Neuroendocrine and autonomic risk factors for disruptive behaviors in young adolescents

Cover: Picture from getty images (royalty-free) edited by Optima Rotterdam

Participating centers of TRAILS include various Departments of the University of Groningen, the Erasmus Medical Center of Rotterdam, the University of Nijmegen, University of Utrecht, and the Trimbos Institute The Netherlands. TRAILS is financially supported by grants from the Netherlands Organization for Scientific Research (GB-MW 940-38-011, GB-MAGW 480-01-006, GB-MAGW 457-03-018, GB-MAGW 175.010.2003.005, ZonMw 100-001-001 "Geestkracht" Program, ZonMw 60-60600-98-018), the Sophia Foundation for Medical Research (project 301 and 393), the Dutch Ministry of Justice (WODC), and by the participating centers.

Copyright © 2006, Frouke Sondeijker

All rights reserved. No part of this publication may be reprinted or utilized in any form or by any electronic, mechanical or other means, now known or hereafter invented, including photocopying and recording, or in any information storage or retrieval system, without prior written permission from the copyright owner.

Printed by Optima, Rotterdam, The Netherlands

ISBN-10: 90-8559-237-2
ISBN-13: 978-90-8559-237-2

Neuroendocrine and autonomic risk factors for disruptive behaviors in adolescents

Neuro-endocrine en autonome risicofactoren voor gedragsproblemen in adolescenten

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. Dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

vrijdag 8 december 2006 om 13.30 uur

door

Frouke Elisabeth Paulus Louise Sondeijker

geboren te Heerlen

Promotiecommissie

Promotoren:	Prof.dr. F.C. Verhulst Prof.dr. J. Ormel
Overige leden**:**	Prof.dr. F. Verheij Prof.dr. R.B. Minderaa Prof.dr. J. Buitelaar
Copromotor:	Dr. R.F. Ferdinand

Paranimfen: Eefje Konings
Sandra Kooijmans

We learn more by looking for the answer to a question and not finding it than we do by learning from the answer itself.

Lloyd Alexander

Contents

Chapter 1

General introduction

GENERAL INTRODUCTION

Background

Disruptive behavior problems in children and adolescents are common, have a negative impact on families, schools, and communities, and predict delinquency and substance abuse in adulthood (e.g., Fergusson et al 1994; Frick et al 1993; Loeber 1982; Moffitt et al 1996, 2002; Nagin and Tremblay 1999; Robbins 1966). Therefore, research aimed at identifying early risk factors and at mechanisms that determine change in symptoms across time is needed (Côté et al 2002; Deater-Deckard et al 1998; Hinshaw 2002; Lahey et al 2002; Loeber et al 1995; Nagin and Tremblay 1999).

Although it is clear that disruptive behaviors are influenced by familial, situational, and societal factors, increasing evidence underscores the importance of genetic and other biological processes (Brunner et al 1993; Caspi et al 2002; Coccaro et al 1996; Kruesi et al 1992). Alterations in the hypothalamic-pituitary-adrenal (HPA) system and the autonomic nervous system (ANS), two major physiological stress response systems, have often been associated with disruptive behavior problems in children and adolescents (e.g. Vanyukov et al 1993; Mc Burnett et al 2000; Pajer et al 2001; Shoal et al 2003; Van de Wiel et al 2004; Scerbo and Kolko, 1994; Ortiz and Raine 2004; Mezzacappa et al 1997; Allen et al 2000).

The introduction comprises four main components. Firstly, the different constructs of disruptive behaviors as provided by the DSM-IV (APA 1994) will be described. The two stress response systems will then be discussed. By explaining the arousal theories in the following part, the link between disruptive behaviors and the stress response systems will be clarified. Thirdly, the aims of the thesis will be formulated and the TRAILS-sample will be described. The introduction concludes with an outline of this thesis.

Taxonomy

Much of the research on disruptive behavior has been based on three distinct constructs provided by the DSM-IV (APA 1994): Attention-Deficit/Hyperactivity (ADH) Problems, Oppositional Defiant (OD) Problems, and Conduct Disorder (CD) Problems. ADH Problems are characterized by inattention, hyperactivity, and impulsive behavior, OD Problems by recurrent patterns of negativistic, defiant, disobedient, and hostile behavior toward authority figures, and CD Problems by a repetitive and persistent pattern of behavior that violates the basic rights of others or societal norms or rules.

The hypothalamic-pituitary-adrenal system

The HPA-axis is a major part of the neuroendocrine system that has important functions in regulating various body processes such as the immune system (Cupps and Fauci 1982; Weicker and Werle 1991), and energy usage (De Boeck et al 2001; Korkach and Prudnikov 1977). Traditionally, however, the HPA-axis has been regarded as the body's stress system (Rosmalen et al 2005, Sapolsky et 2000). Any stress lasting longer than a few minutes results in increased levels of cortisol, the end product of the HPA-axis, to be released from the adrenal cortex. The release of cortisol is controlled by the paraventricular nucleus of the hypothalamus, where the corticotropin releasing hormone (CRH) is released. CRH in turn causes the anterior lobe of the pituitary gland to release adrenocorticotrophic hormone (ACTH), which acts on the adrenal cortex causing it to release cortisol. Glucocorticoids then feedback and act upon the hypothalamus and pituitary (Jacobson and Sapolsky 1991). In healthy individuals, cortisol rises rapidly after awakening, reaching a peak within 30 to 45

minutes after waking up and then gradually reduces throughout the day (Pruessner et al 1997; Weitzman et al 1971; Wüst et al 2000).

The autonomic nervous system

The ANS is the part of the nervous system of the higher life forms that is not consciously controlled. It is commonly divided into two usually antagonistic subsystems: the sympathetic and parasympathetic nervous system, and involves the homeostasis of organs and physiological functions. The parasympathetic (vagal) system is predominantly associated with calm states and homeostasis, while the sympathetic system prepares the body for action (Guyton 1986).

Reductions in heart rate (HR) in children with disruptive behaviors can arise from enhanced vagal activation or from reduced sympathetic activation (Guyton 1986). Therefore, methods that can provide insight into sympathetic and parasympathetic activity are becoming increasingly important (Mezzacappa et al 1997). A measure that is often used for this purpose is heart rate variability (HRV). Autonomic regulatory signals from centers in the mid-brain control beat-to-beat variations in HR. HR fluctuations can be divided into fluctuations with different frequencies. Heart rate variations in the low-frequency band (LF; generally 0.04-0.14 Hz) are primarily influenced by variations in blood pressure (BP). HRV LF is predominantly sympathetically mediated in standing posture, whereas in supine posture vagal effects predominate. HRV measured in the high frequency band (HF; 0.15-0.40 Hz), often called respiratory sinus arrhythmia (RSA), is primarily respiratory in origin, and vagally mediated (Mezzacappa et al 1997).

Baroreflex sensitivity (BRS), which is also a well-known indicator of autonomic regulation that has previously been associated with psychopathology (Allen et al 2000; Watkins et al 1999), plays an important role in short-term BP regulation. Baroreceptors located in the wall of the heart auricles, vena cava, aortic arch, and carotid sinuses, monitor changes in BP. If a rise in BP is perceived, HR will decrease to compensate for the higher BP. If the receptors detect a drop in BP, HR will increase to restore BP levels (Allen et al 2000; Kirchheim 1976). BRS is determined by both vagal and sympathetic influences. However, BRS in supine posture probably primarily reflects vagal control, because sympathetic influences are minimal in resting condition (Allen et al 2000; Dietrich et al 2006; Kamath and Fallen 1993; Pomeranz et al 1985).

Arousal theories

Two influential theories have postulated an association between disruptive behaviors and low arousal (Raine 1996). According to the first, the fearlessness theory, a low tendency to become aroused in reaction to fearful stimuli would result in a higher likelihood to become disruptive (Raine 1993). The immediate fear reaction (increased heart rate, blood pressure, sweat production, etc. within seconds) is mediated by the ANS. The somewhat postponed fear reaction, meant to enable an individual to resist long-term environmental stresses, is mediated by the HPA-axis. Hence, based on the fearlessness theory, an association between high disruptive behavior levels and low HPA-axis activity could be expected (Van Goozen et al 2000).

A second important theory is the sensation-seeking theory (Eysenck 1964; Quay 1965; Raine 1993; Zuckerman and Neeb 1979). In this theory it is hypothesized that low arousal is an unpleasant physiological state. To get rid of this state, individuals with low arousal levels would seek stimulation, for instance by initiating antisocial behaviors that increase tension. It could be argued that sensation-seeking activities would mainly help to temporarily obtain a higher arousal level, and would not induce higher HPA-axis activity. However, mutual functional connections exist between the ANS and the HPA-axis (Chrousos and Gold 1998).

For instance, sympathetic activation results in higher production of corticotropin-releasing hormone (CRH) in the hypothalamus (Calogero 1988), which ultimately induces cortisol production. Vice versa, CRH may stimulate noradrenergic neurons as well (Sapolsky 1986). Hence, individuals with low sympathetic arousal levels, who may tend to seek sensation, may display low HPA-axis activity.

Aims of this thesis

The aim of this thesis is to extend existing knowledge on the etiology of disruptive behaviors in children and adolescents. Special focus is placed on possible biological risk factors for disruptive problems: the HPA-axis and the ANS. The main research questions of this thesis are outlined below:

1. Does the existing distinction between ADH, OD, and CD Problems represent the best way to identify homogeneous groups of individuals with disruptive behaviors?
2. Are high levels of disruptive behaviors indeed associated with low baseline HPA-axis activity?
3. Do low salivary cortisol levels predict future disruptive behavior problems in young adolescents from the general population? And can low HPA-axis activity predict the persistence of such problems?
4. Are measures for autonomic nervous system activity good indicators of OD and CD Problems in children and adolescents from the general population?
5. Does autonomic nervous system functioning, assessed by HR, HRV LF, RSA and BRS, predict disruptive behaviors in boys and girls from the general population?

The TRAILS study

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch early adolescents aged 10-12 years, who are followed biennially until the age of 24. The main objective of TRAILS is to chart and explain the development of mental health from young adolescence into adulthood, both at the level of psychopathology and at the level of underlying vulnerability and environmental risk factors. For the present thesis data from the first (2001-2002) and second (2003-2004) assessment wave of TRAILS are used. The TRAILS target sample consists of young adolescents from five municipalities in the North of the Netherlands, including both urban and rural areas (De Winter et al 2005).

The exclusion criteria for the adolescents include (1) an incapability to participate because of mental retardation or a serious physical illness or handicap and (2) no availability of a Dutch-speaking parent or parent surrogate, and no feasibility to administer a part of the measurements in the parent's own language. Of all subjects approached for enrolment (N=3,145), 6.7% were excluded. Of the remaining 2,935 young adolescents, 76.0% are enrolled in the study (N=2,230, mean age 11.09 years, SD .55, with 50.8% girls). Responders and non-responders differ on various socio-demographic indicators, but not with respect to the proportion of single parent families, nor on the prevalence of teacher-rated problem behavior. Furthermore, no differences between responders and non-responders are found regarding associations between socio-demographic variables and mental health outcomes (De Winter et al 2005). At the second assessment wave, information is obtained from 2,149 (96.4%) of those who participated at wave 1 (mean age 13.56 years, SD 0.53, with 51.0% girls). There is no selective attrition. Depending on the measures we use, sometimes our analyses are based on the whole sample, and sometimes only on a part of it.

Outline of this thesis

In order to adequately study disruptive behaviors, we must distinguish between individuals with different types of problems that may have a different etiology. The availability of a taxonomic system that helps to identify homogeneous groups of individuals, with similar patterns of disruptive behavior, is important to achieve this goal. Therefore, we examine in *Chapter 2* which classes of preadolescents with symptoms of ADH Problems, OD Problems, and CD Problems can be identified in the general population. In *Chapter 3* we test whether the association between disruptive behaviors and HPA-axis functioning, as previously reported in small high risk or clinical samples consisting mainly of boys, can be confirmed in a large representative general population sample of 10- to 12-year-olds, that did not only contain males, but females as well. In *Chapter 4* we investigate whether low salivary cortisol levels predict future disruptive behaviors in young adolescents from the general population. Furthermore, it is examined whether low HPA-axis activity predicts persistence of disruptive behavior problems. Besides an association with HPA-axis activity, disruptive behavior problems have also been associated with autonomic nervous system functioning. A previous study, separate from this thesis but also performed by TRAILS, indicated that disruptive behaviors were associated with lower resting HR and increased vagal activity. In *Chapter 5* of this thesis this work is extended to gain further insight in the association between autonomic functioning and specific disruptive problems (OD and CD Problems). A topic that has not been highlighted sufficiently in previous studies is the role of anxiety. According to the fearlessness-theory, children and adolescents who score low on anxiety and high on disruptive problems, are most likely to experience low arousal levels. In this chapter anxiety is taken into account in order to examine the role of the fearlessness-theory in the general population. In *Chapter 6* we continue our research on this subject by examining whether autonomic nervous system functioning, assessed by HR, HRV LF, RSA and BRS, predicts disruptive behaviors in boys and girls from the general population. Again the role of anxiety is taken into account. Finally, in *Chapter 7* the main findings and conclusions of chapters 2-6 are presented and discussed.

Chapter 2

Classes of adolescents with disruptive behaviors in a general population sample

Frouke Sondeijker
Robert Ferdinand
Tineke Oldehinkel
René Veenstra
Andrea de Winter
Hans Ormel
Frank Verhulst

Social Psychiatry and Psychiatric Epidemiology

CLASSES OF ADOLESCENTS WITH DISRUPTIVE BEHAVIORS IN A GENERAL POPULATION SAMPLE

To study disruptive behaviors adequately, we need to distinguish between individuals with different types of problems that may have a different etiology. The availability of a taxonomic system that helps identifying homogeneous groups of individuals, with similar patterns of disruptive behaviors, is crucial to achieve this goal. Therefore, we examine which classes of preadolescents with symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) can be identified in the general population. Disruptive behaviors of 2,230 10- to 12-year-olds from the Dutch general population were assessed with the Child Behavior Checklist and Youth Self-Report. Latent class analysis revealed three classes of preadolescents: the first characterized by high scores on ADHD, ODD, and CD items, a second by high probabilities of ADHD and ODD symptoms, a third with low scores on all items. Because classes of preadolescents with symptoms of only one type of disruptive behavior problems could not be identified, it can be questioned how useful separate diagnostic distinctions are in general population studies.

Introduction

Childhood and adolescent disruptive behavior disorders are common, disabling, and associated with high costs, both societal and in terms of individual suffering (e.g., Fergusson et al 1994; Moffitt et al 1996, 2002; Nagin and Tremblay 1999). Research regarding disruptive behaviors in children and adolescents from the general population is important to identify risk factors (e.g. Côté et al 2002; Deater-Deckard et al 1998; Lahey et al 2002; Loeber et al 1995) and mechanisms that determine change in symptoms across time (Hinshaw 2002; Nagin and Tremblay 1999). To study disruptive behaviors adequately, we need to distinguish between individuals with different types of problems that may have a different etiology. The availability of a taxonomic system that helps identifying homogeneous groups of individuals, with similar patterns of disruptive behaviors, is crucial to achieve this goal.

