et al 1999). In the present study we explored the predictive value of various family characteristics, psychological and demographic child characteristics, and neurobiological child characteristics on adolescent outcome within a sample of severely disturbed DBD children. Below we discuss some child and family factors that have already been shown to predict outcome or that could be considered as possible candidates for the prediction of outcome in adolescence.

Predictive family characteristics

There are some aspects of family functioning that have proven to be valuable predictors of change in antisocial behaviors. For instance, low family socio-economic status was found to predict a negative outcome, both in a non-referred community sample (Farrington 1991; Nagin and Tremblay 2001; Stattin and Trost 2000) and in a sample of referred DBD boys (Lahey et al 2002). However, another study reported that low SES was clearly associated with the onset of DBD but did not contribute to the prediction of persistence of DBD over a 4-year study (Lahey et al 1995). In addition, boys from a community sample who had a single parent were predicted to have higher levels of antisocial behavior over time (Pevalin et al 2003). In the latter sample also parental depression was found to raise the likelihood of increases in antisocial behavior, although this was not found within a DBD sample (Lahey et al 2002). Several studies on predictors of change have revealed some other family characteristics that might be considered as candidate predictors of adolescent outcome. Boys whose mothers smoked during pregnancy were found to be more likely to develop CD (Wakschlag et al 2002). Rodent studies have shown that prenatal nicotine exposure, even at relatively low levels, negatively affects the development of the noradrenergic system (Levin et al 1996), and, more specifically, interferes with neuronal development in the cerebellum which in turn is implicated in inhibitory processes (Raine 2002a). Difficulties in inhibition caused by smoking during pregnancy thus might result in poor adolescent outcome. Furthermore, research into childhood victimization, such as sexual or physical abuse, suggests that such behaviors significantly increase the risk of CD in children (Fergusson et al 1996a), or later antisocial personality disorder (Luntz and Widom 1994), criminality, and

violence (Maxfield and Widom 1996). Therefore, we expect that childhood abuse and neglect are also predictive of a less favorable adolescent outcome.

Predictive psychological and demographic child characteristics

With respect to the child characteristics, one of the more consistent predictors of poor outcome for children with CD is the severity of the initial disorder (Loeber 1982 and 1991). In addition, other child characteristics have been found to contribute to variations in adolescent outcome. A number of studies among conduct disordered children have shown that intelligence is an inverse predictor of antisocial outcomes over 10 years or more (Farrington 1991; Fergusson et al 1996b; Moffitt 1990). In addition, it has been suggested that a higher verbal intelligence predicts improvement in levels of CD (Lahey et al 2002). Moreover, a large discrepancy between verbal IQ (VIQ) and performance IQ (PIQ), with VIQ lower than PIQ, could be considered as a candidate predictor of poor adolescent outcome since this factor has been shown to play a role in the etiology of DBD (Hinshaw 1992; Moffitt 1993b). A study of a non-referred community sample, however, did not find intelligence to be a significant predictor of antisocial outcome over time (Nagin and Tremblay 2001). There have also been studies of the predictive role of gender in the adolescent outcome of DBD children, but findings have been mixed (Fergusson et al 1996b; Pevalin et al 2003).

Predictive neurobiological characteristics

Until now, there has been some evidence that biological factors have some predictive influence on the persistence of antisocial behavior. Some studies have demonstrated that electrodermal and/or cardiovascular activity is a predictor of later antisocial outcome. High skin conductance half recovery times at the age of 3 years predicted fighting at the age of 9 years (Venables 1989). In a 9-year follow-up of adolescents it was found that those who were sentenced for a crime during the follow-up interval had significantly lower resting levels of spontaneous fluctuations (SF) of skin conductance and heart rate (HR) (Raine et al 1990). In addition, in a 2-year follow-up of disruptive behavior disordered children and adolescents, SCL was found to predict institutionalization (Kruesi et al 1992). Raine (1993) suggested that low autonomic nervous system (ANS) activity (e.g., HR and skin conductance level (SCL)) is related to fearlessness. A lack of fear could predispose children to antisocial and violent behavior because low fear of socializing punishment in childhood would contribute to poor fear conditioning and lack of conscience development (Raine 1993). Some studies on ANS activity in DBD children, conducted at our Department, have shown lower baseline levels of HR (Van Goozen et al 1998a and 2000) and SCL (Van Goozen et al 2000) in DBD than in control children. In addition, children with DBD had a lower hypothalamic-pituitary-adrenal (HPA) axis responsivity than normal controls when exposed to frustration and provocation (Van Goozen et al 1998a and 2000). This was in line with studies conducted by other research groups (e.g., Kruesi et al 1989; McBurnett et al 2000; Pajer et al 2001) on the relationship between cortisol and aggression in clinically referred children. One of these studies (McBurnett et al 2000) found that low cortisol levels were associated with the persistence of aggression. Furthermore, in another study at our Department, it was shown that children with DBD, with or without comorbid attention-deficit-hyperactivity disorder

(ADHD), had a significantly weaker cortisol response than children with ADHD alone (Snoek et al in press). Thus, a pattern of lower HPA axis responsivity during stress probably does not characterize the spectrum of externalizing behaviors as a whole, but is only specifically present in children with DBD, with or without comorbid ADHD. In addition, it was found that DBD children without a cortisol response during stress had more problem behaviors after outpatient treatment than DBD children with a clear cortisol stress response (Van de Wiel et al in press). Although it is not yet clear how the findings on decreased cortisol reactivity should be interpreted, they fit with existing evidence on ANS functioning (HR and SCL), and taken together could be considered consistent with the hypothesis of fearlessness. In the present study we combined data of earlier studies on neurobiological characteristics of DBD children (Matthys et al 1998; Snoek et al in press, Van Goozen et al 1998a, 2000, and 2004), and examined the relationship between these characteristics and the persistence of antisocial behavior into adolescence. We predict that basal HR, SCL, cortisol, and cortisol reactivity all play a predictive role in outcome behavior, and more specifically, that a relatively low basal HR, a low basal SCL, a low basal cortisol and/or a low cortisol reactivity are predictors of a less favorable adolescent outcome.

Response perseveration, i.e., the tendency to continue a response set for reward despite punishment (McCleary 1966), could also be a predictor of the persistence of antisocial behavior in adolescence. Children who have more difficulty in stopping their ongoing behavior, which may well be a biologically based characteristic that is difficult to change, would be more likely to persist in their antisocial behavior. Specifically, oversensitivity to reward or insensitivity to punishment may lead to difficulties in the use of feedback given by others. Several studies have shown that conduct disordered children demonstrate more response perseveration than healthy controls (Daugherty and Quay 1991; Fonseca and Yule 1995; Matthys et al 1998 and in press; Shapiro et al 1988; Van Goozen et al 2004). Response perseveration has been studied with card playing and door-opening tasks (DOT). In these tasks, an initial high rate of reward is used to establish a dominant set of responses that participants need to alter as the response becomes more often punished than rewarded. The number of trials is considered as a measure of response perseveration. At present it is still not clear whether response perseveration in DBD children is due to increased sensitivity to reward or decreased sensitivity to punishment (Matthys et al in press, Van Goozen et al 2004). A measure of impulsivity is included in the DOT. In the present study we investigated whether higher response perseveration, oversensitivity to reward, insensitivity to punishment, and high impulsivity would turn out to be predictors of poor outcome behavior.

Furthermore, it has been demonstrated that the presence of ADHD plays an important role in determining the outcome of DBD children. Boys with DBD and hyperactivity were found to show more violent offending in adulthood than boys who had DBD but who were not hyperactive (Klinteberg et al 1993). In addition, a prospective study showed that measures of restless, impulsive behavior predicted early onset delinquency (Tremblay et al 1994). Furthermore, hyperactivity was found to be a risk factor for impaired social adjustment, including the development of psychiatric disorders, irrespective of the existence

of conduct problems (Taylor et al 1996). Thus, we expect ADHD comorbidity to have a poor influence on adolescent outcome.

In this study we examined a sample of 16 to 18 years old adolescents (*n*= 47) who had been treated in an in-patient and/or daytreatment setting when they were between 7 and 12 years old. The aim of this study was to explore the predictive value of various child and family factors on adolescent outcome in DBD children. To that end, we included well-known predictive family characteristics. Data on family characteristics, recorded in case-records, were scored specifically for this study. In addition, we included demographic, psychological and neurobiological data that had been collected previously in this sample at the beginning of treatment in the course of earlier studies in our Department (Matthys et al 1998; Snoek et al in press; Van Goozen et al 2000) and explored whether these characteristics also had a predictive influence on outcome.