Most researchers of disruptive behaviors have used the three distinct constructs provided by DSM-IV (APA 1994): Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). ADHD is characterized by inattention, hyperactivity, and impulsive behavior, ODD by recurrent patterns of negativistic, defiant, disobedient, and hostile behavior toward authority figures, and CD by a repetitive and persistent pattern of behavior that violates the basic rights of others or societal norms or rules. The mere fact that these disorders have been distinguished in DSM-IV, does not automatically mean that this distinction has validity. Inspection of the different categories would lead one to expect overlap at the very least between ODD and CD.

Individuals who fulfill criteria for ADHD, ODD or CD often also have symptoms of one of the other disorders. The co-occurrence of ADHD, ODD, and CD is greater than expected by chance (Loeber and Keenan 1994), in both clinical (Loeber et al 1995; Lahey et al 1992; Frick 2001) and general population samples (Farrington 1993; Kadesjö and Gillberg 2001; Verhulst and Van der Ende 1993). The high comorbidity rates raise the question whether the existing distinction between ADHD, ODD, and CD represents the best way to identify homogeneous groups of individuals with disruptive behaviors. The present study aims to examine this question in a large sample of early adolescents from the Dutch general population.

General population samples have two major advantages. First, they are representative. The second advantage is that comorbidity rates are generally higher in clinical samples than in general population samples, because, due to Berkson's bias (Berkson 1946), individuals with more than one disorder will more likely be referred to mental health services than those with one single disorder. Hence, if the spectrum of disruptive behaviors consists of the three distinct disorders (ADHD, ODD, and CD), it is most likely that these three separate disorders can be revealed in a general population sample.

To classify individuals as accurately as possible, it is important to use all available information. Previous studies that assessed comorbidity of disruptive behavior disorders mostly used categorical diagnostic information. In other words, they applied decision rules to judge an individual as 'disordered' or 'normal'. This approach may imply loss of valuable information, because sub-threshold individuals, for instance, those who fulfill criteria for 5 symptoms of ADHD, are regarded as 'normal', while they may be quite similar to individuals who fulfill 6 criteria for ADHD and therefore receive a diagnosis. Hence, individuals who are classified as having, for example, 'pure' ADHD can still have several comorbid ODD or CD symptoms (Kadesjö and Gillberg 2001).

In contrast to factor analysis, that yields information about which symptoms co-occur frequently, latent class analysis (LCA) is a technique to investigate empirically whether homogeneous groups of children with similar ADHD, ODD, or CD symptoms can be identified. Instead of pre-defined criteria for the presence or absence of a disorder, LCA uses ratings of children on a number of symptoms. Classes of children are identified who display

similar symptoms. For each class of children, the probability is calculated that a symptom is present or absent. LCA might yield a class of children with, for instance, a high probability to be endorsed positive on ADHD symptoms, but negative on ODD and CD symptoms. This would indicate that it is valuable to make a taxonomic distinction between ADHD and the other disruptive behavior disorders. However, it is also possible that LCA does not identify classes of children with a high likelihood of having symptoms of only one specific disorder. This was the case in a study by Van Lier, Verhulst, van der Ende, and Crijnen (2003) among very young (5-7 years) Dutch school children.

A possible reason why Van Lier and colleagues failed to find a distinct ADHD, OCD, and CD group is the young age of their sample. The prevalence of disruptive behaviors, especially CD, is low in early childhood, and tends to rise with age (Maughan and Rutter 1998; McCabe et al 2001; Moffitt 1993). Furthermore, Van Lier relied on parent reports only, whereas it is known that differences between reports of parents and children are the rule, rather than the exception (Andrews et al 1993; Edelbrock et al 1986; Verhulst and van der Ende 1992).

The aim of the present study is to investigate which classes of 10- to 12-year-olds with disruptive behavior symptoms can be found in the general population, according to self-reports and parent reports. We hypothesize that classes of children with a high probability to have symptoms of one specific disruptive behavior disorder, and simultaneously low probabilities to have symptoms of other disruptive behavior disorders, can not be identified. If our hypothesis would be true, this would indicate that it might not be useful to discern specific disruptive behavior disorders in general population studies, but instead, a category of 'any disruptive disorder', or a total symptom count, would suffice.

Methods

Sample and procedure

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch early adolescents aged 10-12 years, who are followed biennially until the age 24. The main objective of TRAILS is to chart and explain the development of mental health from young adolescence into adulthood, both at the level of psychopathology and at the level of underlying vulnerability and environmental risk factors. The present study used data from the first assessment wave of TRAILS, which ran from March 2001 to July 2002. The TRAILS target sample consisted of young adolescents from five municipalities in the North of the Netherlands, including both urban and rural areas.

The sample selection involved two steps. First, the municipalities selected were requested to give names and addresses of all inhabitants born between 10-01-1989 and 30-09-1990 (first two municipalities) or between 10-01-1990 and 30-09-1991 (last three municipalities), yielding 3,483 names. Simultaneously, primary schools (including schools for special education) within these municipalities were approached with the request to participate. School participation was a prerequisite for eligible adolescents and their parents to be approached by TRAILS, with the exception of adolescents already attending secondary schools (<1%), who were contacted without involving their schools. Of the 135 primary schools within the municipalities, 122 (90.4%) schools agreed to participate, accommodating 90.3% of the adolescents.

Second, if schools agreed to participate, parents (or guardians) received two brochures, one for themselves and one for their adolescents, with information about the study. In addition, a TRAILS staff member visited the schools to inform eligible adolescents about the study. Approximately one week later, a TRAILS interviewer contacted the parents by telephone to provide additional information, answer questions, and ask whether they and their child were willing to participate. Respondents with an unlisted telephone number were

requested by mail to pass on their number. If they reacted neither to that letter, nor to a reminder letter sent a few weeks later, staff members paid personal visits to their house. Parents who refused to participate were asked for permission to call back in about two months, to minimize the number of refusals due to temporary reasons. If parents agreed to participate, an interview was scheduled, during which they were requested to sign informed consent.

The exclusion criteria for the adolescents were (1) incapable to participate because of mental retardation or a serious physical illness or handicap and (2) no availability of a Dutch-speaking parent or parent surrogate, and no feasibility to administer a part of the measurements in parent's own language. Of all subjects approached for enrolment (N=3,145), 6.7% were excluded. Of the remaining 2,935 young adolescents, 76.0% were enrolled in the study (N=2,230, mean age 11.09 years, SD .55, with 50.8% girls). Responders and non-responders differed on various socio-demographic indicators, but not with respect to the proportion of single parent families, nor on the prevalence of teacher-rated problem behavior. Furthermore, no differences between responders and non-responders were found regarding associations between socio-demographic variables and mental health outcomes (De Winter et al 2005).

Measures

Adolescent's disruptive behaviors were assessed with the Child Behavior Checklist/4-18 (Achenbach 1991a), and the Youth Self-Report (Achenbach 1991b).

The Child Behavior Checklist (CBCL) is a parent questionnaire for assessing problems in 4- to 18-year-olds; The Youth Self-Report (YSR) is a self-report questionnaire that was modeled on the CBCL. Both questionnaires contain 120 items on behavioral or emotional problems in the past six months. The response format is 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The good reliability and validity of the American version of the CBCL and YSR were confirmed for the Dutch translations (De Groot et al 1994; Verhulst et al 1997; Verhulst et al 1996).

The original empirical syndrome scales for the CBCL and the YSR were based on multivariate statistical analysis on data from large samples. To fit more closely to the clinical-diagnostic approach, represented by the DSM (APA 1994), the following DSM-IV scales were recently constructed for the CBCL and its derivatives (Achenbach and Dumenci 2001; Achenbach et al 2003): Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems. These CBCL/YSR DSM-IV scales are constructed, based on the opinion of experts from 11 different countries, from all over the world. They, independently, came to a list of main items that are considered representative for the different DSM-IV constructs.

Statistical analyses

Only CBCL/YSR items that are comprised by the DSM-IV scales Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems (see Table 2-1) were used. The CBCL and YSR scores (0 = not true, 1 = somewhat/sometimes true, and 2 = very/often true) were dichotomized in 0 = not true and 1 = somewhat/sometimes true or very/often true, because of the low prevalence of individuals who scored 2 = very/often true. Items with a frequency of less than 5% were excluded, because results of latent class analysis (LCA) tend to become unstable by rare observations (Kovac et al 2002). All analyses were performed separately for CBCL and YSR. Before performing LCA, the remaining items were entered into a confirmatory factor analysis (CFA), to determine whether it was possible to extract the three dimensions of interest in this study (ADHD, ODD, and CD). In this CFA the three factors were allowed to correlate. Items with a factor loading

above .3 were considered to be representative of the scale they were assigned to. For CFA, as well as for LCA, Mplus version 2.14 was used (Muthén and Muthén 2000).

Table 2-1. Factor loadings of confirmatory factor analysis for CBCL and YSR items reflecting DSM-IV ADHD, ODD, and CD

Factors/items	Factor loadings CBCL	Factor loadings YSR
Factor1: Attention Deficit/Hyperactivity Disorder		
1. Fails to finish what is started	.64	.53
2. Can't concentrate, can't pay attention for long	.81	.60
3. Can't sit still, restless, or hyperactive	.74	.56
4. Impulsive or acts without thinking	.79	.71
5. Inattentive, easily distracted	.85	.65
6. Talks too much	.58	.55
7. Unusually loud	.83	.71
Factor 2: Oppositional Defiant Disorder		
8. Argues a lot	.74	.66
9. Disobedient at home	.83	.66
10. Disobedient at school	.73	.73
11. Stubborn, sullen, or irritated	.75	.61
12. Temper tantrums or hot temper	.74	.59
Factor 3: Conduct Disorder		
13. Cruel or mean to people	.75	.76
14. Destroys others' things	.69	.67
15. Doesn't feel guilty after misbehaving	.59	.31
16. Gets in many fights	.78	.64
17. Hangs around with others who get in trouble	.49	.36
18. Lies or cheats	.72	.68
19. Physically attacks people	.75	.68
20. Swears or uses obscene language	.74	.66
21. Breaks rules[1]		.78
22. Runs away from home[1]		.56
23. Sets fires[1]		.55
24. Steals at home[1]		.63
25. Threatens others[1]		.66
26. Truant or skips school[1]		.44

[1]Item only in YSR and not covered by CBCL

Early adolescents with comparable patterns of disruptive behaviors were identified with LCA (McCutcheon 1987). The primary objective of LCA is to find the smallest number of classes of individuals with similar patterns of behavior that can explain the relationship among a set of observed variables. First, we fitted a one-class model. The next analysis concerned a two-class model. The same analyses were run with different starting values to minimize the influence of local extremes. A Bayesian Information Criterium (BIC) (Kass and Wasserman 1995) and the Vuong-Lo-Mendell-Rubin likelihood ratio test (Vuong 1989) were

applied to check whether the two-class model fitted better than the one-class model. In the same way, models with three and more classes were analyzed stepwise, until the model did not improve further. The best model found, according to the BIC and the Vuong-Lo-Mendell-Rubin likelihood ratio test, was examined on model-fit using the fit-indices Root Mean Square Error of Approximation (RMSEA) < .05, Comparative Fit Index (CFI) > .90, and Tucker Lewis Index (TLI) > .90. Finally, to control for possible differences in gender (Leadbeater et al 1999; Zoccolillo 1993), gender was added as a covariate (Dayton and Macready 1988).

The estimated parameters of the latent class model are latent class membership probabilities, which represent the probability for an individual to belong to each of the classes. Adolescents were assigned to a latent class based on their highest class-membership probability. Class-specific symptom endorsement profiles represent the conditional probabilities for individuals in a particular class to have a specific symptom.

Results

CBCL model of disruptive behaviors

The CBCL/DSM-IV scales ADHD, ODD, and CD comprised 28 items. Eight items (cruel to animals, runs away from home, sets fire, steals at home, steals outside home, threatens people, skips school, vandalism) had frequencies below 5% and were excluded. The remaining 20 items were submitted to a CFA. All items had a factor loading above .3 and could therefore be considered to be representative of the scale it was assigned to (Table 1). The model fitted the data well (RMSEA = .06, CFI = .93, and TLI = .96). Correlations between the three scales scores were high (.69-.85).

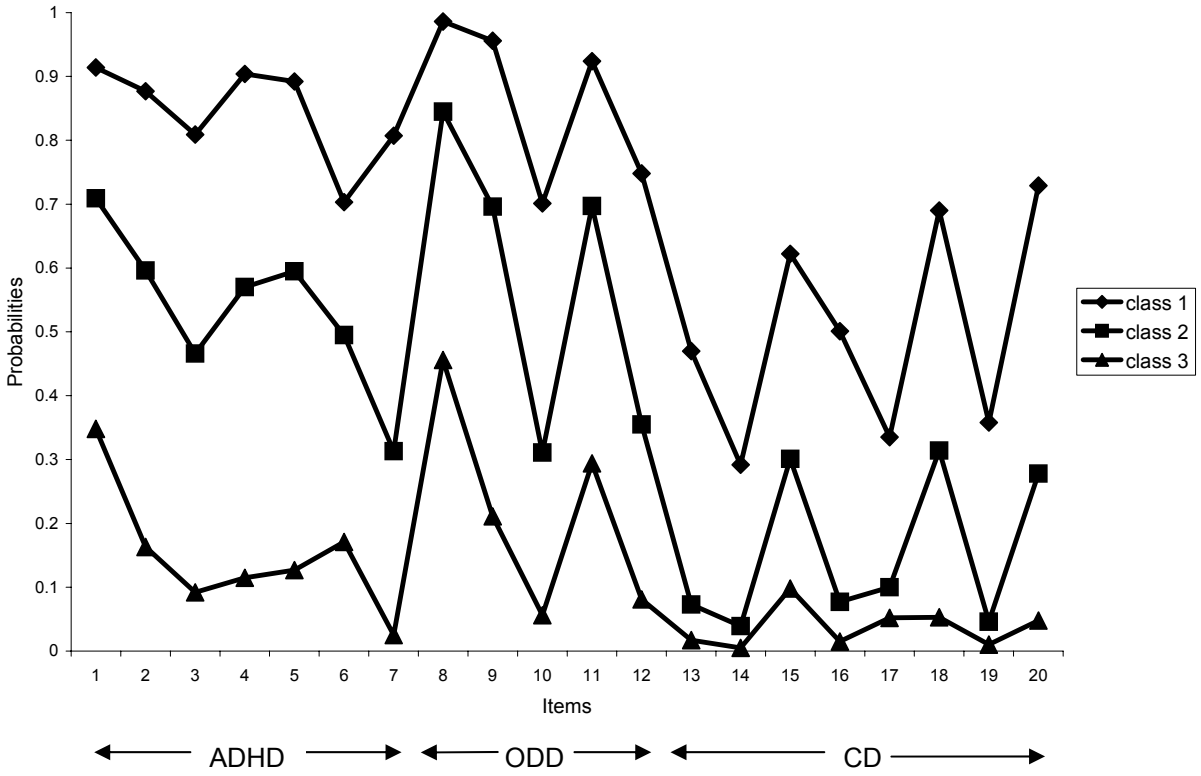
YSR model of disruptive behaviors

Of the 29 items of the YSR/DSM-IV scales ADHD, ODD, and CD, three items (cruel to animals, steals outside home, vandalism) had frequencies below 5% and were excluded. The remaining 26 items were submitted to a CFA. The factor loadings are reported in Table 1. The model fitted the data well (RMSEA = .04, CFI = .93, and TLI = .96). Correlations between the three scales scores were high (.73-.93).

LCA for CBCL item scores

The first analysis, the one-class model, yielded a BIC value of 47,540. Moving from a one-class to a two-class solution resulted in a BIC drop of 5,856 points, which means that adding a second class improved the model. BIC values indicated that a three-class solution fitted the data best; moving from two to three classes resulted in a further BIC drop of 1,133 points. A four-class solution did not result in further improvement of BIC. Class sensitivity, the average class-membership probability after the classification of children, was high (.90-.93), which means that the children are well classified.

Figure 2-1. Probability of positive CBCL item-scores for ADHD, ODD, and CD symptoms for three classes of adolescents.



Note. Numbers 1 to 20 correspond with items 1 to 20 in Table 1.

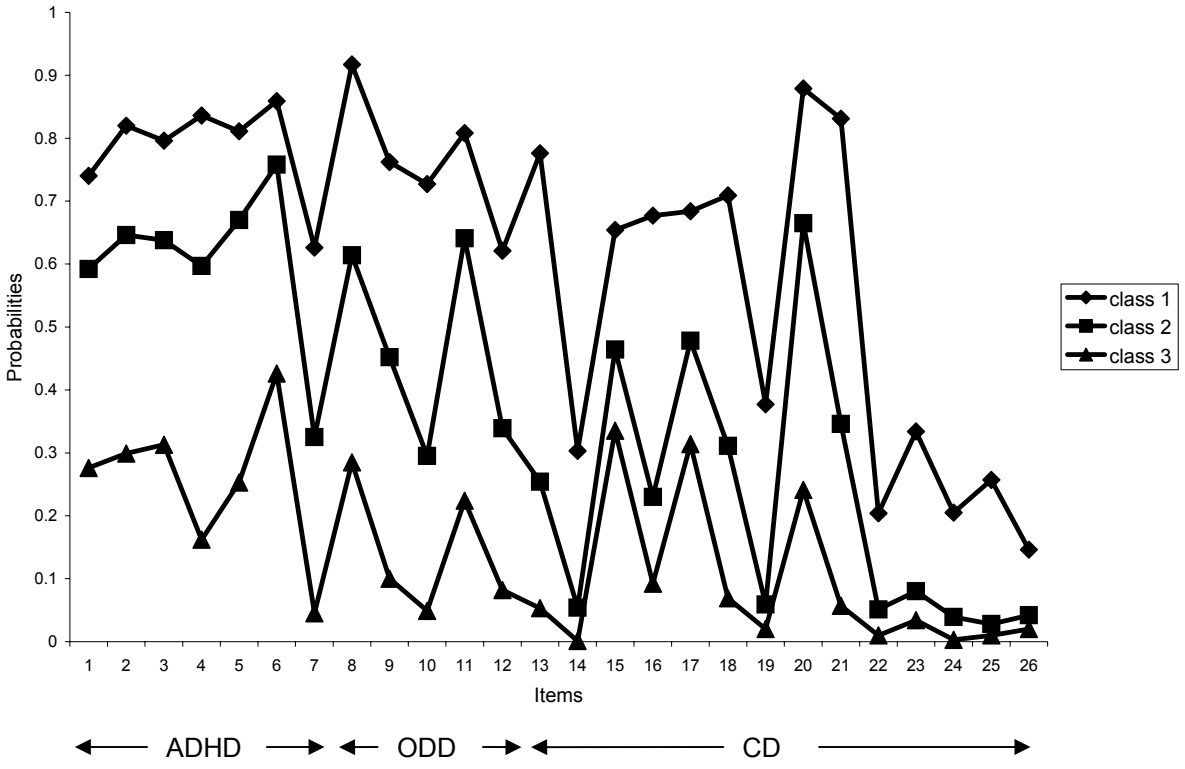
Class specific endorsement probabilities for CBCL are shown in Figure 2-1. Four hundred and thirty-nine (21%) children were assigned to class 1, 926 (45%) to class 2, and 691 (34%) to class 3. Adolescents in class 1 were characterized by high probabilities (median=.74) of symptoms from all three scales (ADHD, ODD, and CD). For example, individuals in class 1 had a probability of 80.9% to score positively on item 3 (Can't sit still; hyperactive). Adolescents in class 2 had intermediate probabilities of ADHD and ODD symptoms, and low probabilities of CD symptoms (median=.33). These adolescents had a probability of 46.6% to have a positive score on item 3. Adolescents in class 3 had low probabilities on all three scales (median=.09). For these adolescents, the probability of a positive score on item 3 was 9.2%. Boys and girls were assigned to the three classes as follows: class 1 contained 301 (69%) boys and 138 (31%) girls, class 2 438 (47%) boys and 488 (53%) girls, and class 3 contained 273 (40%) boys and 418 (60%) girls.

LCA for YSR item scores

Using the YSR, a one-class model with a BIC value of 59,461 was found. Moving from a one-class to a two-class solution resulted in a BIC drop of 2,350 points, which means the model improved. BIC values indicated that a three-class solution fitted the data best; moving from two to three classes resulted in a BIC drop of 903 points. When moving to a four-class solution, BIC still decreased 60 points, but no stable model could be found. To be sure that the three-class model really fitted the data best, a five-class solution was searched for as well. BIC decreased 33 points, but the Vuong-Lo-Mendell-Rubin likelihood ratio test indicated that

adding a fifth class did not significantly improve the model. Class sensitivity, the average class-membership probability after classifying children, was high (.89-.91).

Figure 2-2. Probability of positive YSR item-scores for ADHD, ODD, and CD symptoms for three classes of adolescents.



Note. Numbers 1 to 26 correspond with items 1 to 26 in Table 1.

For the YSR, class specific endorsement probabilities are shown in Figure 2-2. Four hundred and twenty-three (19%) adolescents were in class 1, 972 (45%) in class 2, and 800 (36%) in class 3. Adolescents in class 1 were characterized by high probabilities (median=.71) of symptoms from all three scales (ADHD, ODD, and CD). For example, individuals in class 1 had a probability of 72.7% to score positively on item 10 (Disobedient at school). Adolescents in class 2 had intermediate probabilities of positive ADHD and ODD symptoms (median=.34), and low probabilities of positive CD symptoms (.03-.67). These adolescents had a probability of 29.5% to have a positive score on item 10. Adolescents in class 3 had low probabilities on symptoms of all three scales (median=.09). For these adolescents, the probability of a positive score on item 10 is 5.0%. Boys and girls were assigned to the three classes as follows: class 1 contained 304 (72%) boys and 119 (28%) girls, class 2 contained 418 (43%) boys and 561 (57%) girls, and class 3 357 (45%) boys and 443 (55%) girls.

Discussion

Aim of the study was to examine whether the existing distinction between ADHD, ODD, and CD, that is often made in general population studies is the most useful one, given the high comorbidity rates. For this purpose, 2,230 10- to 12-year-olds from the Dutch general

population were investigated. Because classes of preadolescents with one type of disruptive behavior problems (for instance: ADHD) without having symptoms of other disruptive behavior problems (in that case: ODD or CD) could not be identified, it can be questioned how useful these separate diagnostic distinctions are in general population studies.

CFA of CBCL and YSR items showed that within the spectrum of disruptive behaviors three separate dimensions of ADHD, ODD, and CD symptoms could be discerned. However, the high correlations between these three dimensions, irrespective of the informant (adolescent or parent) who provided the data, indicated that these dimensions do not represent clearly distinct constructs. Such evidence was also provided by latent class analyses. Classes of early adolescents who were characterized by only ADHD, only ODD or only CD could not be identified. Instead a first class characterized by high frequencies of ADHD, ODD, and CD symptoms, a second class characterized by high problem probabilities for ADHD and ODD symptoms, but not for CD symptoms, and a third class characterized by low scores on all items were found. This is in accordance with the study of Van Lier, Verhulst, Van der Ende, and Crijnen (2003).

The results suggest that co-morbidity between ADHD and ODD is the rule rather than the exception. This contrasts with several clinical (Loeber et al 1995; Lahey et al 1992; Frick 2001) and general population studies (Farrington 1993; Kadesjö and Gillberg 2001; Verhulst and Van der Ende 1993), in which ADHD and ODD are described as two distinct constructs. If the present study had relied solely on parent reports, one might have argued that the overlap of ADHD and ODD was caused by an inability of parents to distinguish ADHD symptoms from ODD symptoms. However, in the present study, comparable results were found for self-report data, which makes the hypothesis of informant bias unlikely.

Another finding that argues against the use of three distinct constructs in the general population is that a class of children with pure CD, without comorbid ADHD or ODD, could not be identified. This is in accordance with the results of the LCA that was performed on CBCL data of 5- to 7- year-olds performed by Van Lier and colleagues (2003). It is still possible that CD constitutes a clearly distinct problem area in older individuals. The rates of behavior problems, and especially of CD problems, tend to rise with age (Maughan and Rutter 1998; McCabe et al 2001; Moffitt 1993). Furthermore, Loeber and Keenan (1994) reported that co-occurrence of ADHD, ODD, and CD decreases with age. To identify a sufficiently homogeneous group of adolescents displaying CD symptoms, without ADHD or ODD symptoms, older adolescents than the ones investigated in the present study might be needed.

Furthermore, a general population sample as used in the present study is representative, but is characterized by low frequencies of problem behavior. As a result, we had to dichotomize CBCL and YSR item scores, which means that scores of 1 (=somewhat/sometimes true) and 2 (= very/often true) were treated in a similar way. Because, given the constitution of the sample, the far majority of positive item scores were scored as 1, and not as 2, it is unclear if our findings would also hold true for disruptive behaviors that are very true or often true. Of course, use of a clinical sample might be used to resolve this problem. Although, Wadsworth, Hudziak, Heath, and Achenbach (2001) found that results of LCA on anxiety and depression symptoms were similar in a clinic-referred sample and a non-referred sample of 4- to 18-year-olds, which indicates that use of a clinical sample does not necessarily yield different results.

A reason why use of a clinical sample does not necessarily yield distinct disease categories is constituted by Berkson's bias (Berkson 1946). According to Berkson, comorbidity rates are generally higher in clinical samples than in general population samples, because individuals with more than one disease are more likely to be referred, than those having only one disease, due to the possibility, for both diseases, to result in referral. This undoubtedly will influence the results of LCA in clinical samples. For this reason, it might

even be argued that, if the spectrum of disruptive behaviors would consist of ADHD, ODD, and CD, it might be more likely to find evidence for the existence of 'pure' disorders in a general population than in a clinical sample.

Because the prevalence of disruptive behaviors tends to rise with age (Maughan and Rutter 1998; McCabe et al 2001; Moffit 1993) and the risk for comorbidity of disruptive behaviors decreases with age (Loeber and Keenan 1994), sharper distinctions between ADHD, ODD, and CD could still be found in older samples.

The fact that it is possible to use LCA to carve out clinically significant phenomena in adolescents from the general population, was demonstrated earlier by Hudziak et al. (1998). They found evidence for the existence of three types of ADHD: an Inattention type, a Hyperactive/Impulsive type, and a combined type. This indicated that, even if symptoms with high inter-correlations are studied, different classes, that do not only differ with respect to the frequency of symptoms, but also with respect to the type of symptoms, may be found with LCA.

Conclusions

The findings of the present study raise the question whether it is useful to distinguish ADHD, ODD, and CD from one another in a general population sample. Results indicate that a concept based on the hypothesis of discrete disruptive behavior disorders is not useful to discriminate classes of children with different types of disruptive behaviors. These findings contrast with some studies that assessed differences in biological correlates of ADHD, ODD, and CD. For instance, Herpertz, Wenning, Mueller, Qunaibi, Sass, and Herpertz-Dahlman (2001) studied a clinical sample of 8- to 13-year-old boys with behavior disorders. They found that individuals with ADHD plus CD showed a decrement of autonomic arousal responses and a more rapid habituation to orienting and aversive startling stimuli, compared to age-matched children with pure ADHD. This indicates that based on biological measures there seems to be a differentiation between pure ADHD and ADHD with comorbid CD. Hence, while differentiation at the level of observable behaviors may not be possible, different classes of children might be constituted on the basis of biological characteristics. Unfortunately, Herpertz et al. (2001) did not give any information about comorbid ODD, which makes it difficult to compare their findings with the classes found in the present study.

In the present study, CD symptoms were unlikely to occur without ADHD or ODD symptoms. It might be that in individuals from class 1, symptoms of CD, ODD, and ADHD might share the same origins. Hence, in search for the etiology of disruptive behaviors, when homogeneous groups from the general population are required, it may be more useful to look for individuals with all kinds of symptoms of disruptive behaviors, than to merely gather information on CD symptoms.

ADHD and ODD symptoms appeared to be intertwined. If this would be similar in clinical samples, this might indicate that, with respect to treatment, it might not be useful to develop different treatment modules for ADHD and ODD. In fact, this is supported by research that has already shown, that similar types of behavior therapy are effective for these two problem areas (Abikoff and Klein 1992; Kolko et al 1999). Drug–trials often focus on ADHD symptoms (Barkley et al 1991; Pelham, et al 2002). Only few studies are available that demonstrate that drug therapy, intrinsically developed for ADHD also works for ODD symptoms (Abikoff and Klein 1992). Our study indicates that it might not be needed to discern pure ADHD and pure ODD, but instead, to view these 'disorders' as strongly overlapping, that conceivably might share favorable drug responses. This, of course, requires more research.

The debate regarding whether it is useful to discern ODD and CD in a general population sample is unresolved. Previous evidence suggested that ODD is a mild variant of

CD (Rey et al 1988; Schachar and Wachsmuth 1990; Werry et al 1987). Findings of the present study are in accordance with above-mentioned evidence. The results suggest that the often used taxonomy of three distinct disorders, ADHD, ODD, and CD, is not the most useful approach to find homogeneous groups in a general population sample of adolescents. Instead, the present study revealed two subtypes of disruptive behavior disorders. A first subtype might contain symptoms of ADHD, ODD, and CD, whereas a second subtype might contain symptoms of ADHD and ODD, but no symptoms of CD. This indicates that the distinction between moderate (class 2) versus severe (class 1) behavior disorders is related with the presence or absence of CD symptoms. An alternative approach to a similar problem is discussed by Freeman et al. (2005), who examined the hierarchy of paranoia. The relationship between CD and ADHD/ODD is likely to be hierarchical and non-reflexive. In other words, ADHD/ODD is considerably less predictive of CD than CD is of ADHD/ODD. Future research is needed to investigate to which extent class membership shifts across time, and to assess if membership of class 2 (ADHD+ODD) is a risk factor for future class 1 (ADHD+ODD+CD) membership.