METHODS

Participants

Our study population consisted of 5 girls and 42 boys. All participants met the criteria for ODD (*n*= 34) or CD (*n*= 18), and/or comorbid ADHD (*n*= 33), as set out in the DSM-IV (APA 1994). At the time of follow-up the mean age of the participants was 16.9 (± 0.8) years, which was on average 5.1 (± 1.0) years after discharge from our Department. When participants were on average 10.1 (± 1.2) years, they had received treatment in in-patient or day-treatment settings at our Department, in units that are specialized in treating DBD children. Only children with a DSM-IV (APA 1994) diagnosis of DBD and an IQ of at least 80 are admitted to these units. The clinical diagnosis of the participants was based on the information obtained from multiple informants. During a period of observation participants were observed intensively by childcare workers and teachers; they were also examined psychiatrically and (neuro-) psychologically. Because the hospital is a teaching hospital, psychiatrists and residents provided feedback on a regular basis; they had case discussions based on information collected from various informants. After the period of observation, a consensus on the diagnoses was reached between child psychiatrists and residents. According to the Child Behavior Checklist/ 4-18 (CBCL; Achenbach 1991a; Verhulst et al 1996), which was administered to the caregivers of 37 participants in the first months of treatment (pre-CBCL), the average of participants' externalizing problems (mean T-score ± SD: 75.4 ± 8.1) was in the clinical range (T-score > 63). To be included in this study, subjects had to have participated in a stressful experiment (see instruments) at the time they were treated, and they had to be sixteen years or older at follow-up.

Treatment

The treatment involved a standardized package, which was given in the context of either in-patient or day-treatment. The package consisted of a comprehensive and integrated programme based on cognitive behavioral and operant procedures, i.e., social-problem-

solving skills training, contingency management, and parent management training, in combination with pharmacotherapy for the treatment of ADHD and severe aggression (Matthys 1997; Van de Wiel et al 2002). Some children received treatment in an in-patient setting (*n*= 29), some in a day-treatment setting (*n*= 10), and some in both kinds of settings (*n*= 8). The duration of the treatment ranged from 0.7 to 2.8 years (mean duration: 1.7 ± 0.5).

Procedure and instruments

Neurobiological measures

Data on salivary cortisol, SCL, and HR were collected during a procedure of stress exposure (Van Goozen et al 1998a and 2000), and have been reported in earlier studies (Snoek et al in press; Van Goozen et al 1998a and 2000). For the present purposes we used the basal level of cortisol (within non-stress phase), and the cortisol reactivity level (both in nmol/L) as independent variables. The cortisol reactivity level was calculated by subtracting the cortisol level at baseline from the mean cortisol response during stress. Furthermore, since we were interested in the baseline levels of HR and SCL, we used the average of the samples of HR (in BPM) and SCL (in µSiemens) within the non-stress phase. Because SCL data were not collected in those participants involved in the Van Goozen et al (1998a) study, basal SCL data were missing for 16 participants. No basal HR data were available for 3 participants.

Data on the DOT have also been reported in earlier studies (Matthys et al 1998 and in press; Van Goozen et al 2004). As independent measures we used: 1) the total number of doors opened before the subject quits (range 0-110), a response perseveration measure, 2) the number of premature responses as an index of impulsivity, 3) mean time (in seconds) after punishment (TAP), a punishment sensitivity measure, and 4) mean time (in seconds) after reward (TAR), a reward sensitivity measure.

WISC-R

Intelligence was assessed by means of the Dutch version of the Wechsler Intelligence Scale for Children - Revised (WISC-R; Wechsler 1974), the WISC-RN (Vandersteene et al 1986). The test yields three IQs: 1) a total IQ (TIQ), 2) a verbal IQ (VIQ), 3) and a performance IQ (PIQ). In addition to these three variables, we also included a score of VIQ-PIQ.

Case-Records

At the first contact, the child psychiatrist collected information about the patient as part of a general assessment procedure; all this information was then recorded in case-records. From these records, data on child factors, family factors, and environmental factors were collected as part of this study. Specifically, 3 raters were trained to collect and code the T1 information in a standardized way. After training, 10 records were used to establish cross-rater agreement. Raters' scores agreed with the consensus scores (mean agreement 89%), ranging from 57-100% for 19 different variables. The reliability of the information obtained was maintained or, where possible, further increased by continuous supervision during the actual coding process. Case-records were scored on various family characteristics (parental psychopathology, parental SES, family composition, smoking during pregnancy, physical

abuse, sexual abuse, neglect) connected with the situation or circumstances before intake. These characteristics were designated as dichotomous variables. To ensure that the data obtained were reliable, family characteristics were strictly defined, in that variables such as parental psychopathology or abuse were only scored as present when there were clear indications in the case-records.

Outcome measure

At follow-up, the Youth Self-Report (YSR) (Achenbach 1991b; Verhulst et al 1997) was administered to the participants. In addition, both the CBCL (Achenbach 1991a; Verhulst et al 1996) and the ODD and CD module of the Diagnostic Interview Schedule for Children, Version IV (DISC-IV; Shaffer et al 2000) were administered to the children's parents. In the case of 12 participants, the CBCL and DISC-IV were administered to someone other than the parent (e.g., childcare worker, foster parent, guardian). YSR, CBCL, and DISC-IV data were not available for two, one, and two participant(s), respectively. Since the problem behavior of our sample was in the externalizing spectrum, we decided to use the YSR and CBCL T-scores of externalizing behavior, consisting of the aggression and delinquency syndrome scores.

Statistical analysis

Linear regression analyses were used to examine the predictors of CBCL and YSR externalizing problems. In addition, we used a binary logistic regression analysis in order to examine how many of the participants were correctly predicted to have a DBD diagnosis at follow-up. As some predictor variables were highly skewed (skewness > 2), they were Log-transformed. The regression analyses were accomplished in two steps. First, the predictive influence of each of the independent variables was examined separately by computing a standardized regression coefficient (SRC), with the possible predictor as independent variable, and the outcome measure as dependent variable. In the second step, the independent variables with the highest SRCs were simultaneously entered into a linear multiple regression analysis. Given the number of participants, we concentrated on the predictor variables with the strongest values of SRC. Single isolated outlier values, with an outlier defined as an individual value more than 2.5 SDs above the mean value of the group, were removed from the final regression analysis. In order to evaluate predictors and reduce redundancy in the analyses, we computed r between different independent predictors. No correlation met the criterion of collinearity and therefore none of the predictor variables was deleted from any further analyses for reasons of redundancy.

RESULTS

Outcome measures at follow-up

First we checked whether participants who had only received treatment in an in-patient setting (IN, *n*= 29) and those who had only received treatment in a day-treatment setting (DAY, *n*= 10) differed with regard to CBCL and YSR externalizing problems (T-scores) at

follow-up. We did not find any significant differences (Mean ± SD: IN-CBCL = 68.1 ± 9.7, DAY-CBCL= 65.3 ± 9.3, $F(1,37)= 0.65$, $p= .43$; Mean ± SD: IN-YSR = 55.2 ± 9.3, DAY-YSR= 57.8 ± 7.8, $F(1,35)= 0.63$, $p= .43$. Therefore, in the remainder of the analyses they were considered to be one single group ($n= 47$). According to the caregivers, 12 participants (26%) were in the non-clinical range (T-score < 60), 2 (4%) in the borderline range (T-score 60-63), and 32 (67%) were in the clinical range (T-score > 63) with regard to CBCL externalizing problems at follow-up. According to the adolescents themselves, 32 participants (71%) were in the non-clinical range, 4 (9%) in the borderline range, and 9 (20%) were in the clinical range with regard to YSR externalizing problems. Although parent-rated (CBCL) scores differed significantly from self-rated (YSR) externalizing problem scores (Mean ± SD: CBCL= 66.9 ± 10.0, YSR= 55.4 ± 8.6, t=7.49, $p< .01$), CBCL and YSR externalizing problems scores were significantly correlated ($r= .40$, $p< .01$). On the basis of the parent-version of the DISC-IV, at follow-up 21 (47%) participants no longer had an ODD or a CD diagnosis, whereas 24 (53%) participants were rediagnosed as having either an ODD ($n= 8$) or a CD ($n= 16$).

Relationship between pre-CBCL scores and CBCL and YSR externalizing scores at follow-up

Pre-CBCL scores were found to have a low correlation with either CBCL ($r= .11$, $p= .54$) or YSR ($r= -.06$, $p= .72$) externalizing problem scores at follow-up. Therefore, we decided not to enter pre-CBCL scores as covariate.

Relationship predictors and outcome variables

In a preliminary step of the analysis, SCL turned out to be a good predictor of CBCL externalizing score, YSR externalizing score, and the presence of a DBD diagnosis, as was indicated by high SCRs. Therefore, SCL might be an important predictor of outcome and would be entered in the final regression analyses. However, this would lead to a limitation of the sample size, since SCL data had been collected for only 31 participants, and would thus influence the power of the results. Therefore, we decided to perform all analyses 1) within a sample of those 31 participants who had complete SCL data (limited sample), as well as 2) within a sample of 47 participants (total sample), not including SCL as a possible predictor. Table 1 (limited sample) and Table 2 (total sample) show the SRCs of the different child and family characteristics related to CBCL and YSR externalizing problems, and DBD diagnosis at follow-up.