Chapter 3

Disruptive behaviors and HPA-axis activity in young adolescent boys and girls from the general population

Frouke Sondeijker
Robert Ferdinand
Tineke Oldehinkel
René Veenstra
Henning Tiemeier
Hans Ormel
Frank Verhulst

Journal of Psychiatric Research

DISRUPTIVE BEHAVIORS AND HPA-AXIS ACTIVITY IN YOUNG ADOLESCENT BOYS AND GIRLS FROM THE GENERAL POPULATION

It is important to investigate associations between biological factors and disruptive behaviors in children and adolescents. Antisocial, aggressive, and criminal behaviors in adults often begin early in life. Disruptive behaviors are often thought to be associated with low activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Cortisol, the end-product of this axis, can be measured to investigate HPA-axis activity. Previous studies on this topic concerned clinical or high risk samples. The aim of the present study was to investigate to which extent HPA-axis functioning plays a role in disruptive behaviors in pre-adolescents from the general population. 1,768 10- to 12-year-olds from the Dutch general population were investigated. Disruptive behaviors were assessed with the Child Behavior Checklist, the Youth Self-Report, and the Antisocial Behavior Questionnaire. Baseline morning and evening salivary cortisol levels were assessed. Unexpectedly, small associations were found between disruptive behaviors, including attention problems, and higher cortisol levels. However, all effect sizes of significant effects were very small. Our study indicated that HPA-axis functioning may be more relevant in clinical or high risk samples than at the general population level. The association between HPA-axis functioning and attention problems, that has gotten less attention than that with aggressive or delinquent behaviors, requires further research. Furthermore, because effect sizes were relatively small, it can be concluded that, in pre-adolescence, the measures of baseline HPA-axis functioning that were used for the present study can not be used as biological markers for disruptive behaviors.

Introduction

It is important to investigate associations between biological factors and disruptive behaviors in children and adolescents, because antisocial, aggressive, and criminal behaviors often have their onset early in life (Moffitt 1993). Disruptive behaviors in children and adolescents are often thought to be associated with low activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Van Goozen et al 2000; McBurnett et al 2000; Raine 1993; Raine 1996). Cortisol, the end-product of this axis, is often measured to investigate HPA-axis activity. It is obvious why HPA-axis functioning and antisocial behaviors are often mentioned in the same breath. Two influential theories have postulated an association between disruptive behaviors and low arousal (Raine 1996). According to the first, the fearlessness theory, a low tendency to become aroused in reaction to fearful stimuli would result in a higher likelihood to become disruptive (Raine 1993). The immediate fear reaction (increased heart rate, blood pressure, sweat production, etc. within seconds) is mediated by sympathetic nervous system activity. The somewhat postponed fear reaction, meant to enable an individual to resist long-term environmental stresses, is mediated by the HPA-axis. Hence, based on the fearlessness theory, an association between high disruptive behavior levels and low HPA-axis activity could be expected (Van Goozen et al 2000).

A second important theory is the sensation-seeking theory (Eysenck 1964; Quay 1965; Raine 1993; Zuckerman and Neeb 1979). This theory hypothesizes that low arousal is an unpleasant physiological state. To get rid of this state, individuals with low arousal levels would seek stimulation, for instance by initiating antisocial behaviors that increase physical tension. It could be argued that sensation seeking activities would mainly help to temporarily obtain a higher sympathetic arousal level, and would not induce higher HPA-axis activity. However, mutual functional connections exist between the sympathetic nervous system and the HPA-axis (Chrousos and Gold 1998). For instance, sympathetic activation results in higher production of corticotropin-releasing factor (CRF) in the hypothalamus (Calogero 1988), which ultimately induces cortisol production. Vice versa, CRF may stimulate noradrenergic neurons as well (Sapolsky 1986). Hence, individuals with low sympathetic arousal levels, who may tend to seek sensation, may display low HPA-axis activity as well.

Several studies found low basal HPA-axis activity in disruptive individuals (Vanyukov et al 1993; Moss et al 1995; Van Goozen et al 1998; Mc Burnett et al 2000; Pajer et al 2001; Kariyawasam et al 2002; Shoal et al 2003; Van de Wiel et al 2004). McBurnett et al. (2000) found evidence for an association between low salivary cortisol levels and high symptom levels in 38 referred 7- to 12-year-old boys with conduct disorder. A single saliva cortisol sample – time of sampling was not standardized - was obtained during two visits to the clinic. Vanyukov et al. (1993) studied a high-risk sample of 78 10- to 12-year-old sons of fathers with addiction problems. Low saliva cortisol concentrations - assessed at 9 a.m. - were associated with high levels of conduct problems. Pajer et al. (2001) found lower morning basal plasma cortisol levels in 47 15- to 17- year-old girls with conduct disorder than in 37 control girls from the community. However, there are also studies reporting a lack of associations (Dabbs et al 1991; Stoff et al 1992; Scerbo and Kolko 1994; Schulz et al 1997; Jansen et al 1999, Van Goozen et al 2000; Snoek et al 2002; Oosterlaan et al 2005). All in all, evidence for low basal cortisol in children with disruptive behavior problems is inconsistent.

Previous studies mainly concerned relatively small samples, and some suffered from methodological problems with cortisol measurements, such as the fact that cortisol levels were not assessed at a standardized time point during the day (McBurnett et al 2000), despite the abundant knowledge we have about diurnal fluctuations (Pruessner et al 1997; Wüst et al 2000). However, an even more important methodological obstacle is the fact that previous studies mainly investigated clinical or high risk samples, and did not address the importance of HPA-axis functioning as a possible correlate of disruptive behaviors in the general

population. Hence, important evidence that may help us to understand etiological mechanisms that determine the occurrence of disruptive behaviors at the level of the general population is lacking. Of course, it would be valuable to gather empirical data regarding the HPA-axis – disruptive behavior association in the general population. If the association that was found in clinical and high risk samples would be confirmed in the general population, this would help us to formulate further hypotheses regarding the mechanisms that might explain this association. Further, the usefulness of early assessment of HPA-axis functioning, for the purpose of early detection of those who are at risk for future adverse development, should be tested as a next step. However, if an association between disruptive behaviors and low HPA-axis activity would not be confirmed in the general population, this would indicate that efforts to reveal putative etiological mechanisms should be made in other directions.

Another area that received too little attention thus far is HPA-axis functioning in girls with disruptive behaviors. Although lower than in boys, the prevalence of disruptive behavior problems in girls is not negligible (Côté et al 2001; Tremblay et al 1992). Cortisol levels are associated with pubertal stage (Keiss et al 1995), and gonadal steroids interact with HPA-axis functioning (Burgess and Handa 1992; Handa et al 1994; Roy et al 1999; Vamvakopoulos and Chrousos 1993). Hence, associations between disruptive behaviors and HPA-axis functioning might be different in girls than in boys. Studies aimed at revealing etiological mechanisms, in our opinion, are equally important for both sexes. Given the paucity of empirical data on this topic in girls, studies filling this gap are needed.

The aim of the present study was to investigate if high levels of disruptive behaviors are indeed associated with low baseline HPA-axis activity. More specifically, the present study tested if the association between disruptive behaviors and HPA-axis functioning, as previously found in small high risk or clinical samples that mainly consisted of boys, could be confirmed in a large representative general population sample of 10- to 12-year-olds, that did not only contain males, but females as well.

Methods

Sample and procedure

This study was part of the TRacking Adolescents' Individual Lives Survey (TRAILS) study. The target sample of TRAILS consisted of 10- to 12-year-olds from five municipalities in the North of the Netherlands, that includes urban and rural areas, who were assessed between March 2001 and July 2002. Of all eligible individuals (N=2,935), 76.0% participated in the study (N=2,230, mean age 11.09 years, SD .55, 50.8% (1,132) girls, 15.3% (341) single parent families, 9.0% (201) participants without siblings, 7.9% (176) used mental health services). Participants did not differ from those who refused with respect to the proportion of single parent families (15.3% versus 16.5%), and the prevalence of teacher-rated problem behaviors measured with vignettes of the Teacher Report Form (internalizing 22.0% versus 25.1%; externalizing 13.0% versus 14.4%). This supported the representativeness of the TRAILS sample (De Winter et al 2005).

Saliva samples were received from 1,768 children (79.3% of all TRAILS participants). Those who did not provide saliva samples did not differ from those who did with respect to gender (48.5% male versus 49.4% male, $\chi^2(df=1)=0.13$; p=.72), pubertal development (average Tanner stage score=1.92 versus 1.86, t=-1.39; p=.16), or levels of disruptive behaviors (CBCL ADH Problems scale t=1.40; p=.16, OD Problems scale t=.14; p=.89, CD Problems scale t=.21; p=.83, YSR ADH Problems scale t=-1.20; p=.23, OD Problems scale t=-.36; p=.72, CD Problems scale t=1.10; p=.27). However, those who did not provide saliva samples were slightly older (11.16 years versus 11.08 years, t=-3.08; p=.002), had a higher BMI (18.50 versus 17.92 kg/m^2, t=-3.22; p=.001), and had a slightly higher ASBQ total score t=3.23; p=.001; explained variance = .7%). However, given the fact that the differences

between those who provided saliva samples versus those who did not were very small, the sub-sample that was used for the present manuscript can be regarded as representative of the TRAILS sample at large.

Measures

The Child Behavior Checklist (CBCL) is a parent questionnaire for assessing problems in 6- to 18-year-olds. The Youth Self-Report (YSR) is a self-report questionnaire that was modeled on the CBCL. The questionnaires contain - respectively - 113 and 112 items on behavioral or emotional problems in the past six months. The response format is 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The good reliability and validity of the American version of the CBCL and YSR were confirmed for the Dutch translations (De Groot et al 1994; Verhulst et al 1997; Verhulst et al 1996).

The original empirical syndrome scales for the CBCL and the YSR were based on multivariate statistical analysis on data from large samples. To fit more closely to the clinical-diagnostic approach, represented by the DSM (APA 1994), the following DSM-IV scales were constructed for the CBCL and its derivatives: Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity (ADH) Problems, Oppositional Defiant (OD) Problems, and Conduct (CD) Problems (Achenbach and Dumenci, 2001; Achenbach et al., 2003). A confirmatory factor analyses proved the good fit of these scales (Sondeijker et al 2005).

Antisocial behavior pertains to behavior that results in physical or mental harm, property loss, or damage to others. It is behavior that lowers the well being of other persons to a large degree (Loeber and Schmaling 1985; Rutter et al 1998; Coie and Dodge 1998). Although the CBCL and YSR contain the OD and CD Problems scales, it can be argued that these scales do not contain enough items that reflect extreme antisocial behaviors. The more severe the disruptive behaviors, the stronger associations with cortisol levels might be. Therefore, scores on the Antisocial Behavior Questionnaire (ASBQ), that contains a large number of items on severe antisocial behaviors, were also used for the present study. The ASBQ is comparable to the Self-Report Delinquency Scale (Moffitt and Silva 1988), and consists of 31 items on lifetime antisocial behaviors (e.g. 'Have you ever destroyed something on purpose?', 'Have you ever used a weapon?', 'Have you ever used drugs?', 'Have you ever been in contact with the police?'). Questions can be rated as (1) no, never, (2) once, (3) two or three times, (4) four to six times, (5) seven times or more. The internal consistency of total score of the items of the ASBQ in the TRAILS sample was .88.

Collection of salivary cortisol does not induce stress, which is an advantage compared to collection via venipuncture. Furthermore, total plasma cortisol levels represent all the cortisol that is present in the blood, whereas the effect of plasma cortisol is only caused by the proportion of free cortisol, that is not attached to carrier-proteins. Salivary cortisol levels represent free cortisol only, because free cortisol is able to pass to saliva, and correlate considerably with free plasma cortisol levels (Kirschbaum and Hellhammer 1994; van Goozen et al 1998). TRAILS participants provided two samples of saliva in the morning, shortly after waking up (Cort 1) and half an hour later (Cort 2), and one at 8.00 P.M. (Cort 3), by means of salivettes. All participants were instructed to collect saliva on a normal day, without special events or stressful circumstances, when they were not ill, did not have a cold, and, preferably, did not take any medication. If any of these requirements were not met, this could be noted down on an accompanying form. The saliva samples were stored at –20ºC until analysis. Previous studies suggested that salivary cortisol levels are stable for prolonged periods of time at –20ºC (Aardal and Holm, 1995). After completion of the data collection, all samples were sent in one batch (frozen, by courier) to the laboratory (Department of Clinical and Theoretical Psychobiology, University of Trier, Germany) for analysis.

Cortisol levels were determined with a competitive solid phase time-resolved fluorescene immunoassay with fluorometric end point detection (DELFIA). Ninety-six well Maxisorb microtiterplates (Nunc) were used, that were coated with rabbit-anti-ovine immunoglobulin. After an incubation period of 48 hours at 4ºC, the plates were washed with washbuffer (pH=7.4), coated with an ovine anti-cortisol antibody and incubated again. Synthetic saliva mixed with cortisol in a range from 0-100 nmol/l served as standards. Standards, controls (saliva pools) and samples were tested in duplicate wells. Fifty µl of biotin-conjugated cortisol was added and after 30 minutes of incubation the non-binding cortisol/biotin-conjugated cortisol was removed by washing. Two-hundred µl europium-streptavidin (Wallac, Turku, Finnland) was added to each well and after 30 minutes and 6 times of washing 200 µl enhancement solution was added (Pharmacia, Freiburg, Germany). Within 15 minutes on a shaker the enhancement solution induced fluorescene that could be detected with a DELFIA-Fluorometer (Wallac, Turku, Finnland). A standard curve was generated and the cortisol concentrations of the samples were calculated with a computer program. The intra-assay coefficient of variation was between 4.0% and 6.7%, and the corresponding inter-assay coefficients of variation between 7.1% and 9.0% (Rosmalen et al 2005).

Cortisol samples were obtained from 1,768 children. Twenty-two of those were excluded because of use of antibiotics or corticosteroids. Furthermore, for each time-point, cortisol values that were above 3 SD of the mean were excluded, to reduce the impact of outliers (Cort 1 21 excluded, 1,666 valid measurements; Cort 2 11 excluded, 1,683 valid measurements; Cort 3 18 excluded, 1,683 valid measurements in the final dataset). The area under the curve (AUC) was computed for the first two cortisol measures by using the following formula (Pruessner et al 2003):

$$\text{AUC} = \frac{(\text{Cort 2} - \text{Cort 1}) * 0.5}{2} + (0.5 * \text{Cort 1})$$

This AUC yielded a measure of morning cortisol concentration. In other studies, AUC is often computed based on cortisol concentrations that cover an entire day, to obtain a cortisol measure that represents the total cortisol production on a day. Because, in TRAILS, only morning and evening cortisol samples were obtained due to financial constraints, it was not possible to compute such an AUC.