Predictors of CBCL externalizing problems (limited sample)

The following three independent variables were entered simultaneously into a linear regression analysis; basal SCL, psychopathology father, and TIQ. This resulted in a significant model ($F(3,23)= 6.85$, $p< .01$), explaining 47.2% of the variance. Basal SCL was the only variable having a unique significant prediction of CBCL externalizing behaviors at follow-up (see Table 3). Thus, children with a lower basal SCL were predicted to have more parent-rated externalizing problems at follow-up.

Predictors of YSR externalizing problems (limited sample)

The following independent variables were entered simultaneously into a linear regression analysis; number of premature responses (Log-transformed), ADHD comorbidity, and basal SCL. This resulted in a significant model ($F(3,24)= 10.25$, $p< .01$), explaining 56.2% of the variance. All three variables that were entered in the analysis had a unique significant prediction of YSR externalizing behaviors at follow-up (see Table 3). Thus, children who had a lower basal SCL, who had had an ADHD comorbidity, and who had given less premature responses, were predicted to have more self-rated externalizing problems at follow-up.

Table 1. *Standardized Regression Coefficients (SRCs) for independent variables and their relation to parent-rated (CBCL) and self-rated (YSR) externalizing problems, and to the presence of a DBD diagnosis at follow-up in the limited sample.*

	CBCL		YSR		DBD	
Independent variables	SRC	*p*	SRC	*p*	SRC	*p*
Demographic						
Gender	.06	.75	.12	.53	.24	.20
Neurobiological						
Basal SCL	-.47	.01	-.30	.11	-.53	.00
Basal HR	-.05	.81	-.28	.14	-.03	.89
Basal cortisol level	.25	.19	.18	.34	.27	.15
Cortisol reactivity level	-.02	.91	.04	.82	-.06	.76
ADHD comorbidity	.26	.17	.32	.09	.01	.96
No of doors	-.11	.58	-.28	.14	.05	.82
No of premature responses (Log-transformed)	-.20	.31	-.35	.06	-.10	.61
TAP (Log-transformed)	.05	.82	.12	.55	.12	.55
TAR	.07	.71	.16	.43	.06	.75
Psychological						
PIQ	-.28	.14	-.10	.60	-.20	.30
VIQ	-.21	.26	-.25	.18	-.06	.77
TIQ	-.29	.13	-.18	.33	-.17	.38
VIQ-PIQ	.09	.67	-.13	.50	.16	.41
Family						
SES father	-.26	.23	-.11	.60	-.25	.25
SES mother	.17	.38	.27	.16	.30	.11
Psychopathology mother	.14	.46	.09	.65	.16	.41
Psychopathology father	-.43	.02	-.22	.25	-.21	.28
Smoking during pregnancy	-.03	.86	.26	.17	-.22	.24
Physical abuse	-.07	.71	.08	.68	-.28	.14
Sexual abuse	.03	.87	-	-	.18	.34
Neglect	.03	.90	.05	.82	.20	.30
Family composition	.05	.79	.05	.79	.26	.16

Notes. Higher scores on all family characteristics reflect greater dysfunction. A score of 0 corresponds to a boy, whereas a 1 corresponds to a girl.

Table 2. *Standardized Regression Coefficients (SRCs) for independent variables and their relation to parent-rated (CBCL) and self-rated (YSR) externalizing problems, and to the presence of a DBD diagnosis at follow-up in the total sample.*

	CBCL		YSR		DBD	
Independent variables	SRC	*p*	SRC	*p*	SRC	*p*
Demographic						
Gender	.05	.73	.10	.51	.19	.21
Neurobiological						
Basal HR	.03	.83	-.12	.46	.06	.69
Basal cortisol level	.09	.57	.12	.43	.20	.21
Cortisol reactivity level	.00	.99	-.07	.64	-.06	.68
ADHD comorbidity	.10	.51	.22	.16	-.05	.75
No of doors	-.11	.47	-.19	.23	-.08	.62
No of premature responses (Log-transformed)	-.24	.13	-.32	.04	-.28	.07
TAP (Log-transformed)	.05	.76	.15	.35	.16	.32
TAR	.02	.90	.05	.76	.09	.59
Psychological						
PIQ	-.22	.14	-.23	.14	-.05	.73
VIQ	-.26	.08	-.25	.10	-.02	.92
TIQ	-.28	.06	-.26	.09	-.06	.70
VIQ-PIQ	.03	.85	.05	.77	.05	.74
Family						
SES father	-.09	.62	.05	.77	-.10	.57
SES mother	.23	.14	.31	.05	.29	.06
Psychopathology mother	-.03	.85	-.14	.37	-.01	.97
Psychopathology father	-.35	.02	-.14	.37	-.16	.30
Smoking during pregnancy	-.02	.93	.20	.20	-.17	.28
Physical abuse	-.14	.37	.10	.54	-.17	.26
Sexual abuse	.04	.80	.29	.06	-.01	.95
Neglect	.02	.88	.15	.33	.18	.25
Family composition	.01	.96	.03	.83	.19	.21

Notes. Higher scores on all family characteristics reflect greater dysfunction. A score of 0 corresponds to a boy, whereas a 1 corresponds to a girl.

Predictors of DBD diagnosis (limited sample)

The following independent variables (namely basal SCL, basal cortisol level, and SES mother) were entered into a logistic regression analysis, predicting whether participants have a DBD diagnosis or not. These variables were entered into the analysis simultaneously, resulting in a significant model (Chi-square= 13.4, $p< .01$), correctly predicting the outcome of 79% of the participants. Again, it was basal SCL that had a unique significant prediction of outcome (see Table 3). Thus, children who had a low basal SCL were predicted to be rediagnosed as having DBD at follow-up.

Predictors of CBCL externalizing problems (total sample)
The following four independent variables were entered simultaneously into a linear regression analysis: number of premature responses (Log-transformed), SES mother, psychopathology father, and TIQ. This resulted in a significant model ($F(4,34)= 3.42$, $p= .02$), explaining 28.7% of the variance. The number of premature responses was the only variable with a unique significant prediction of CBCL externalizing behaviors at follow-up (see Table 3). Thus, children who had shown less premature responses during the DOT were predicted to have more parent-rated externalizing problems at follow-up.

Predictors of YSR externalizing problems (total sample)
The following four independent variables were entered simultaneously into a linear regression analysis: number of premature responses (Log-transformed), SES mother, ADHD comorbidity, and TIQ. This resulted in a significant model ($F(4,33)= 9.17$, $p< .01$), explaining 52.6% of the variance. All variables, except TIQ, had a unique significant prediction of YSR externalizing behaviors at follow-up (see Table 3). Thus, children who had shown less premature responses during the DOT, who had had an ADHD comorbidity, and who had a mother with a low SES, were predicted to have more self-rated externalizing problems at follow-up.

Predictors of DBD diagnosis (total sample)
The following independent variables (namely number of premature responses (Log-transformed), basal cortisol level, SES mother, family composition, and gender) were entered into a logistic regression analysis, predicting whether participants have a DBD diagnosis or not. These variables were entered into the analysis simultaneously, resulting in a significant model (Chi-square= 16.14, $p< .01$), correctly predicting the outcome of 70% of the participants. Both the SES of the mother and the number of premature responses had a unique significant prediction of outcome (see Table 3). Thus, children who had given less premature responses during the DOT, and who had a mother with a low SES were predicted to be rediagnosed as DBD at follow-up.

On account of the unexpected finding that poor adolescent outcome was predicted by fewer premature responses, and in order to get a better understanding, we did some post-hoc analyses. First, we inspected the scores on premature responses, and found out that, even after a Log-transformation, the variable remained unevenly distributed. About half of the children gave a premature response either once or not at all, whereas the other children responded two or more times, with some children showing extreme numbers of premature responses. Therefore, we created a low premature response group (LPR: ≤ 1 premature response) and a high premature response group (HPR: > 1 premature responses), and examined whether these groups differed in ADHD comorbidity at intake; for this purpose we used a Chi-Square test. No significant differences were found. Thus, the number of premature responses did not seem to be a measure of impulsivity.

Table 3. *Linear multiple regression analyses in the case of predicting parent-rated (CBCL), and self-rated (YSR) externalizing problems, and logistic regression analysis in the case of predicting the presence of a DBD diagnosis.*

Limited sample		
Predicting CBCL externalizing scores	SRC	*p*
Basal SCL (in µsiemens)	-.461	.01
TIQ	-.128	.44
Psychopathology of father	-.274	.14
Predicting YSR externalizing scores	SRC	*p*
Basal SCL (in µsiemens)	-.430	.01
Number of premature responses (Log-transformed)	-.550	.00
ADHD comorbidity	.466	.00
Predicting DBD diagnosis	*B*	*p*
Basal SCL (in µsiemens)	-.217	.03
Basal cortisol (in nmol/L)	.563	.17
SES mother	1.721	.22
Total sample		
Predicting CBCL externalizing scores	SRC	*p*
Psychopathology of father	-.273	.09
TIQ	-.208	.18
Number of premature responses (Log-transformed)	-.299	.05
SES mother	.196	.21
Predicting YSR externalizing scores	SRC	*p*
Number of premature responses (Log-transformed)	-.485	.00
SES mother	.341	.01
TIQ	-.134	.29
ADHD comorbidity	.442	.00
Predicting DBD diagnosis	*B*	*p*
SES mother	2.562	.02
Number of premature responses (Log-transformed)	-.928	.03
Basal cortisol (in nmol/L)	-.236	.39
Family composition	1.899	.06
Gender	2.649	.06

DISCUSSION

In this exploratory study we examined a sample of adolescents who had been treated as children in an in-patient and/or day-treatment setting because of their severely disruptive behavior. At the start of treatment, all children had met the criteria for DBD as set out in the DSM-IV (APA 1994) and had been assessed by the child psychiatrist. At the follow-up

assessment, half of the participants (53%) were rediagnosed as DBD, using the parent version of the DISC-IV. In addition, 74% of the participants were found to score above the 90th percentile of the norm group with respect to parent-rated CBCL externalizing problems, whereas 29% of the participants were found to do so with respect to self-rated YSR externalizing problems. As in other studies (e.g., Offord et al 1992; Tremblay et al 1992), these findings suggest a substantial stability of conduct problems, although a visible variance in antisocial behavior remains present.

The main purpose of the present study was to explore the predictive influence of various child and family factors on adolescent outcome in a sample of DBD children. We consistently found that SCL, once entered in the analysis together with other predictors, has a unique predictive influence on future adolescent outcome, either when rated by caregivers or by adolescents themselves. Children with a lower basal SCL in childhood were predicted to have more externalizing problems, and to have a higher chance of being rediagnosed as DBD in adolescence. These findings are in line with the theory that low ANS activity, as manifested by low SCL, is a marker of low fear. To engage in antisocial behavior one has to have a degree of fearlessness. A lack of fear of socializing punishment is likely to contribute to poor fear conditioning, a deficient development of conscience and poorly socialized behavior (Raine 1993). In addition, this result extended the earlier finding in which basal SCL was found to predict change during treatment in DBD children (see chapter 5). However, in contrast to other studies (Raine et al 1990; Van Goozen et al 1998a), no significant correlation was found between externalizing problems and basal HR, basal cortisol, or cortisol responsivity. SCL may be a better measure of fearlessness than HR, since HR reflects both sympathetic and parasympathetic nervous system activity, whereas SCL reflects sympathetic processes only (Scarpa and Raine 1997). In addition, there appears to be no unitary arousal system, because intercorrelations between these different measures of arousal are low or even non-existent in the general population (e.g., Raine et al 1990).

In addition to basal SCL, ADHD comorbidity was found to constitute a unique prediction of YSR externalizing problems in adolescence. When children have not only a low basal SCL, but also a comorbid ADHD, they were predicted to have more externalizing problem behaviors at follow-up assessment, as rated by the adolescents themselves. Hence, in line with existing literature (Klinteberg et al 1993; Taylor et al 1996; Tremblay et al 1994), we observed that hyperactivity, when co-occurring with early behavioral problems, is a risk factor for poor adolescent outcome.

Furthermore, contrary to expectations, we found that fewer premature responses during the DOT, which was assumed to be a measure of impulsivity, predicted more externalizing problems in adolescence. The number of premature responses is probably not a measure of impulsivity. Not only was the number of premature responses in the present study not related to ADHD, but in a study on executive functioning in DBD children (Van Goozen et al 2004) no evidence was found of deficits in inhibition, with the exception of premature responses.

When performing the analyses within the total sample (n= 47), in which SCL data for 16 participants were missing, we found that in addition to the number of premature responses and ADHD comorbidity, the SES of the mother had a predictive influence on antisocial

behaviors, although it was dependent on the kind of outcome measure. Thus, in line with previous longitudinal studies of community samples (Nagin and Tremblay, 2001; Stattin and Trost 2000), DBD children with low SES mothers were predicted to have more antisocial problems in adolescence.

Among the many variables of interest, only a few factors were found to have a predictive influence on outcome at follow-up, and the contribution of these factors to the prediction of outcome was relatively small. This may be due to the fact that some characteristics of DBD children (e.g., low cortisol responsivity, high response perseveration) did not vary much within a DBD sample, although they were found to differ markedly from those of normal controls. This may be the reason why, once the problem behaviors existed, these factors did not have a predictive influence on outcome.

Some limitations of the present study need to be considered. First, this study was not a planned prospective study, but a follow-up study in which we made use of data collected previously. Second, two different methods were used to diagnose participants as having a DBD; during intervention a clinical diagnosis was made, whereas the diagnosis at follow-up reflects a DISC-IV (Shaffer et al 2000) diagnosis. Nevertheless, they were both based on the criteria set out in the DSM-IV (APA 1994). Third, the procedure of stress exposure, during which neurobiological data had been collected, was adjusted somewhat between studies (Van Goozen et al 1998a and 2000). In the first (1998a) study, no data on SCL were collected, and therefore SCL data existed for only 66% (Moffitt 1990) of the participants. Fourth, in the present study, neurobiological and psychological measures were collected routinely in the assessment phase, whereas the data on family characteristics prior to treatment were collected later by a review of case-records. Indeed, in contrast to the neurobiological and psychological child factors that were measured as continuous variables, some family characteristics such as depression in the mother were designated as dichotomous variables, although they were continuous by nature. Since the latter could result in a loss of information, we were not in any position to judge the relative importance of the predictive value of neurobiological and psychological child factors versus family factors. Therefore, future studies should measure child and family characteristics prospectively in a way that would make them more comparable.

In sum, within this sample we consistently found that SCL had a predictive influence on adolescent outcome. Thus, our results are in line with the fearlessness theory, according to which low activity of the autonomous nervous system, as manifested in low SCL, is related to the effectiveness of socializing punishment and accordingly to both poor socialization and a poor adolescent outcome.

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7

Summary and General Discussion

Research suggests that neurobiological processes play a role in childhood antisocial and aggressive behavior, but it is still unclear how these mechanisms exert their influence in predisposing towards antisocial behavior (Raine 2002a). In addition, it is recognized that environmental processes produce physiological changes in both CNS and ANS functioning in a way that can predispose to antisocial and aggressive behavior (Raine 1997; Suomi 2000). Thus there is a strong reason to believe that neurobiological processes play an important role in the development and persistence of antisocial behavior in both children and adults. In the present study, we investigated neurobiological correlates of aggression and the role they play in the stability of antisocial behavior and/or in changes that occur in that behavior. We did this by focusing on the relationship of aggression to cortisol and testosterone in a population-based sample (as described in chapter 2 and 3), and on the relationship of aggression to cortisol and the autonomic nervous system (ANS) in a sample of referred DBD children (as described in chapter 5 and 6). In chapter 4, we described the functioning of formerly treated DBD children as adolescents in terms of their disruptive behaviors, depression, institutionalization, police contacts, smoking behavior, substance use, and educational status.

Stability and change of antisocial behavior

Many studies based on community samples have shown great stability in antisocial behavior from late childhood to early adolescence (Caspi et al 1996; Moffitt 1990; Offord et al 1992). A longitudinal study (Nagin and Tremblay 1999) identified developmental trajectories for problem behaviors such as physical aggression, oppositional aggression, and hyperactivity, with 5% and 6% of the children studied being in the persistently aggressive or oppositional groups, respectively. Moreover, problems reported in these specific groups, such as a higher probability of becoming delinquent or physically violent (Nagin and Tremblay 1999), are in line with the prognosis for children diagnosed with DBD. Among the few studies that were conducted on the persistence of disruptive behaviors in referred DBD children, there was a substantial stability in antisocial behavior (42% - 88%) at 2 to 7-year follow-ups (Grizenko 1997; Kazdin 1989; Lahey et al 1995 and 2002; Sourander and Piha 1998). In the present thesis, we report on our investigations of a sample of referred disruptive behavior disordered children, all having a clinical diagnosis of ODD or CD at the start of treatment (chapter 4 to 6). At the start of treatment, 94% had externalizing problems within the clinical range according to the Child Behavior Checklist (CBCL; Achenbach 1991a) (described in chapter 5). In agreement with previous findings, we found that 71% of the children were still in the clinical range at the end of treatment. In addition, 67% of the participants were shown to be in the clinical range for CBCL externalizing problems even after a 5-year follow-up (described in chapter 4 and 6). Moreover, half of the participants (53%) were rediagnosed as having either ODD or CD at follow-up. There was, however, a large variance among the outcome for adolescents.