Given possible confounding effects, pubertal stage and BMI were assessed as well. Pubertal stage was assessed using schematic drawings of secondary sex characteristics associated with the five Tanner stages of pubertal development (Tanner 1962). Within a questionnaire, individuals were provided with gender-appropriate sketches and were asked to select the sketches that looked most like themselves. These ratings have been widely used and have demonstrated good reliability and validity (Brooks-Gunn et al 1987; Dorn et al 1990). Height and weight were measured in school on the day that the young adolescents completed the questionnaires. Height was measured in meters and weight in kilograms. The same height meter and weighing scale were used throughout the study. Body mass index (BMI), a standard index of a person's weight in relation to height, was determined for each subject by dividing weight (kg) by the square of height (m^2).

Statistical analyses

Descriptives for the CBCL/YSR scales ADH Problems, OD Problems, and CD Problems scores, for the total score of the ASBQ, and for Cort 1, Cort 2, Cort 3, and AUC were computed.

Then, a set of 11x4 linear regression analyses was conducted (11 candidate predictors, 4 dependent variables), with scores on the CBCL/YSR ADH, OD, and CD Problems scales, the ASBQ total score, and gender (coded '0' for girls and '1' for boys), age, BMI, and Tanner stage as predictors, and Cort 1, Cort 2, Cort 3, and AUC as dependent variables.

Subsequently, linear regression analyses were conducted to test the predictive power of the interactions between gender and disruptive behaviors in one statistical model (but still separately for Cort 1, Cort 2, Cort 3, and AUC). First, a linear regression analysis was performed with Cort 1 as dependent variable and age, Tanner stage, and BMI as candidate predictors. Subsequently, gender was added to the model as predictor, and after that, scores on the CBCL scale ADH Problems were added. Finally, the interaction between the CBCL ADH Problems scores and gender was added. Exactly the same analyses were performed with the CBCL ADH Problems scale as predictor and the other cortisol measures (Cort 2, Cort 3, and AUC) as dependent variables.

Then, similar as for the ADH Problems scale of the CBCL, regression analyses were conducted for the CBCL scales OD Problems and CD Problems, the YSR scales ADH Problems, OD Problems, and CD Problems, and ASBQ total score.

Results

Descriptive information, including raw data separately for boys and girls, regarding the CBCL/YSR ADH, OD, and CD Problems scales, the ASBQ total score, and Cort 1, Cort 2, Cort 3, and AUC is presented in Table 3-1.

Table 3-1. Means, standard deviations, and ranges of predictor and dependent variables.

	Instrument	Mean (st. dev.) Boys	Mean (st. dev.) Girls	Range
ADH Problems scale	CBCL	4.53 (3.34)	3.37 (2.99)	0 – 14
OD Problems scale	CBCL	3.14 (2.15)	2.66 (1.97)	0 – 10
CD Problems scale	CBCL	2.34 (2.71)	1.26 (1.87)	0 – 22
ADH Problems scale	YSR	4.09 (2.57)	4.11 (2.42)	0 – 14
OD Problems scale	YSR	2.36 (1.82)	2.08 (1.64)	0 – 9
CD Problems scale	YSR	4.25 (3.29)	2.81 (2.34)	0 – 20
ASBQ total score	ASBQ	13.35 (12.63)	6.56 (7.26)	0 – 88
Cort 1	-	11.20 (4.72)	11.83 (4.71)	.71 – 29.42 nmol/l
Cort 2	-	14.72 (6.27)	16.02 (6.77)	.22 – 38.42 nmol/l
Cort 3	-	1.90 (1.33)	1.99 (1.34)	.01 – 8.17 nmol/l
AUC	-	6.48 (2.21)	6.95 (2.24)	.52 – 14.36 nmol/l

Note. CBCL = Child Behavior Checklist; YSR = Youth Self Report; ASBQ = Antisocial Behavior Questionnaire; ADH = Attention Deficit Hyperactivity; OD = Oppositional Defiant; CD = Conduct Disorder; Cort 1 = cortisol directly after awakening; Cort 2 = cortisol half an hour after awakening; Cort 3 = cortisol at 8.00 p.m.; AUC = area under the curve.

Separate regression analyses

Results of the set of 11x4 linear regression analyses are presented in Table 3-2. Effect sizes (explained variance = R^2) are presented for those associations that were significant.

Table 3-2. Independent associations between CBCL, YSR, and ASBQ scores, and age, gender, BMI , and Tanner stage as predictors, and cortisol measures as dependent variables.

	Cort 1		Cort 2		Cort 3		AUC	
	beta	R^2	beta	R^2	beta	R^2	beta	R^2
CBCL								
ADH Problems scale	-.024	-	-.041	-	.021	-	-.038	-
OD Problems scale	-.012	-	.001	-	.005	-	-.003	-
CD Problems scale	-.008	-	-.017	-	-.004	-	-.018	-
YSR								
ADH Problems scale	-.005	-	.042	-	.057*	0.3%	.024	-
OD Problems scale	.007	-	.045	-	.035	-	.029	-
CD Problems scale	-.021	-	-.029	-	.006	-	-.038	-
	-.027	-	-.035	-	.031	-	-.040	-
ASBQ total score								
Age	.046	-	.018	-	.098*	1.0%	.043	-
Gender	-.067*	0.4%	-.099*	1.0%	-.036	-	-.106*	1.1%
BMI	-.013	-	.026	-	-.016	-	.011	-
Tanner stage	-.015	-	.026	-	.008	-	.012	-

Note. Betas are standardized betas: *indicates that β is significant ($p<.05$). Effect sizes (R^2) are reported for significant effects only. CBCL = Child Behavior Checklist; YSR = Youth Self Report; ASBQ = Antisocial Behavior Questionnaire; ADH = Attention Deficit Hyperactivity; OD = Oppositional Defiant; CD = Conduct Disorder; Cort 1 = cortisol directly after awakening; Cort 2 = cortisol half an hour after awakening; Cort 3 = cortisol at 8.00 p.m.; AUC = area under the curve.

Table 3-2 showed that the association between scores on the YSR scale ADH Problems and Cort 3 was significant. This means that self-reported ADH Problems are positively associated to cortisol levels at 8.00 P.M. Hence, the more ADH problems are present, the higher cortisol levels are at 8.00 P.M. Individuals with ADH problems seemed to get overaroused instead of underaroused, but only in the evening. The effect size of this association was very small.

No significant associations were found between any of the cortisol measures and CBCL scale scores or ASBQ total scores, or with BMI or Tanner stage. Thus, parent reported disruptive behaviors and self reported disruptive behaviors as measured with the CBCL or ASBQ were not related to cortisol levels at all. Age explained 1.0% of the variance in Cort 3; hence, older individuals had higher cortisol levels in the evening. Gender was negatively associated with cortisol and explained .4% of the variance in Cort 1, 1.0% of the variance in Cort 2, and 1.1% of the variance in AUC. In other words, girls had higher cortisol levels than boys in the morning, but in the evening there was no difference in cortisol levels between boys and girls.

Interaction models

Results of the subsequent linear regression analyses are presented in Table 3-3. Results regarding age, gender, BMI, and Tanner stage are not presented in Table 3-3, because these possible confounders did not change the regression models in these analyses, and because separate effects of these predictors were already given in Table 3-2.

It is shown that the interaction between scores on the ADH Problems scale of the CBCL and gender contributed significantly to the prediction of Cort 1. This indicated that the association between ADH problems and cortisol directly after waking up was different for boys and girls. When levels of ADH Problems were low, girls showed higher cortisol levels than boys. When levels of ADH Problems were high, boys had higher cortisol levels than girls. Moreover, it seemed that girls with attention problems were underaroused, but boys were not. This effect accounted for .3% of the variance in Cort 1. No associations were found between scores on the parent-reported OD or CD Problems scales or the interaction terms and any of the cortisol measures.

A significant association was found between scores on the YSR scale ADH Problems and Cort 3. Another significant association was found between YSR OD Problems scores and Cort 2. Both associations were positive, which means that disruptive individuals were overaroused instead of, as is described in the arousal theories, underaroused. The effect size was .3% for both associations. Furthermore, for the AUC, a significant association was found with the interaction-term between YSR OD Problems scores and gender (effect size = .3%). This indicated that the association between the area under the curve and self-reported OD Problems was different for boys versus girls. The more OD Problems were present, the higher cortisol levels in girls were, whereas cortisol levels in boys decreased when levels of OD Problems became higher.

Results of the linear regression analyses with the ASBQ as predictor and the different cortisol measures as dependent variables were also presented in Table 3-3. The interaction between ASBQ total score and gender was associated with AUC (effect size =.3%). This indicated that, if ASBQ scores became higher, cortisol levels in girls increased, whereas those in boys decreased.

Table 3-3. Standardized betas and effect sizes for associations between CBCL, YSR, and ASBQ scores, and interactions with gender, as predictors, and cortisol measures as outcome.

	Cort 1		Cort 2		Cort 3		AUC	
	beta	R^2	beta	R^2	beta	R^2	beta	R^2
CBCL								
ADH Problems scale	-.027	-	-.035	-	.024	-	-.037	-
Gender * ADHD	.108*	0.3%	.011	-	-.006	-	.050	-
OD Problems scale	-.016	-	.007	-	.015	-	-.003	-
Gender * ODD	.017	-	-.008	-	-.017	-	-.015	-
CD Problems scale	-.018	-	-.015	-	-.001	-	-.023	-
Gender * CD	.005	-	-.019	-	-.109	-	-.056	-
YSR								
ADH Problems scale	-.006	-	.048	-	.052*	0.3%	.029	-
Gender * ADHD	-.074	-	-.084	-	.010	-	-.090	-
OD Problems scale	.011	-	.051*	0.3%	033	-	.036	-
Gender * ODD	-.091	-	-.071	-	-.003	-	-.118*	0.3%
CD Problems scale	-.025	-	-.030	-	-.002	-	-.040	-
Gender * CD	-.027	-	-.083	-	.006	-	-.066	-
ASBQ								
ASBQ total score	-.038	-	-.028	-	.027	-	-.040	-
Gender * ASBQ	-.101	-	-.103	-	-.086	-	-.140*	0.3%

Note. Betas are standardized betas: *indicates that β is significant ($p<.05$). Effect sizes (R^2) are reported for significant effects only. CBCL = Child Behavior Checklist; YSR = Youth Self Report; ASBQ = Antisocial Behavior Questionnaire; ADH = Attention Deficit Hyperactivity; OD = Oppositional Defiant; CD = Conduct Disorder; Cort 1 = cortisol directly after awakening; Cort 2 = cortisol half an hour after awakening; Cort 3 = cortisol at 8.00 p.m.; AUC = area under the curve.

Discussion

The present study indicated that, in a large representative general population sample of pre-adolescent boys and girls, the association between disruptive behaviors and indices of basal HPA-axis functioning were weak, and not always in the direction we expected a priori (McBurnett et al 2000; Pajer et al 2001; Vanyukov et al 1993). Hence, the findings from previous studies, that were conducted with clinical or high risk samples, could not be generalized to this general population sample. Furthermore, given the finding that effect sizes were relatively small, it can be concluded that, in pre-adolescence, the measures of baseline HPA-axis functioning that were used for the present study can not be used as biological markers for disruptive behaviors.

To explain discrepancies with previous studies, the severity of problems in high risk groups versus general population samples could be of importance. In clinical samples, problems are more severe and likely to have persisted for several years before referral to mental health services takes place (Sayal 2004). Hence, the HPA-axis may have become less sensitive to stress (Van de Wiel et al 2004). This could be a useful form of protection against long-term high cortisol levels, due to the stress that accompanies disruptive behaviors. As a result, in these individuals, much more stress may be needed to activate the HPA-axis, which would result in decreased basal levels of cortisol (under-arousal) in individuals with severe disruptive behaviors. Such a phenomenon might play a less important role in the general population.

Although associations between disruptive behaviors and cortisol levels apparently were weaker in general population samples than in clinical or high-risk samples, we did find an association between ADH Problems and cortisol levels at 8.00 P.M. In contrast to what we expected based on previous studies (McBurnett et al 2000; Pajer et al 2001; Vanyukov et al 1993; King et al 1998), it was a positive association. The more ADH Problems were present, the higher the cortisol levels we found. The finding that cortisol levels were associated with ADH Problems scores and not with OD or CD scores may indicate that, despite high comorbidity rates between attention problems and aggressive or delinquent behaviors (Angold et al 1999), the biological antecedents or consequences of these different areas of behavior problems may not be similar. Although the size of the effect that was found was small, results of the present study indicate that the association between HPA-axis functioning and attention problems, that has gotten less attention than that with aggressive or delinquent behaviors, requires further research.

In accordance with previous work (Klimes-Dougan et al 2001), girls had higher cortisol levels than boys. There is no clear explanation for the gender differences in basal cortisol levels in 10- to 12- year-olds. Netherton et al. (2004) suggested that gonadal steroids might play an important role. Gonadal steroids, and estrogens in particular, are known to interact with the HPA-axis. Increased HPA-axis activity in girls might be related to the direct effect of estrogens on CRH (Vamvakopoulos and Chrousos 1993), although, in the present study sample an association between pubertal stage and cortisol levels was not found (Rosmalen et al 2005). During puberty gender effects might become more clear, at least if gonadal steroids do have an influence on cortisol levels.

More interestingly however, gender interaction-effects were found, indicating that associations between cortisol levels and disruptive behaviors were different in boys versus girls. The first interaction effect concerned cortisol levels just after awakening. High rates of ADH problems were associated with higher early morning cortisol levels in boys, but with lower levels in girls. Several studies indicated that compared with boys, girls with ADH Problems displayed lower levels of hyperactivity and lower rates of other externalizing behaviors; among children with ADH Problems identified from non-referred populations, girls with ADH Problems displayed lower levels of inattention, internalizing behavior, and peer aggression than boys with ADH Problems (e.g. Gaub and Carlson 1997; Gershon 2002). Because of the gender differences in ADH Problems, gender differences in arousal levels, and thus gender differences in cortisol levels were expected. However, since ADH Problems seem to be more severe in boys than in girls, we expected lower cortisol levels in boys, but not in girls (Klimes-Dougan et al 2001).

The other interaction effects, for ODD and CD problems remarkably, were opposite to the interaction effect for ADH problems. Higher rates of OD or CD Problems were associated with higher morning cortisol levels (AUC) in girls, and lower cortisol levels in boys. The finding that lower cortisol levels in boys were associated with higher levels of OD or CD Problems was in accordance with previous studies (McBurnett et al 2000; Vanyukov et al

1993; King et al 1998). Hence, in a way, the results provided support for the arousal theories that were mentioned in the introduction (Van Goozen et al 2000; Raine 1993; Zuckerman and Neeb 1979), indicating that low arousal levels put boys at risk for higher rates of disruptive behaviors.

In girls, however, higher levels of disruptive behaviors were associated with higher, and not with lower, morning cortisol levels. Girls did not receive much attention thus far in this field of research. However, the results of our study contrasted with those of Pajer and colleagues (2001), who suggested that conduct disorder in 15- to 17-year-old girls was associated with lower morning cortisol levels. The latter study seemed to support the fearlessness and sensation-seeking theories. However, the results of Pajer et al. (2001) were based on a small and selected sample. Results of the present study did not support the two arousal theories for a large representative sample of girls. Other endocrine mechanisms might be responsible for the positive association that was found between disruptive behaviors and HPA-axis activity in the present study. For instance, estrogens, which are known to influence HPA-axis activity, might play a role (Burgess and Handa 1992; Handa et al 1994; Roy et al 1999; Vamvakopaulos and Chrousos 1993). Still, this is purely hypothetically. Regardless of the mechanism that is responsible for the gender differences that were found, the present study indicated that different biological factors may be responsible for disruptive behaviors in boys versus girls, and indicated that gender specific research on this topic is needed (Rutter et al 2003).

The strengths of the present study were the large sample size, use of multiple informants to assess disruptive behaviors, and assessment of three cortisol measures on relevant time points during the day. Yet, the results of the present study should be interpreted against the limitations in our study. First, the cortisol response to stress was not assessed, whereas stress sensitivity may be a key factor in the link between HPA-axis functioning and disruptive behaviors (Bartels et al 2003). Second, individuals collected cortisol at home, which may be a less standardized procedure than collecting it at a clinic, but also less stressful, which is an important advantage.

It can be concluded that, although studies in high risk groups of mainly boys found evidence for an association between low basal HPA-axis activity and high levels of disruptive behavior problems, this association could hardly be confirmed in a large representative population sample of boys and girls. This casted doubt on the usefulness of cortisol measurements to estimate risk for behavior problems, and on a putative important role for HPA-axis functioning in the etiology of disruptive behavior problems.

Chapter 4

HPA-axis activity as a predictor of future disruptive behaviors in young adolescents

Frouke Sondeijker
Robert Ferdinand
Tineke Oldehinkel
Henning Tiemeier
Hans Ormel
Frank Verhulst

Submitted for publication

HPA-AXIS ACTIVITY AS A PREDICTOR OF FUTURE DISRUPTIVE BEHAVIORS IN YOUNG ADOLESCENTS

Low HPA-axis activity has been proposed as a risk factor for disruptive behaviors. However, longitudinal data on this topic are practically lacking. In the present study, it was investigated if low HPA-axis activity predicted future disruptive behaviors. 1,399 Individuals from the Dutch general population, initially aged 10-12 years, were included. At the first assessment, basal cortisol levels were assessed to measure HPA-axis activity. At both assessments, disruptive behaviors were assessed with parent and self-report questionnaires. The results suggest that low HPA-axis activity is not a good predictor for disruptive behaviors, but could be valuable to identify those with a poor prognosis, once disruptive behaviors are present in pre-adolescence. This may also explain why, in referred samples, associations between HPA-axis activity and disruptive behaviors are being found more often.

Introduction

Disruptive behaviors in children and adolescents are common, have a negative impact on families, schools, and communities, and predict delinquency and substance abuse in adulthood (e.g., Fergusson et al 1997; Frick et al 1993; Loeber 1982; Moffitt et al 1996, 2002; Nagin and Tremblay 1999; Robbins 1966). This warrants research aimed at early risk factors and at mechanisms that determine change in symptoms across time (Côté et al 2002; Deater-Deckard et al 1998; Hinshaw 2002; Lahey et al 2002; Loeber et al 1995; Nagin and Tremblay 1999).

In the past ten years, data have become available suggesting that low activity of the HPA-axis is a risk indicator for disruptive behaviors in children and adolescents (Grossman 1991; Lahey et al 1993; McBurnett and Lahey 1994). Theoretically, low HPA-axis activity is associated with low levels of arousal of the central nervous system (Chrousos and Gold 1998; Van Goozen et al 2000), which would predispose to disruptive behaviors. According to the stimulation-seeking theory (Eysenck 1964; Quay 1965; Raine 1993; Zuckerman and Neeb 1979), low arousal represents an unpleasant physiological condition. To attain a higher, more pleasant level of arousal, individuals would seek stimulation by becoming aggressive or delinquent.

Several studies examined cross-sectional associations between activity of the HPA-axis and disruptive behaviors in children and adolescents. Some studies found an association between low basal cortisol levels and disruptive behaviors (McBurnett et al 2000; Pajer et al 2001; Vanyukov et al 1993), while others did not (Scerbo and Kolko 1994; Schultz 1997). However, to test whether low HPA-axis activity is a risk factor for future disruptive behaviors, or predicts the persistence of behavior problems across time, a longitudinal design is needed. To our knowledge only two studies applied a longitudinal approach. McBurnett et al. (2000) examined 38 7- to 12-year-old boys who had been referred for disruptive behaviors, and found that low basal cortisol levels were associated with persistence of aggressive behaviors across a period of at least two years. A second longitudinal study (Shoal et al 2003), examined 314 10- to 12-year-old boys who were recruited from the greater Pittsburgh area through media advertisements (78%), random telephone listings (11%), and substance use disorder training programs in which their fathers were participating (11%). In this study low cortisol levels predicted aggressive behaviors five years later.

The two previous longitudinal studies that investigated if low HPA-axis activity predicts future disruptive behaviors did not provide information regarding the role of HPA-axis activity as a risk factor for disruptive behaviors in the general population. Instead, a referred sample was studied (McBurnett et al., 2000), or a sample that consisted of high-risk individuals and individuals that were selected with media advertisements (Shoal et al 2003), which may have biased the constitution of the sample in an uncontrollable way, and can make us doubt whether the findings can be generalized. Given this lack of generalizability, it can not be assumed automatically that HPA-axis activity can be assessed to estimate the risk of future disruptive behaviors. Finally, both previous studies concerned boys only, whereas gender differences in associations between HPA-axis activity and disruptive behaviors may be present (Keiss et al 1995; Klimes-Dougan et al 2001; Vamvakopoulos and Chrousos 1993).

The aim of the present study was twofold. First, it was investigated whether low salivary cortisol levels predicted future disruptive behaviors in young adolescents from the general population. Second, it was investigated if low HPA-axis activity predicted persistence of disruptive behavior problems.

Methods

Sample and procedure

The present study was part of the TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS is a prospective cohort study of Dutch early adolescents aged 10-12 years, who were followed across a period of two years. The first assessment took place in 2001-2002, the second in 2003-2004. The TRAILS target sample consisted of young adolescents from five municipalities in the North of the Netherlands, including both urban and rural areas. Of all eligible individuals (N=2,935), 76.0% participated in the study (N=2,230, mean age 11.09 years, SD .55, 50.8% girls). Participants did not differ from those who refused with respect to the proportion of single parent families, the prevalence of teacher-rated problem behavior, several socio-demographic variables, and mental health outcomes provided by the teacher (De Winter et al 2005).

At the second assessment wave, information was obtained from 2,149 (96.4%) of those who participated at wave 1 (Mean age 13.56 years, SD .53, with 51.0% girls). To assess disruptive behaviors, two questionnaires were used at wave 1 and wave 2, the Child Behavior Checklist (CBCL) and the Youth-Self Report (YSR). The number of individuals for whom questionnaires were available at both assessment waves were 1,765 for the CBCL and 1,941 for the YSR. Furthermore, at wave 1, cortisol levels were determined for 1,768 individuals, of whom 22 were excluded because of use of antibiotics or corticosteroids. In addition, cortisol values that were above 3 SD of the mean were excluded, to reduce the impact of outliers (cortisol directly after waking up (Cort 1) 21 excluded, 1,666 valid measurements; cortisol half an hour after awakening (Cort 2) 11 excluded, 1,683 valid measurements; cortisol at 8.00 P.M. (Cort 3) 18 excluded, 1,683 valid measurements in the final dataset). This resulted in 1,399 individuals for whom wave 1 and wave 2 CBCL's and YSR's, plus at least one wave 1 cortisol measure were available.

To examine possible selective attrition a stepwise logistic regression analysis was performed with 'all information available' as a dependent variable and age, gender, social-economic-status (SES), the different cortisol measures, and the scores on the CBCL and YSR disruptive scale as predictors. Low SES scores and high disruptive behavior scores according to the CBCL predicted attrition. However, the effect size of the entire model was very small (Cox and Snell R^2=2.4%).

Written consent was obtained from the children's parents. The study was approved by the Central Dutch Medical Ethics Committee.

Questionnaires

The *Child Behavior Checklist* (CBCL; Achenbach 1991a) is a parent questionnaire for assessing problems in 6- to 18-year-olds. The *Youth Self-Report* (YSR; Achenbach 1991b) is a self-report questionnaire that was modeled on the CBCL. The questionnaires contain - respectively - 113 and 112 items on behavioral or emotional problems in the past six months. The response format is 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The good reliability and validity of the American version of the CBCL and YSR were confirmed for the Dutch translations (De Groot et al 1996; De Groot et al 1994; Verhulst et al 1997; Verhulst et al 1996).

The original empirical syndrome scales for the CBCL and the YSR were based on multivariate statistical analysis on data from large samples. To fit more closely to the clinical-diagnostic approach, represented by the DSM (APA 1994), the following DSM-IV scales were constructed for the CBCL and its derivatives: Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity (ADH) Problems, Oppositional Defiant (OD) Problems, and Conduct (CD) Problems (Achenbach and Dumenci 2001; Achenbach et

al 2003). For the present study we used the scales OD Problems and CD Problems. A confirmatory factor analyses proved the good fit of these scales (Sondeijker et al 2005).

Cortisol

At wave 1 participants provided salivary cortisol. Collection of salivary cortisol does not induce stress, which is an advantage compared to collection via venipuncture. Furthermore, total plasma cortisol levels represent all the cortisol that is present in the blood, whereas the effect of plasma cortisol is only caused by the proportion of free cortisol, that is not attached to carrier-proteins. Salivary cortisol levels represent free cortisol only, because free cortisol is able to pass to saliva, and correlate considerably with free plasma cortisol levels (Kirschbaum and Hellhammer 1994; Van Goozen et al 1998). TRAILS participants provided two samples of saliva in the morning, shortly after waking up (Cort 1) and half an hour later (Cort 2), and one at 8.00 P.M. (Cort 3), by means of salivettes. All participants were instructed to collect saliva on a normal day, without special events or stressful circumstances, when they were not ill, did not have a cold, and, preferably, did not take any medication. If any of these requirements were not met, this could be noted down on an accompanying form.

Concerning the sampling procedure itself, subjects were instructed to keep a glass of water next to their bed and to thoroughly rinse their mouth with tap water before sampling saliva, and not to consume sour products or brush their teeth shortly before that. Saliva samples were stored by the participants in their freezer directly after sampling and mailed to the institute as soon as possible (but not on Fridays and Saturdays in order to prevent unnecessary delay due to the weekend). Participants who did not return the salivettes within a couple of months were sent a reminder letter. In total, we received saliva samples of 1,768 children (79.3% of all TRAILS participants), for characteristics of this study population see (Rosmalen et al 2005). Non-responders did not differ from responders in terms of gender (48.4% male vs. 49.4% male for non-responders vs. responders, respectively, $\chi^2(df=1)=.13$; p=.72) or pubertal development (average tanner score=1.92 vs. 1.86, t=-1.39; p=0.16); non-responders were slightly older (11.16 years vs. 11.08 years, t=-3.08; p=.002) and had a higher mean BMI (18.50 vs. 17.92 kg/m^2, t=-3.22; p=.001). The saliva samples were stored at –20ºC until analysis. Previous studies suggested that salivary cortisol levels are stable for prolonged periods of time at –20ºC (Aardal and Holm 1995). After completion of the data collection, all samples were sent in one batch (frozen, by courier) to the laboratory (Department of Clinical and Theoretical Psychobiology, University of Trier, Germany) for analysis.

Cortisol levels were determined with a competitive solid phase time-resolved fluorescene immunoassay with fluorometric end point detection (DELFIA). Ninety-six well Maxisorb microtiterplates (Nunc) were used, that were coated with rabbit-anti-ovine immunoglobulin. After an incubation period of 48 hours at 4ºC, the plates were washed with washbuffer (pH=7.4), coated with an ovine anti-cortisol antibody and incubated again. Synthetic saliva mixed with cortisol in a range from 0-100 nmol/l served as standards. Standards, controls (saliva pools) and samples were tested in duplicate wells. Fifty µl of biotin-conjugated cortisol was added and after 30 minutes of incubation the non-binding cortisol/biotin-conjugated cortisol was removed by washing. Two-hundred µl europium-streptavidin (Wallac, Turku, Finnland) was added to each well and after 30 minutes and 6 times of washing 200 µl enhancement solution was added (Pharmacia, Freiburg, Germany). Within 15 minutes on a shaker the enhancement solution induced fluorescene that could be detected with a DELFIA-Fluorometer (Wallac, Turku, Finnland). A standard curve was generated and the cortisol concentrations of the samples were calculated with a computer program. The intra-assay coefficient of variation was between 4.0% and 6.7%, and the

corresponding inter-assay coefficients of variation between 7.1% and 9.0% (Rosmalen et al 2005).

Besides the three cortisol measures (Cort 1, Cort 2, and Cort 3), we also computed the area under the curve (AUC). The area under the curve (AUC) was computed for the first two cortisol measures by using the following formula (Pruessner et al 2003):

$$AUC = \frac{(Cort\ 2 - Cort\ 1) * 0.5}{2} + (0.5 * Cort\ 1)$$

This AUC yielded a measure of morning cortisol concentration. In other studies, AUC is often computed based on cortisol concentrations that cover an entire day, to obtain a cortisol measure that represents the total cortisol production on a day. Because, in TRAILS, only morning and evening cortisol samples were obtained due to financial constraints, it was not possible to compute such an AUC.

Statistical analyses

First scores on the DSM-IV CBCL scales OD Problems and CD Problems were summed. This combined scale was designated as CBCL disruptive scale. The same was done for the DSM-IV YSR scales OD and CD Problems, which yielded the YSR disruptive scale.

To investigate whether cortisol levels predicted *future disruptive behaviors*, regression analyses were performed with the CBCL disruptive scale scores at wave 2 as the dependent variable and wave 1 Cort 1 as an independent variable. To control for possible effects of gender and age, these variables were also added to the model as independent variables. Wave 1 scores of disruptive behaviors were available, so it would have been possible to correct for these wave 1 scores, but since preliminary analyses indicated that there was no significant association between cortisol levels and disruptive behaviors at wave 1 (Sondeijker et al in press), there was no need to control for wave 1 disruptive behavior scores. Similar analyses were conducted with Cort 2, Cort 3, and AUC as independent variables. The analyses were repeated with wave 2 scores on the YSR disruptive scale as the dependent variable.

Most of the literature concerning the question whether cortisol levels predict future disruptive behaviors was performed within clinical samples. To make our study more comparable to those studies, all regression analyses were repeated for the youths who scored above the 90th percentile (P90) on the wave 1 CBCL disruptive scale. These analyses were also performed for the children who scored above the P90 on the YSR disruptive scale.