Although disruptive behavior disorders seem to be relatively stable, various behavioral intervention strategies, aimed at changing the prognosis of DBD, have proved to be

effective, at least in the short-term. Specifically, it has been demonstrated that parent management training and cognitive behavioral therapy, when combined with pharmacotherapy, positively affect conduct disorder in children (Brestan and Eyberg 1998; Kutcher et al 2004; Van de Wiel et al 2002). Likewise, in our study of a referred DBD sample we found a decrease in externalizing behaviors as a result of intensive treatment (chapter 5). Moreover, 38% of this DBD sample had a clearly positive outcome. Thus, antisocial behavior can be stable but can also be susceptible to change.

Cortisol and antisocial behavior

Chronic antisocial behavior in children and adolescents has been associated with cortisol, which is generally regarded as an indicator of stress reactivity. However, although some studies found low cortisol levels related to antisocial behavior (McBurnett et al 2000; Pajer et al 2001; Shoal et al 2003; Van Goozen et al 1998a and 2000), others found elevated levels (Gerra et al 1997; Susman et al 1997), and there were also some studies in which no relationship was found (Azar et al 2004; Klimes-Dougan et al 2001; Kruesi et al 1989; Scerbo and Kolko 1994; Schultz et al 1997; Stoff et al 1992; Susman et al 1999). These conflicting results may be due to differences in the samples studied. For instance, in the studies using referred samples (e.g., McBurnett et al 2000; Pajer et al 2001; Scerbo and Kolko 1994; Van Goozen et al 1998a and 2000), an inverse relationship was found between cortisol and aggression, or no relationship was found. On the other hand, in the studies using a community sample (Gerra et al 1997; Klimes-Dougan et al 2001; Susman et al 1997) either a positive relationship or no relationship between cortisol and aggression has been found. In chapter 2, we described a study in which variously defined aggressive subgroups were compared with regard to differences in salivary cortisol. A population-based sample of boys was followed longitudinally between the ages of 6 and 15. Assessments of different forms of antisocial behavior were obtained from various informants at several points in time, and cortisol was collected at age 13. In line with studies at our Department (Van Goozen et al 1998a and 2000), based on referred samples, we expected to find an inverse relationship between cortisol and aggression. However, in contrast to these expectations, we found that early adolescent boys with a history of relatively high levels of antisocial behavior had higher levels of cortisol than those who had fewer behavioral problems. Specifically, boys who scored relatively high on aggressive CD symptoms as well as those who had reactive forms of aggression were the ones who had higher levels of cortisol. This finding may be related to differences in the types of participants involved in the studies. Apparently, the finding of a negative association between cortisol and aggression, which seems to be evident in referred DBD samples (e.g., McBurnett et al 2000; Pajer et al 2001; Van Goozen et al 1998a and 2000), could not simply be translated to community or population-based samples. One explanation for the differences in outcome might be the moderating effect of social backgrounds. A number of studies have demonstrated that psychophysiological factors show stronger relationships to antisocial behavior in children from positive home backgrounds that lack the characteristic psychosocial risk factors for crime (Raine 2002b). This pattern of

results may be explained from the 'social push' perspective, i.e., if an antisocial child lacks social factors that 'push' or predispose him/her to antisocial behavior, biological factors may be more likely to explain antisocial behavior (Mednick 1977; Raine and Venables 1981). Although we have no way of comparing the socioeconomic backgrounds of our Dutch referred samples to that of a population sample with low SES in Montreal, it is true that our referred DBD samples had a more mixed socioeconomic background than the Montreal sample. Furthermore, since referred DBD children often have a history of negativistic, aggressive, and oppositional behaviors, resulting in poor parent-child relations, they might have experienced higher levels of stress over a longer period of time, for example, since their early childhood. This may have led to alterations in the setpoint of the HPA axis (Liu et al 1997).

With regard to the predictive value of cortisol in relation to antisocial outcome, McBurnett et al (2000) demonstrated that low levels of cortisol were associated with persistence of aggression. Moreover, the results of an exploratory study at our Department (Van de Wiel et al in press), which examined DBD children receiving an outpatient treatment, indicated that low cortisol responsivity in response to stress predicted low treatment outcome. In the present thesis, we explored the predictive value of some neurobiological child characteristics, including basal cortisol and cortisol reactivity, on the effect of treatment (chapter 5), as well as on adolescent outcome (chapter 6). Contrary to the earlier findings, we did not find that cortisol in childhood had a predictive influence either on treatment effect or adolescent outcome. This may have been due to some methodological differences between the studies that were conducted. Whereas we used a linear regression analysis, which is quite common for prediction studies, this procedure was not used in the studies by Van de Wiel et al (in press) and McBurnett et al (2000). Moreover, instead of using outpatients, as did Van de Wiel et al (in press), the children in the current study were treated in in-patient or day-treatment settings, and were therefore more severely disturbed. These discrepancies may be a possible reason for the different outcomes.

In conclusion, although most studies, some having been conducted at our Department (Snoek et al submitted; Van Goozen et al 1998a and 2000), found that psychiatrically treated DBD children and adolescents are characterized by low levels of cortisol (see chapter 1), our findings in a non-referred low SES sample suggest a positive relationship between cortisol and aggression. In addition, we did not find baseline cortisol level and cortisol reactivity in childhood to have a predictive influence on either treatment effect or on adolescent outcome. We can therefore conclude that the direction of the relationship between cortisol and aggression is highly dependent on the type of population examined.

Testosterone and antisocial behavior

Among the few studies linking testosterone to antisocial behavior in children and adolescents, some found a positive relationship (e.g., Chance et al 2000; Maras et al 2003; Sánchez-Martín et al 2000; Scerbo and Kolko 1994; Udry 1990), whereas others did not find any relationship (e.g., Constantino et al 1993; Halpern et al 1993; Susman et al 1987; Van

Goozen et al 1998b). In addition, some studies found that high testosterone levels were not related to physical aggression, but to social dominance (Rowe et al 2004; Tremblay et al 1997).

In the study described in chapter 3, we examined whether physical aggression, social dominance and/or delinquent behavior, measured from childhood to adulthood, was positively related to (changing) testosterone levels. In boys aged 6 to 21 years, antisocial behavior was assessed repeatedly by different informants, and multiple testosterone samples had been provided over these years of assessment. Boys who had a criminal record as adults (18 to 20 years of age), had higher testosterone levels at age 16. In addition, positive relations were observed between testosterone and proactive and reactive aggression and self-reported delinquent behavior, but for each type of antisocial behavior the association was not consistent over the pubertal years. At present it is not clear why this is the case. Rubinow and Schmidt (1996) suggested that many moderators could influence the relationship between testosterone and antisocial behavior, including metabolism, age, sex, circadian rhythm, stress, past experience. A further issue concerns the moderating role of social context in adolescence. The study by Mazur and Booth (1998) indicates that the social setting has to be taken into account in an assessment of the relationship between testosterone, on the one hand, and dominance, aggressive behavior, or antisocial behavior, such as norm breaking, on the other. This relationship is particularly clear in settings in which individuals are required to conform to rigid standards (e.g., such as in schools or in prisons). Boys who are likely to act in a dominant manner may be tempted to do so by breaking these norms or laws. In such cases, high testosterone could result in types of behavior that are regarded as rebellious, antisocial, or even criminal (Mazur and Booth 1998). Moreover, from a primate study it has been suggested that the link between testosterone and dominance is a reciprocal one; not only does testosterone affect dominance, but changes in dominance behavior or in social status could also result in changes in testosterone level (Rose et al 1975). As we examined boys over a period of important physical, emotional and social change, the question of whether testosterone was related to antisocial, aggressive or dominant behavior might have depended on the precise timing of the measurements and the circumstances of the boys.

Psychophysiological predictors of outcome

As far as we know, no studies to date have been conducted on the predictive role that psychophysiological factors play on the effect of treatment. However, some studies have demonstrated that electrodermal and/or cardiovascular activity is a predictor of later antisocial outcome (Kruesi et al 1992; Raine et al 1990; Venables 1989). Some studies on autonomic nervous system (ANS) activity in DBD children, conducted at our Department, have shown lower baseline levels of heart rate (HR; Van Goozen et al 1998a and 2000) and lower skin conductance levels (SCL; Matthys et al in press; Van Goozen et al 2000) in DBD than in control children. In chapter 5, we described a study in which we explored the predictive value of various family and child characteristics, including basal HR and SCL, on

the effect of treatment in a sample of DBD children who had been referred for long-term psychiatric treatment. Psychophysiological data had been collected previously in this sample in the course of former studies in our Department (Snoek et al in press; Van Goozen et al 2000). In chapter 6, a similar study is described, although in that study we explored the predictive influence of the above-mentioned characteristics on the persistence of antisocial behavior in adolescence. In line with most other studies, low basal SCL in childhood was found to be a predictor of both a poor treatment effect and a poor adolescent outcome. According to the *fearlessness theory* (Raine, 1993; see also chapter 1), low ANS activity, as manifested by measures such as HR and SCL, is related to fearlessness. A lack of fear would predispose children to antisocial and violent behavior because low fear of socializing punishment in childhood would contribute to poor fear conditioning and lack of conscience development (Raine 1993). In addition, social conditioning plays a central role in behavior therapy. Difficulty in social conditioning due to fearlessness thus would result in low treatment effect.

By Raine (2002a) and by Ortiz and Raine (2004) it was indicated that low resting HR would be the best-replicated biological correlate of antisocial and aggressive behavior in child and adolescent populations, because it might be a broad, global construct that taps into multiple physiological and psychological processes of relevance to antisocial behavior. However, in a study based on a referred DBD sample, the importance of baseline levels of SCL, rather than HR, was demonstrated in the highly significant negative correlations with antisocial behavior (Van Goozen et al 2000). In the current study, we did not find any correlation between basal HR and either treatment effect or adolescent outcome. SCL is probably a better measure of fearlessness than HR since it reflects sympathetic processes only, whereas HR reflects both sympathetic and parasympathetic nervous system activity.

ADHD as predictor of outcome

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common co-occurring problems in children with DBD. The comorbidity of ADHD in children with DBD is often found to complicate treatment (Burke et al 2002), and to predict a poorer outcome (Hinshaw 1994; Klinteberg et al 1993; Satterfield and Schell 1997). In this thesis, we explored whether ADHD comorbidity would be a predictor of poor treatment effect (chapter 5) and poor adolescent outcome (chapter 6). In line with the existing literature we observed that hyperactivity, when co-occurring with early behavioral problems, is a risk factor for poor adolescent outcome. However, in line with another study conducted at our Department (Van de Wiel et al submitted), we did not find ADHD comorbidity to have the expected negative influence on treatment outcome. In both studies, pharmacotherapy was administered for the treatment of comorbid ADHD, and thus the role of ADHD as predictor of the effect of treatment might have been mitigated. A possible reason why this was not the case for the effect of ADHD comorbidity on adolescent outcome was that the adolescents had probably discontinued their ADHD medication.

Neuropsychological predictors of outcome

Although in risk and resilience research several child and family characteristics have been shown to be related to an increased risk of developing problem behavior (Fergusson and Lynskey 1996; Rutter 1992), less is known about the predictive value of aspects of behavioral change once problem behavior exists (Mathijssen et al 1999). Nevertheless, some neuropsychological child characteristics have been shown to predict outcome or could be considered as possible candidates for the prediction of treatment effect or outcome in adolescence (see chapter 1). In the studies described in chapter 5 and 6, we explored whether some measures of IQ had a predictive value in relation to treatment effect and/or adolescent outcome. Among these measures, the discrepancy between children's verbal IQ (VIQ) and performance IQ (PIQ) was shown to be a predictor of treatment effect, in that a relatively large discrepancy between VIQ and PIQ, with VIQ<PIQ, was a predictor of a less favorable treatment outcome. However, no relationship was found between VIQ-PIQ discrepancy and adolescent outcome. In contrast to other studies (Lahey et al 2002; Vance et al 2002), we did not find that other IQ measures (i.e., total IQ, VIQ, or PIQ) had a predictive effect on both treatment effect and adolescent outcome. At the moment it is unclear how these findings can be explained.

Response perseveration was also considered as a possible candidate for the prediction of treatment effect and adolescent outcome. Children who have difficulty in stopping their ongoing behavior under changing reward and punishment conditions were expected to profit less from an intervention and to have more problems in adolescence. Findings showed, however, that this was not the case. Although we found earlier that response perseveration was clearly different in DBD children as compared to normal controls (Matthys et al 1998 and in press; Van Goozen et al 2004), response perseveration as a within-group variable did not have a predictive influence on outcome, probably because of a small variance within the DBD group. This might also be the case for other neurobiological variables, such as baseline cortisol, cortisol reactivity and HR.

Family and contextual predictors of outcome

Amongst the various family and demographic characteristics that were explored for their predictive influence on treatment effect and/or adolescent outcome, low SES of the mother was the only characteristic that was found to predict a poor adolescent outcome. This was in line with the results of previous longitudinal studies of community samples (Nagin and Tremblay 2001; Stattin and Trost 2000). In addition, none of the family and demographic characteristics, i.e., parental SES, parental psychopathology, smoking during pregnancy, physical abuse, sexual abuse, neglect, family composition, parental cooperation, gender, and age at intake, was found to be related to treatment outcome. This could be due to the fact that in contrast to the neurobiological and psychological child factors that were measured as continuous variables, most family characteristics were designated as dichotomous variables, although they were continuous by nature.

Future research on neurobiological correlates of antisocial behavior

So far, little is known about the causal link between neurobiological characteristics and antisocial behavior. Moreover, it is not clear to what extent environmental factors, such as stressful life events, have an interacting influence on the association between neurobiology and antisocial behavior. In this respect, future studies will need to give more attention to the interaction between neurobiology (e.g., cortisol, SCL and HR) and environmental factors, including adverse life events. We suggest conducting a prospective longitudinal study, starting at birth, since we expect stressful life events to have a major effect on neurobiology early in life. In such a study different types of aggression and antisocial behavior constructs need to be assessed, like reactive and proactive aggression, and involve multiple informants. It is also of great importance that neurobiological measurements are performed systematically using the same methods. In addition, one must take into account the properties of the different neurobiological systems, such as the HPA axis, the HPG axis, and the ANS.

Regarding the assessment of cortisol, which is complicated by its marked diurnal cycle, one should take repeated measurements of cortisol while keeping the timing for all participants equal. Since it was suggested that low cortisol levels in referred DBD children could be due to modifications in adrenocortical activity following adverse life experiences (Van Goozen et al 2000), it would be interesting to investigate at more than one time point both the awakening cortisol response and cortisol reactivity to stress.

With respect to testosterone, one should also take repeated measurements, preferably in the afternoon, while keeping the timing for all participants equal, since the time of measurement during the daily circadian rhythm affects the magnitude of the observed relationship.

As to the ANS, one should take into account that HR reflects both sympathetic and parasympathetic nervous system activity, whereas SCL reflects sympathetic processes only. In addition, although a low ANS activity, specifically a low HR and a low SCL, was considered to be related to fearlessness (Raine 1993), it is still unclear what these variables actually measure. In order to obtain more insight into the meaning of different psychophysiological measurements, we suggest that psychophysiology should be studied along with neuropsychological characteristics such as punishment and reward sensitivity, as in the study by Matthys et al (in press).

Furthermore, in order to examine the interacting influence of social environment on the link between neurobiology and antisocial behavior, our study emphasized the importance of measuring environmental factors in a qualitatively good manner. We suggest using thoroughly validated questionnaires, e.g., the Parenting Stress Index (Loyd and Abidin 1985), and different informants. These questionnaires should be administered at different points in the child's life in order to adequately assess the stress experienced.

In conclusion, earlier studies on the relation between neurobiology and antisocial behavior have produced some evidence that HR, SCL, cortisol, and testosterone are correlates, although findings are inconsistent. These inconsistencies may be due to some methodological differences between studies, e.g., some studies were based on non-referred

community samples (Raine et al 1997 and 2001), whereas others used referred DBD samples (McBurnett et al 2000; Van Goozen et al 1998a and 2000). The studies presented in this thesis also provide some evidence that cortisol and testosterone are correlates of aggressive and antisocial behavior in a population sample. In a sample of referred DBD children, SCL in particular was found to have a predictive influence on the stability of antisocial behaviors. However, the mechanisms underlying these correlates need to be clarified.

Nederlandse Samenvatting

Agressie en antisociaal gedrag

Agressie, gedefinieerd als gedrag dat gericht is op het opzettelijk toebrengen van fysieke schade aan personen of eigendommen, vormt al geruime tijd een groot probleem in onze samenleving. Naast fysieke agressie bestaan er ook andere vormen van agressief gedrag, zoals psychologische en relationele agressie. Het begrip antisociaal gedrag omvat behalve agressief gedrag ook een bredere reeks aan activiteiten, waaronder diefstal, vandalisme, brandstichting, liegen, en oppositioneel gedrag. Verschillende termen worden gehanteerd als het gaat om antisociaal gedrag, waaronder externaliserende gedragsproblemen, disruptief gedrag, antisociale gedragsstoornis, en delinquentie. Deze aggregatie van gedragingen kan een probleem vormen voor onderzoekers die het ontstaan en de ontwikkeling van agressief en antisociaal gedrag proberen te begrijpen.