In order to investigate whether cortisol levels predicted *persistence of disruptive behaviors*, the score on the CBCL disruptive scale that belonged to the P90 was used as a cut-off point. Youths who scored above this cut-off point on wave 1 and wave 2 were designated as ‘the persisters’ (N=93). All the others were ‘the non-persisters’. Next, regression analyses were performed with the dichotomous variable ‘persistence CBCL’ as the dependent variable and wave 1 Cort 1 as an independent variable. To control for possible effects of gender and age, these variables were also added to the model as independent variables. Identical analyses were performed for the YSR (N=110 persisters).

Results

Regarding our first aim, regression analyses were performed to examine whether cortisol levels predicted future disruptive behaviors. The results of these analyses are presented in Table 4-1. The results indicate that none of the wave 1 cortisol measures predicted disruptive behaviors two years later.

Table 4-1. Predictive value of cortisol measures regarding disruptive behaviors two years later.

Wave 2 scores disruptive behaviors	Wave 1 cortisol levels	Beta	P-value	R^2	CI
CBCL disruptive scale					
	Cort 1	.000	.997	-	-.047 - .047
	Cort 2	.007	.799	-	-.030 - .039
	Cort 3	-.030	.273	-	-.263 - .074
	AUC	.008	.767	-	-.087 - .117
YSR disruptive scale					
	Cort 1	-.022	.423	-	-.062 - .026
	Cort 2	.025	.372	-	-.017 - .047
	Cort 3	-.001	.961	-	-.164 - .156
	AUC	.004	.893	-	-.089 - .102

Note. β's are standardized betas: *indicates that β is significant (p<.05). Effect sizes (R^2) are reported for significant effects only. CI = confidence interval, CBCL = Child Behavior Checklist; YSR = Youth Self Report; Cort 1 = cortisol directly after awakening; Cort 2 = cortisol half an hour after awakening; Cort 3 = cortisol at 8.00 p.m; AUC = area under the curve.

To make our study more comparable to previous clinical studies, regression analyses were performed for the youth who scored above the P90 on disruptive behaviors at wave 1. The results of these analyses are presented in Table 4-2. Cortisol levels directly after waking up predicted the wave 2 YSR disruptive scale (t=-2.11, p=0.04, R^2=2.6%). No other cortisol measure predicted disruptive behaviors within the high-scoring group.

Table 4-2. Predictive value of cortisol measures regarding disruptive behaviors two years later within the group scoring high on wave 1 disruptive behaviors.

Wave 2 scores disruptive behaviors	Wave 1 cortisol levels	Beta	P-value	R^2	CI
CBCL disruptive scale					
	Cort 1	.022	.769	-	-.145 - .196
	Cort 2	-.045	.542	-	-.153 - .081
	Cort 3	-.057	.449	-	-.813 - .362
	AUC	-.026	.736	-	-.423 - .300
YSR disruptive scale					
	Cort 1	-.164	.036*	2.6%	-.324 - -.011
	Cort 2	-.081	.301	-	-.161 - .050
	Cort 3	-.116	.148	-	-.976 - .149
	AUC	-.144	.071	-	-.608 - .025

Note. β's are standardized betas: *indicates that β is significant (p<.05). Effect sizes (R^2) are reported for significant effects only. CI = confidence interval, CBCL = Child Behavior Checklist; YSR = Youth Self Report; Cort 1 = cortisol directly after awakening; Cort 2 = cortisol half an hour after awakening; Cort 3 = cortisol at 8.00 p.m; AUC = area under the curve.

Regarding our second aim, regression analyses were performed to examine whether cortisol levels predicted the persistence of disruptive behaviors. The results of these analyses are presented in Table 4-3. The results indicate that none of the wave 1 cortisol measures predicted the persistence of disruptive behaviors.

Table 4-3. Predictive value of cortisol measures regarding the persistence of disruptive behaviors.

Wave 2 scores disruptive behaviors	Wave 1 cortisol levels	Beta	P-value	R^2	CI
Persistance CBCL					
	Cort 1	-.015	.594	-	-.004 - .002
	Cort 2	-.020	.475	-	-.003 - .001
	Cort 3	-.029	.291	-	-.016 - .005
	AUC	-.014	.615	-	-.008 - .005
Persistance YSR					
	Cort 1	-.019	.487	-	-.004 - .002
	Cort 2	-.009	.739	-	-.003 - .002
	Cort 3	.029	.293	-	-.005 - .017
	AUC	-.020	.474	-	-.009 - .004

Note. β's are standardized betas: *indicates that β is significant ($p<.05$). Effect sizes (R^2) are reported for significant effects only. CI = confidence interval, CBCL = Child Behavior Checklist; YSR = Youth Self Report; Cort 1 = cortisol directly after awakening; Cort 2 = cortisol half an hour after awakening; Cort 3 = cortisol at 8.00 p.m; AUC = area under the curve.

Discussion

This study was the first to assess longitudinal associations between HPA-axis activity and disruptive behaviors in a representative sample of pre-adolescents from the general population. Previous evidence regarding such longitudinal associations was derived only from clinical or high risk samples. Further, earlier studies that assessed HPA-axis functioning in a sample as large as that of the present study do not exist. Identical instruments were used at the initial and follow-up assessments which enabled us to detect changes across time; parent and child information was obtained at both assessments, which reduced the likelihood of informant biases; and information from boys and girls was obtained, whereas previous work mainly concerned boys. Low HPA-axis activity in the sample as a whole did not predict future disruptive behaviors. However, in those with high levels of disruptive behaviors at the beginning of the study, low morning cortisol levels predicted future behavior problems as indicated by self-reports. Hence, low HPA-axis activity seemed to become a significant predictor of future behavior problems, once pre-adolescents have begun to display disruptive behaviors, but did not predict the new cases. This corroborated results of previous authors (McBurnett et al 2000; Shoal et al 2003) but also indicated that low HPA-axis activity is a risk factor in high risk groups, but not at a general population level.

Our study may have important implications for theory building. Well-known theories are the sensation-seeking theory, that was mentioned in the introduction, or the fearlessness theory, that implies that low arousal levels – associated with low HPA-axis activity – would make people fearless, and therefore vulnerable to disruptive behaviors (Zuckerman and Neeb 1979; Raine 1993). These theories imply that low arousal levels put individuals at risk for future behavior problems. This was not supported by the present study, since individuals with low cortisol levels who were drawn randomly from the general population were not at risk for

future behavior problems. Moreover, only in those who displayed high levels of behavior problems already, low HPA-axis activity was a risk factor for future problems. This may even imply that low HPA-axis activity may be a consequence of persistent behavior problems, instead of a cause (Gunnar and Vazquez 2001). Further, it is in line with previous studies in boys from clinical or high risk groups (McBurnett et al 2000; Shoal et al 2003) that probably contained a high proportion of individuals with persistent disruptive behavior problems (Sayal 2004). Moreover, low HPA-axis activity could be valuable to identify those with a poor prognosis, once disruptive behaviors are present in pre-adolescence.

Some authors have explained the association between low HPA-axis activity and persistent disruptive behaviors by postulating that a high threshold for activation of the HPA-axis may be a useful protection against high levels of environmental stress that children with disruptive behaviors often have to cope with (Van de Wiel et al 2004). It is also possible that genetic or environmental influences alter the HPA-axis in an early stage of life, or even before birth in environments that are characterized by environmental stress (Gunnar et al 2001; Seckl and Meaney 2004). These mechanisms may well play a role in individuals diagnosed with disruptive behaviors, given their long lasting high levels of environmental stress, but these kinds of alterations in HPA-axis sensitivity and activity may play a less prominent role in a general population sample.

The present study shows that, for building theories regarding the etiology of disruptive behavior problems, it is very risky to rely only on data from clinical or high risk samples. Apparently, use of such data, that are subject to all kinds of selection processes, may result in theories that do not necessarily pertain to the population as a whole. However, the results of the present study should be viewed from the right perspective, taking into account a number of limitations. Cortisol samples were collected at home which is a drawback of this study, despite the fact that other studies, that succeeded in gathering information regarding HPA-axis activity and future behavior problems in such a large representative sample of pre-adolescents, do not exist. Despite thorough instructions, it can be expected that especially the morning levels of cortisol may have been more unreliable than we would wish, given problems with sampling immediately after awakening, level of physical activity in the morning (ideally, individuals should lay down for 30 minutes between cort 1 and cort 2), or problems with timing between cort 1 and cort 2. Although it is valuable to collect cortisol levels on a normal day, collection of cortisol levels in a lab would probably have resulted in higher reliability of cortisol data. This may indicate that the findings of the present study represent an underestimation of the associations between HPA-axis activity and disruptive behaviors.

It could also be that HPA-axis activity in itself does not constitute a risk factor for disruptive behaviors, but that, in combination with other factors, such as socio-economic status, parental rearing practices, early adversities, or adverse peer relationships, low HPA-axis activity may become more important. This is not entirely unlikely, given the growing knowledge about the importance of interactions between biological/individual factors and environmental influences (Moffit et al 2005; Rutter and Silberg 2002). However, it is always easy to say that studies that did not confirm existing theories probably did not use the right instruments or the right methods, did not enter the appropriate covariates or interaction terms into their models, or, as in our case, did not assess cortisol levels accurately enough. However, the results of this study could also indicate that, as much as we would want that too, HPA-axis activity does not really put individuals at risk for future behavior problems. Of course, replication studies are needed in other countries, using other measures, to put the findings of the present study to the test.

Chapter 5

Disruptive behaviors and regulation of the autonomic nervous system in young adolescents

Frouke Sondeijker
Andrea Dietrich
Kirstin Greaves-Lord
Judith Rosmalen
Tineke Oldehinkel
Hans Ormel
Frank Verhulst
Robert Ferdinand

Submitted for publication

DISRUPTIVE BEHAVIORS AND REGULATION OF THE AUTONOMIC NERVOUS SYSTEM IN YOUNG ADOLESCENTS

Studies that investigate the biology of disruptive behavior disorders in children and adolescents are important because Oppositional Defiant (OD) Problems and Conduct (CD) Problems often begin in childhood or adolescence. Disruptive behavior problems have often been associated with autonomic nervous system functioning. We aimed to gain more insight in the association between autonomic functioning and OD or CD problems. Participants were 1,027 10- to 13-year-old boys and girls from the Dutch general population. Self-reports and parent reports were used to assess disruptive behaviors. Heart rate and variations in heart rate and blood pressure were measured with a sophisticated physiological recording technique. Associations between disruptive problems and autonomic measures were analyzed by performing linear regression analyses. Anxiety was included in these analyses because lack of fear might predispose an individual to demonstrate disruptive behaviors. By themselves, OD or CD Problems were not associated with any of the autonomic measures. However, there were some interaction effects with anxiety. In accordance with the fearlessness-theory, the more low-anxious/high-disruptive children were, the lower their HR was. However, heart rate variability in the low frequency band in standing posture, was higher in children who were more low anxious/high disruptive. This contrasted with the fearlessness-theory. In children and adolescents from the general population autonomic measures may be poor indicators of OD and CD Problems. Furthermore, the fearlessness-theory may be too simple to explain associations between autonomic measures and disruptive behaviors.

Introduction

Better indicators are needed for identifying children and adolescents with early signs of disruptive behaviors such as oppositional defiant problems and conduct problems. Although it is clear that such behaviors are influenced by family, situational, and societal factors, increasing evidence underscores the importance of genetic and other biological processes (Brunner et al 1993; Coccaro et al 1996; Kruesi et al., 1992). A recent meta-analysis indicated that low resting heart rate (HR) is the most robust biological marker of antisocial and aggressive behavior in children and adolescents (Ortiz and Raine 2004). In a previous study (Dietrich et al submitted) we replicated the negative association between HR and disruptive behaviors to some extend, that is, we found a statistically significant but weak association. The association between low HR and disruptive behaviors is often explained by the fearlessness theory or the sensation-seeking theory (Raine 1996; Zuckerman and Neeb 1979). Lack of fear might predispose an individual to demonstrate disruptive behaviors, because such behaviors require a degree of fearlessness to execute (Raine 1994, 1996). Sensation-seeking behaviors such as fighting or cruelty might be intended to restore low arousal levels back to a higher level (Raine 1994, 1996; Zuckerman and Neeb 1979).

Previous studies found that disruptive behaviors are not only related to HR (Pine et al 1996; Raine et al 1997; Rogeness et al 1990), but also to autonomic measures that reflect fluctuations in HR (Boyce et al 2001; Mezzacappa et al 1997; Pine et al 1998). Measures that are based on fluctuations in HR can be used to study autonomic nervous system regulation in detail. There are two branches of the autonomic nervous system, the sympathetic and the parasympathetic nervous system. The parasympathetic (vagal) system is predominantly associated with calm states and homeostasis, while the sympathetic system prepares the body for action. Reductions in HR in children with disruptive behaviors can arise from enhanced vagal activation or from reduced sympathetic activation (Guyton 1986). Therefore, methods that can yield an impression of sympathetic and parasympathetic activity are becoming increasingly important (Mezzacappa et al 1997). A measure that is often used for this purpose is heart rate variability (HRV). Autonomic regulatory signals from centers in the mid-brain control beat-to-beat variations in HR. HR fluctuations can be divided into fluctuations with different frequencies. Heart rate variations in the low-frequency band (LF; generally 0.04-0.14 Hz) are primarily influenced by variations in blood pressure. HRV LF is predominantly sympathetically mediated in standing posture, whereas in supine posture vagal effects predominate. HRV measured in the high frequency band (HF; 0.15-0.40 Hz), often called respiratory sinus arrhythmia (RSA), is primarily respiratory in origin, and vagally mediated (Mezzacappa et al 1997).

Some previous studies have attempted to unravel the association between activity of the two autonomic branches and disruptive behaviors. Pine et al. (1998) studied 120 7- to 11-year-old younger brothers of adjudicated juvenile delinquents. Boys with higher levels of externalizing psychopathology had lower levels of RSA. In the study of Mezzacappa et al. (1997), in which 175 15-year-old boys participated, it was found that those with antisocial behaviors had a lower HRV LF and a lower RSA. From the studies described above it can be concluded that parasympathetic activity is diminished in male children and adolescents with disruptive behaviors. In contrast, other studies have reported a positive association between RSA and disruptive behavior problems (Beauchaine et al 2001; Cole et al 1996). Hence, whereas results regarding the association between disruptive behaviors and HR are quite consistent, the association between disruptive behaviors and HRV LF, as well as the association between disruptive behaviors and RSA, is ambiguous.

In addition to HR, HRV LF, and RSA, we measured baroreflex sensitivity (BRS), which is a well-known indicator of autonomic regulation that has been associated with psychopathology previously (Allen et al 2000; Watkins et al 1999). BRS plays an important

role in short-term BP regulation. Baroreceptors located in the wall of the heart auricles, vena cava, aortic arch, and carotid sinuses, monitor changes in BP. If a rise in BP is perceived, HR will decrease to compensate for the higher BP. If the receptors detect a drop in BP, HR will increase to restore BP levels (Allen et al 2000; Kirchheim 1976). BRS reflects both vagal and sympathetic influences. However, BRS in supine posture would primarily reflect vagal control, because sympathetic influences are minimal in resting condition (Allen et al 2000; Dietrich et al 2006; Pomeranz et al 1985). Dietrich et al. (submitted) established that BRS was not related to disruptive problems, but according to Allen et al. (2000) BRS correlated negatively with disruptive behavior problems in children, and males, but not in adolescents or females.