Als verschillende oppositionele, antisociale of agressieve gedragingen een patroon gaan vormen, met een duidelijke ongunstige invloed op het functioneren van het kind of de jeugdige, is er volgens de DSM-IV (APA, 1994) sprake van een oppositioneel-opstandige gedragsstoornis (ODD) of een antisociale gedragsstoornis (CD). De term disruptieve gedragsstoornis (DBD) omvat beide stoornissen. De prevalentie van deze gedragsstoornissen is hoog (2.0% voor CD en 3.2% voor ODD).

In toenemende mate bestaat er consensus dat het ontstaan van DBD ligt in de interactie tussen biologische kindkenmerken en niet-optimale omgevingskenmerken van het kind. In dit proefschrift onderzochten we de neurobiologische aspecten van agressie en hun rol in de stabiliteit en verandering van agressief en antisociaal gedrag. Dit hebben we gedaan door ons te richten op de relatie van agressie met cortisol en testosteron in een steekproef van de mannelijke bevolking met een lage sociaal-economische status, en op de relatie van agressie met cortisol en het autonome zenuwstelsel in een steekproef van verwezen DBD kinderen. Ook is de rol van enkele neuropsychologische- en gezinskenmerken in de relatie met agressie onderzocht, hoewel deze aspecten een bescheiden plaats innemen in dit proefschrift.

In hoofdstuk 1 van dit proefschrift wordt een literatuuroverzicht gegeven van reeds eerder gedaan onderzoek naar de relatie van neurobiologische-, neuropsychologische- en gezinsfactoren met agressief en/of antisociaal gedrag, evenals de rol van deze factoren in de stabiliteit en verandering van dit gedrag. In hoofdstuk 2 en 3 worden twee onderzoeken beschreven waarin bij een steekproef van niet-verwezen adolescente jongens, afkomstig uit Montreal, de relatie tussen cortisol en agressie (hoofdstuk 2), en de relatie van testosteron met agressie, delinquentie en sociale dominantie werd bestudeerd (hoofdstuk 3). Hoofdstuk 4 beschrijft hoe een groep DBD kinderen, die als kind een dagklinische en/of klinische behandeling kregen in de buitenkliniek Vosseveld van het Universitair Medisch Centrum Utrecht, functioneert in de adolescentie. In hoofdstuk 5 en 6 worden twee onderzoeken beschreven naar de predictieve waarde van neurobiologische-, neuropsychologische- en omgevingskenmerken van een groep verwezen DBD kinderen op het effect van de behandeling in (dag)klinisch verband (hoofdstuk 5) en op de persistentie van antisociaal gedrag bij deze patiëntjes in hun adolescentie (hoofdstuk 6). Dit proefschrift eindigt met een algemene discussie in hoofdstuk 7.

Stabiliteit en verandering van antisociaal gedrag

Studies gebaseerd op steekproeven van de algemene bevolking laten een hoge stabiliteit van antisociaal gedrag zien van de kindertijd tot de adolescentie. Van de weinige studies die zijn uitgevoerd binnen een verwezen groep DBD kinderen, vonden de meeste studies een redelijke stabiliteit van antisociaal gedrag (42%-88%) bij 'follow-up' van 2 tot 7 jaar. In hoofdstuk 5 van dit proefschrift wordt een studie beschreven van een groep verwezen DBD kinderen die gedragstherapeutisch en farmacotherapeutisch werd behandeld in een dagklinische en/of klinische setting van het Universitair Medisch Centrum Utrecht. 94% van deze kinderen lieten aan het begin van behandeling zodanig veel externaliserende probleemgedragingen zien dat ze volgens een door hun ouders ingevulde vragenlijst (CBCL) binnen het klinische gebied van functioneren vielen. In overeenstemming met resultaten uit andere onderzoeken vonden we dat direct na behandeling 71% binnen het klinische gebied viel, en dit was nog 67% 5 jaar na behandeling. Echter, de variantie in hun functioneren was groot op dat moment. Wanneer het functioneren in de adolescentie werd gedefinieerd in termen van DBD diagnose, woonsituatie, delinquentie, het volgen van onderwijs, en rookgedrag, bleek een derde relatief slecht en een derde relatief goed te functioneren als adolescent.

Hoewel DBD een relatief constant verloop heeft, hebben verschillende gedragsmatige interventie strategieën aangetoond tot op zekere hoogte effectief te zijn, zeker op de korte termijn. Hiermee in overeenstemming werd in de studie, beschreven in hoofdstuk 5 van dit proefschrift, als gevolg van intensieve behandeling, een significante afname van externaliserend probleemgedrag waargenomen op het einde van de behandeling. Daarnaast bleek 38% van de groep verwezen DBD kinderen 5 jaar na behandeling relatief goed te functioneren (zie hoofdstuk 4). Antisociaal gedrag kan dus enerzijds stabiel zijn maar is anderzijds mogelijk ook voor verandering vatbaar.

Relatie cortisol en antisociaal gedrag

Er zijn aanwijzingen dat stress een belangrijke rol speelt in het verklaren van de individuele verschillen in antisociaal en agressief gedrag. Stress wordt voor een belangrijk gedeelte gereguleerd door de hypothalamus-hypofyse-bijnier (HPA) as, waarvan cortisol het eindproduct is. Hoewel in meerdere studies een negatief verband is gevonden tussen cortisol en antisociaal gedrag, zijn er ook een heel aantal studies waarin dit verband niet werd gevonden, of waarin een positief verband werd gevonden. Mogelijk zijn deze tegenstrijdige resultaten veroorzaakt door de verschillende steekproeven die werden bestudeerd.

In hoofdstuk 2 wordt het onderzoek beschreven waarin verschillend gedefinieerde agressieve subgroepen werden vergeleken met betrekking tot hun cortisol waarden in speeksel. Hiertoe werd een niet-verwezen mannelijke steekproef van hun 6^{e} tot 15^{e} jaar vervolgd en werd hun agressieve gedrag op meerdere momenten door meerdere informanten beoordeeld. Naar aanleiding van eerdere bevindingen op onze afdeling, gebaseerd op een verwezen groep DBD kinderen, verwachtten we een negatieve relatie

tussen cortisol en agressie te vinden. Echter, in tegenstelling tot deze verwachting vonden we dat jongens die over een bepaalde periode meer agressie vertoonden hogere cortisol waarden lieten zien dan degenen die over eenzelfde periode relatief weinig agressief waren. Met name de jongens met relatief veel agressieve CD symptomen, en degenen die relatief veel reactief agressief gedrag vertoonden, waren degenen met hogere cortisol waarden. Deze bevinding zou een gevolg kunnen zijn de verschillen in onderzoeksgroepen in de verschillende studies. Blijkbaar kan de negatieve relatie tussen cortisol en agressie, die binnen een groep verwezen DBD kinderen herhaaldelijk werd gevonden, niet simpelweg worden vertaald naar een steekproef van een niet-verwezen bevolkingsgroep.

Met betrekking tot de predictieve waarde van cortisol op behandeleffect dan wel op de persistentie van antisociaal gedrag, zijn voor zover bekend twee eerdere studies verricht, waaronder een werd uitgevoerd op onze afdeling. Men toonde in deze laatstgenoemde studie aan dat binnen een groep ambulant behandelde DBD kinderen degenen met een relatief lage cortisol reactiviteit op stress minder profijt van de behandeling ondervonden. In dit proefschrift werd de predictieve waarde van een aantal neurobiologische factoren, waaronder basale cortisol waarden en cortisol reactiviteit, op het effect van behandeling (hoofdstuk 5) en de persistentie van antisociaal gedrag (hoofdstuk 6) onderzocht, binnen een verwezen groep DBD kinderen. In tegenstelling tot eerdere bevindingen werd geen verband gevonden tussen enerzijds basaal cortisol of cortisol reactiviteit, en anderzijds het behandeleffect of de persistentie van antisociaal gedrag. Mogelijk is dit het gevolg van methodologische verschillen tussen verschillende studies. Zo gebruikten wij, anders dan de twee eerdere studies, een lineaire regressie analyse, welke een vrij gebruikelijke analyse is voor dit type studies. Daarnaast werd de huidige studie uitgevoerd binnen een groep DBD kinderen die in dagklinische en/of klinische settings werden behandeld, terwijl de eerdere studie op onze afdeling werd uitgevoerd binnen een groep minder ernstig gedragsgestoorde DBD kinderen die ambulant werden behandeld. Deze discrepanties zijn een mogelijke verklaring voor de verschillen in bevindingen.

Relatie testosteron en antisociaal gedrag

Testosteron heeft niet alleen invloed op de fysieke aspecten maar ook op de gedragsaspecten van de vermannelijking. In volwassenen is gevonden dat testosteron positief gerelateerd is met delinquentie, drugsgebruik en geweldsmisdrijven, maar andere studies vonden geen verband. Er is nog maar weinig bekend over de relatie tussen testosteron en agressief of antisociaal gedrag bij kinderen en adolescenten, en de bevindingen zijn niet geheel consistent. Hoewel de meeste studies zich richten op de relatie tussen testosteron en agressie, tonen een aantal dierstudies aan dat er ook een relatief sterk verband bestaat tussen testosteron en sociale dominantie.

Hoofdstuk 3 beschrijft een onderzoek naar de relatie van fysieke agressie, sociale dominantie en/of delinquentie met testosteron binnen een niet-verwezen mannelijke onderzoeksgroep. Vanaf het 6^{e} jaar tot in de volwassenheid werd hun gedrag op meerdere momenten beoordeeld en daarnaast werd op een aantal momenten testosteron gemeten.

Jongens die tussen hun 18e en 21e jaar een strafblad kregen hadden op 16-jarige leeftijd gemiddeld hogere testosteron waarden dan jongens zonder strafblad. Daarnaast werd er een positief verband gevonden tussen testosteron en zowel proactieve als reactieve agressie, als delinquent gedrag volgens de jongens zelf, maar deze relaties bleken niet consistent over de puberteit. We hebben hier nog geen duidelijke verklaring voor. Mogelijk speelt, met name in de adolescentie, de sociale context waarin de jongens zich bevinden een rol in de relatie tussen antisociaal gedrag en testosteron. Verder wordt vanuit dierstudies gesuggereerd dat de relatie tussen testosteron en antisociaal gedrag wederkerig zou zijn. Aangezien wij de groep jongens bestudeerden in een periode van belangrijke lichamelijke, emotionele, en sociale veranderingen, was het verband dat wij vonden tussen testosteron en antisociaal, agressief, en/of dominant gedrag mogelijk afhankelijk van het precieze moment van meting en de omstandigheden waarin de jongens zich op dat moment bevonden.

Psychofysiologische predictoren van behandeleffect en persistentie van antisociaal gedrag

Voor zover bekend zijn er nog geen eerdere studies verricht naar de predictieve waarde van psychofysiologische factoren op het effect van behandeling. Wel blijkt uit verschillende prospectieve studies dat jonge kinderen met een laag activatieniveau van het autonome zenuwstelsel een verhoogd risico lopen op agressief en delinquent gedrag. Ook binnen onze afdeling heeft men laten zien dat DBD kinderen een lagere basale hartslagfrequentie (HR) en huidgeleidingsactiviteit (SCL) hebben dan een groep gezonde controle kinderen. Hoofdstuk 5 beschrijft een studie binnen een groep verwezen DBD kinderen, waarin de predictieve waarde werd onderzocht van verschillende gezins- en kindkenmerken, waaronder basale HR en SCL, op het effect van behandeling enerzijds en de persistentie van antisociaal gedrag in de adolescentie anderzijds. De psychofysiologische data werden verzameld toen de kinderen (dag)klinisch werden behandeld. Hierover werd al eerder gepubliceerd door onderzoekers van onze afdeling. In overeenstemming met voorgaande studies waarbij gebruik gemaakt werd van deze psychophysiologische data, vonden we dat een lage basale SCL een voorspeller was van enerzijds een minder effectieve behandeling, en anderzijds meer antisociale probleemgedragingen in de adolescentie.

Volgens de 'fearlessness theory' zijn een lage HR en SCL de uiting van een geringe vrees voor dreigend gevaar of dreigende straf. Als kinderen minder bang of gevoelig zijn voor straf, of voor dreigen met straf, dan zouden zij minder makkelijk conditioneerbaar zijn en minder makkelijk te socialiseren. Omdat sociale conditionering een centrale rol speelt in gedragstherapieën, hangen problemen in de sociale conditionering wellicht samen met een minder effectieve behandeling en persistentie van antisociaal gedrag.

Men suggereert dat een lage basale HR het best gerepliceerde biologische kenmerk van agressief en antisociaal gedrag zou zijn bij kinderen en adolescenten met antisociaal gedrag. In de huidige studie (hoofdstuk 5 en 6) is echter, in tegenstelling tot basale SCL, geen relatie gevonden tussen basale HR en behandeleffect of persistentie van antisociaal gedrag. Mogelijk is SCL een betere maat voor bevreesdheid omdat het de activiteit van het

sympathische zenuwstelsel weergeeft, terwijl HR de activiteit van zowel het sympathische als het parasympathische zenuwstelsel weergeeft.

Overige predictoren van behandeleffect en persistentie van antisociaal gedrag

Uit verschillende studies is gebleken dat meerdere neuropsychologische- (b.v. IQ, response perseveratie) en omgevingsfactoren (sociaal-economische status ouders, psychopathologie ouders, sexueel en lichamelijk misbruik, verwaarlozing) een relatie hebben met antisociaal gedrag. Een aantal van deze factoren blijkt tevens een voorspeller te zijn van de mate van behandelingeffect en de persistentie van antisociaal gedrag. In hoofdstuk 5 wordt een studie beschreven naar de predictieve waarde van verschillende kind- en gezinskenmerken waaronder een aantal neuropsychologische- en omgevingsfactoren op het effect van behandeling binnen een groep verwezen DBD kinderen. Van al deze neuropsychologische- en omgevingsfactoren bleek alleen het verschil tussen het verbale IQ (VIQ) en het performale IQ (PIQ), met VIQ<PIQ, een voorspeller te zijn van een minder effectieve behandeling. Hoewel uit eerder onderzoek is gebleken dat een groep DBD kinderen wel significant verschilden van een groep gezonde controle kinderen op response perseveratie, had response perserveratie als variabele binnen de DBD groep geen predictieve waarde op het behandeleffect, mogelijk door de geringe variantie binnen een groep DBD kinderen. Van de in hoofdstuk 6 beschreven studie naar de predictieve waarde van diezelfde factoren op de persistentie van antisociaal gedrag in de adolescentie, bleek een groter aantal ADHD kenmerken, een kleiner aantal premature responsen op de response perseveratie taak, en een lagere sociaal-economische status van de moeder de persistentie van antisociaal gedrag te voorspellen.

Conclusie

Uit de studies die zijn beschreven in hoofdstuk 2 en 3 is gebleken dat, hoewel er een relatie is gevonden tussen antisociaal gedrag enerzijds en cortisol en testosteron anderzijds, deze niet altijd consistent was met, of zelfs tegengesteld was aan, de in de literatuur bekende bevindingen. Wij vermoeden dat de soort onderzoeksgroep die werd bestudeerd een rol speelt in deze relatie.

Verder vonden we, in overeenstemming met de literatuur, dat antisociaal gedrag in een groep DBD kinderen een relatief stabiel verloop heeft. Desondanks was de variantie in het functioneren in de adolescentie groot. Wanneer het functioneren in de adolescentie werd gedefinieerd in termen van DBD diagnose, woonsituatie, delinquentie, het volgen van onderwijs, en rookgedrag, bleek eenderde relatief slecht en eenderde relatief goed te functioneren als adolescent. In hoofdstuk 5 en 6 is gevonden dat, binnen de voorhanden zijnde kind- en omgevingsfactoren, met name een lage SCL een goede voorspeller was voor zowel een geringe effectiviteit van de behandeling als voor meer antisociale gedragsproblemen in de adolescentie.

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Curriculum Vitae

Irene van Bokhoven werd geboren op 6 mei 1973 te Hoog-Keppel. In 1992 behaalde zij het VWO diploma aan het St.-Ludgercollege te Doetinchem. Na een jaar Gezondheidswetenschappen te hebben gestudeerd aan de Universiteit Maastricht, begon zij in 1993 aan de studie Medische Biologie aan de Universiteit van Amsterdam. Ten behoeve van haar eindscriptie deed ze een literatuurstudie naar het effect van traumatische stress op het geheugen. In november 1998 haalde zij haar doctoraal examen. Na ruim een jaar uitzendwerk te hebben gedaan, startte zij in april 2000 als assistent in opleiding bij de afdeling Kinder- en Jeugdpsychiatrie van het Universitair Medisch Centrum Utrecht met het onderzoek dat leidde tot dit proefschrift. Tijdens deze periode was zij werkzaam in de buitenkliniek Vosseveld te Soest. Deze kliniek maakt deel uit van de afdeling Kinder- en Jeugdpsychiatrie en richt zich specifiek op de behandeling van kinderen met een oppositioneel-opstandige of een antisociale gedragsstoornis.