Our previous study (Dietrich et al submitted) indicated that disruptive behaviors were associated with lower resting HR and increased vagal activity. We aimed to extend this work and to gain further insight into the association between autonomic functioning and specific disruptive problems. In the present study we therefore distinguished oppositional defiant (OD) Problems from conduct (CD) Problems and examined their association with HR, HRV LF, RSA, and BRS separately. Another topic that has not been highlighted sufficiently in previous studies is the role of anxiety. According to the fearlessness-theory, children and adolescents who score low on anxiety and high on disruptive problems, are most likely to experience low arousal levels. In the present study anxiety was taken into account in order to examine the role of the fearlessness-theory in the general population.

Methods

Sample and procedure

The TRacking Adolescents' Individual Lives Survey (TRAILS), is an ongoing Dutch longitudinal cohort study in which 2,230 10- to 13-year-old boys and girls were included. The data were collected in five municipalities in the North of the Netherlands, including both urban and rural areas (De Winter et al 2005).

For the present manuscript we used data from 1,027 boys and girls (47% vs 53%, mean age 11.0 years, SD .50) for whom reliable autonomic measures could be computed in supine and standing position. To examine possible selective attrition a stepwise regression analysis was performed. The 1,027 children included in the present study did not differ from those who were not regarding gender, pubertal stage, Body Mass Index, and the OD and CD Problems scales scores. Age predicted attrition. The older the children were, the less likely they were to be included. Nevertheless, the age difference (11.02 vs 11.15 years) and the effect size (explained variance = 1.2%) were very small.

Written consent was obtained from the children's parents. The study was approved by the Central Dutch Medical Ethics Committee.

Questionnaires

Disruptive behaviors were assessed with the Child Behavior Checklist/4-18 (CBCL; Achenbach 1991a) and the Youth Self-Report (YSR; Achenbach 1991b). The Child Behavior Checklist (CBCL) is a parent questionnaire for assessing problems in 4- to 18-year-olds. The Youth Self-Report (YSR) is a self-report questionnaire that was modeled on the CBCL. The questionnaires contain respectively 113 and 112 items on behavioral or emotional problems in the past six months. The response format is 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The good reliability and validity of the American version of the CBCL and YSR were confirmed for the Dutch translations (De Groot et al 1994; Verhulst et al 1996, 1997). The original empirical syndrome scales for the CBCL and the YSR were based on multivariate statistical analysis on data from large samples. To fit more closely to the clinical-diagnostic approach, represented by the DSM (APA 1994), new DSM-IV scales

were constructed for the CBCL and its derivatives (Achenbach and Dumenci 2001; Achenbach et al 2003). In the present study we used the Anxiety Problems scale, the OD Problems scale, and the CD Problems scale, that are presumed to be associated with the DSM-IV diagnoses of Anxiety, Oppositional Defiant Disorder, and Conduct Disorder. A confirmatory factor analyses proved the good fit these scales (Sondeijker et al 2005).

Autonomic measures

HR and blood pressure (BP) measurements were conducted in a quiet room at school, one child at a time. First, participants were asked to lie down and not to move or talk. While supine, the procedure was explained to them, a cuff was fixed around the middle phalanx of the third finger of the right hand to measure spontaneous fluctuations in continuous beat-to-beat systolic finger BP using a Portapres device (FMS Finapres Medical Systems BV, Amsterdam, the Netherlands). A three-lead electrocardiogram was derived to register HR. Recordings did not start until participants had a few minutes of supine rest and signals reached a stabilized steady-state. Then, HR and BP signals were registered for 4 minutes in supine position during spontaneous breathing, followed by 2 minutes in standing position, again after signals had stabilized. Recordings were digitized (sample rate 100Hz, using a DAS-12 data acquisition card for notebooks, Keithley Instruments, Cleveland, Ohio, USA) and stored on hard disk for off-line analysis. Internal reliability of the data has been reported in a previous study (Dietrich et al 2006).

HR was calculated as 60,000/mean interbeat-interval (IBI), expressed in beats per minute (bpm). Calculation of HRV LF, RSA, and BRS was performed by spectral analysis in the CARSPAN software program using the transfer function technique as previously described (Robbe et al 1987). CARSPAN allows for discrete Fourier transformation of non-equidistant systolic BP and IBI-series. The analyzed time series were checked and corrected for artifacts. RSA was defined as the high-frequency power (ms^2) in the .15-.40 Hz respiratory band, whereas BRS was defined as the mean modulus between systolic BP and IBI in the .07-.14 Hz frequency band (ms/mmHg) with a coherence of more than .3. A coherence level of .3 has been shown to produce comparable BRS values to the frequently used level of .5 (Dietrich et al 2006).

Statistical analyses

General information

We transformed HRV LF, RSA, and BRS values to their natural logarithm to approximate a normal distribution. Descriptives for total scores on the CBCL and YSR scales OD Problems CD Problems, and Anxiety Problems, and for the autonomic measures (HR, HRV LF, RSA, BRS), in supine as well as in standing posture, were computed.

Main effects

A linear regression analysis was performed with HR measured in supine posture as the dependent variable and scores on the CBCL scale OD Problems as the predictor. We adjusted for gender and anxiety (CBCL scale Anxiety Problems). Identical analyses were performed with the other autonomic variables (HRV LF, RSA, BRS) measured in supine and in standing posture as dependent variables. Similar regression analyses were conducted for the scores on the CBCL scale CD Problems, and the YSR scales OD Problems and CD Problems. When scores on the CBCL scales OD and CD Problems were used as predictors, we adjusted for the scores on the CBCL scale Anxiety Problems. When scores on the YSR scales OD and CD Problems were the predictors, we adjusted for scores on the YSR scale Anxiety Problems.

Interaction effects

After recoding the scores on the CBCL Anxiety Problems scale (20=0; 19=-1; 18=-2 etc.), an interaction-term was computed between scores on the CBCL scale OD Problems and the

CBCL scale Anxiety Problems. Another interaction-term was computed between scores on the CBCL scale CD Problems and the CBCL scale Anxiety Problems. After recoding scores on the YSR scale Anxiety Problems (22=0; 21=-1; 20=-2 etc.), interaction-terms between scores on this re-coded scale and the YSR OD and CD Problems scales scores were computed. The interaction terms, added to the regression models to test the fearlessness-theory, were computed in such a way that the lower their score on the interaction term, the more low-anxious/high-disruptive these participants were. All interaction-terms were added as predictor variables to the corresponding regression models in order to examine the fearlessness-theory.

Preliminary analyses indicated that there were no significant main effects or interactions for age, Body Mass Index, and pubertal stage. Hence, these factors were not considered in further analyses (Dietrich et al 2006).

Results

General information

Table 5-1 presents descriptive information regarding scores on the CBCL/YSR OD, CD, and Anxiety Problems scales, and HR, HRV LF, RSA, and BRS.

Table 5-1. Means, standard deviations, and ranges of predictor and dependent variables.

	N	Mean	Standard deviation	Range
CBCL OD Problems	937	2.81	2.07	0 - 10
CBCL CD Problems	925	1.65	2.18	0 - 9
CBCL Anxiety Problems	949	3.64	3.22	0 - 16
YSR OD Problems	995	2.18	1.72	0 - 15
YSR CD Problems	973	3.39	2.85	0 - 20
YSR Anxiety Problems	1,021	4.26	3.56	0 - 20
HR supine	1,027	77.60	10.91	49.08 - 115.92 bpm
HR standing	1,027	94.19	13.39	57.75 - 143.03 bpm
HRV supine	1,027	6.42	1.06	3.02 - 9.66 ms^2
HRV standing	1,027	6.19	.94	2.87 - 8.85 ms^2
RSA supine	1,027	7.33	1.31	3.01 - 10.55 ms^2
RSA standing	1,027	5.96	1.28	1.33 - 9.71 ms^2
BRS supine	1,027	2.56	.59	0 - 4.29 ms/mmHg
BRS standing	1,027	2.05	.55	.08 - 3.76 ms/mmHg

Note. CBCL = Child Behavior Checklist; YSR = Youth Self Report; OD = Oppositional Defiant; CD = Conduct; HR = heart rate; HRV = Heart rate variability; RSA = respiratory sinus arrhythmia; BRS = baroreflex sensitivity.

Main effects

Results of the linear regression analyses with the CBCL OD Problems and CD Problems scores, and with the YSR OD Problems and CD Problems scores as candidate predictor variables and autonomic measures as dependent variables are presented in Table 5-2. All analyses were adjusted for gender and Anxiety Problems scores.

Table 5-2. Standardized betas and p-values for main effects between disruptive behaviors and autonomic measures adjusted for gender and Anxiety Problems scores.

	CBCL OD Problems		CBCL CD Problems		YSR OD Problems		YSR CD Problems	
	ß	p	ß	p	ß	p	ß	p
HR supine	-.049	.17	-.061	.09	-.043	.22	-.044	.22
HR standing	-.048	.18	-.012	.74	-.035	.32	-.038	.30
HRV LF supine	.036	.32	.021	.55	.021	.56	.013	.72
HRV LF standing	.006	.86	-.002	.95	-.017	.73	.034	.34
RSA supine	.054	.13	.044	.22	.028	.42	.008	.82
RSA standing	.030	.40	-.012	.74	-.005	.88	.000	.99
BRS supine	-.004	.90	.017	.64	.017	.64	-.050	.17
BRS standing	-.008	.82	-.024	.52	-.040	.26	-.035	.33

Note. Betas are standardized betas. CBCL = Child Behavior Checklist; YSR = Youth Self Report; OD = Oppositional Defiant; CD = Conduct; HR = heart rate; HRV LF = Heart rate variability in the low frequency band; RSA = respiratory sinus arrhythmia; BRS = baroreflex sensitivity.

No significant associations were found between CBCL or YSR OD Problems or CD Problems scores on the one hand and any of the autonomic measures on the other hand.

Interaction effects

Associations that included interactions between OD and CD Problems scores on the one hand and Anxiety Problems scores on the other hand revealed a somewhat different picture (Table 5-3). A number of significant interactions were revealed. These interactions were between YSR OD or CD Problems scores and autonomic measures (HR, HRV LF, or BRS). Some of the interactions were positive. Lower HR in supine posture was associated with lower scores on the interaction variable YSR CD Problems x Anxiety Problems (explained variance = .6%); lower HR in standing posture was associated with lower scores on the interaction variable YSR OD Problems x Anxiety Problems (explained variance = .3%); and lower HR in standing posture was associated with lower scores on the interaction variable YSR CD Problems x Anxiety Problems (explained variance = 1.2%). These positive interactions supported the fearlessness-theory; the more the children were low-anxious/high- disruptive, the lower their arousal levels. Other interactions were negative. Higher HRV LF in standing posture was associated with lower scores on the interaction variable YSR CD Problems x Anxiety Problems (explained variance = .5%) and higher BRS in standing posture was associated with lower scores on the interaction variable YSR OD Problems x Anxiety Problems (explained variance = .4%). These negative interaction between HRV LF in standing posture and YSR CD Problems x Anxiety Problems contrasted with the fearlessness-theory; the more the children were low-anxious/high-disruptive, the higher their arousal levels. How to interpret the negative interaction with BRS in standing posture is unclear.

Table 5-3. Standardized betas and p-values for interaction effects adjusted for gender.

	CBCL OD Problems x CBCL Anxiety Problems		CBCL CD Problems x CBCL Anxiety Problems		YSR OD Problems x YSR Anxiety Problems		YSR CD Problems x YSR Anxiety Problems	
	ß	p	ß	p	ß	p	ß	p
HR supine	.107	.49	.005	.97	.064	.60	.307*	.01
HR standing	.119	.44	-.043	.76	.238*	.05	.405*	.00
HRV LF supine	-.206	.18	-.231	.10	-.095	.43	-.116	.33
HRV LF standing	-.001	.99	.122	.39	-.190	.12	-.269*	.02
RSA supine	.080	.61	-.027	.85	-.072	.55	-.151	.21
RSA standing	.075	.63	.132	.35	-.205	.09	-.217	.07
BRS supine	-.118	.45	-.146	.30	-.084	.49	-.159	.18
BRS standing	.061	.70	.027	.85	-.238	.05	-.213	.07

Note. Betas are standardized betas. CBCL = Child Behavior Checklist; YSR = Youth Self Report; OD = Oppositional Defiant; CD = Conduct; HR = heart rate; HRV LF = Heart rate variability in the low frequency band; RSA = respiratory sinus arrhythmia; BRS = baroreflex sensitivity.

Discussion

Results of previous studies suggested that the negative association between disruptive behaviors and cardiovascular measures is important and robust (Ortiz and Raine 2004), has implications for therapy (Klein et al 1997; Raine et al 1997), and might even play a major role in the etiology of disruptive behaviors (Raine 2002). The present study, in which a general population sample of 1,027 10- to 13-year-old boys and girls was examined, found no evidence for significant main effects between OD or CD Problems and cardiovascular measures. However, we did find a number of interaction effects. Some of them supported the fearlessness theory, an often used explanation for the association between low levels of autonomic activity and disruptive behaviors, while others contrasted with this theory.

Our findings regarding the main effects between HR and disruptive behaviors were not in accordance with the meta-analysis from Ortiz and Raine (2004). Based on this meta-analysis, these authors concluded that HR is the best replicated biological correlate of antisocial behavior in children and adolescents. It is hard to offer a reasonable explanation for this inconsistency, especially because Ortiz and Raine (2004) demonstrated that the association between HR and disruptive problems was not moderated by gender, age, method of recording, use of a psychiatric control group, recruitment source, concurrent versus prospective nature of testing, and source of behavioral rating. However, the tendency of journals to accept publications that report significant results that are in accordance with the current opinion, and to reject studies with negative findings, may partly be responsible for the unexpected difference between our and others' findings.

Since we did not find associations between OD or CD Problems and HR, it might seem illogical to examine the influence of the autonomic branches. However, HR reflects the balance between sympathetic and parasympathetic activity (Guyton 1986), and if both branches are altered in adolescents with higher levels of disruptive behavior problems, HR can still be the same as in adolescents without such problems. In our analyses, in which just main effects were assessed, associations between HRV LF or RSA and oppositional defiant or

conduct problems were not found. This also contrasted with the few previous studies that concerned the same topic (Mezzacappa et al 1997; Pine et al 1998) and indicated that both the level of sympathetic as well as the level of vagal or parasympathetic activation in young adolescents with high levels of OD or CD Problems were unchanged.

Analyses in which only main effects, and no interactions, were assessed did not reveal an association between BRS and disruptive behavior problems. In the study by Allen et al. (2000), BRS correlated negatively with disruptive behavior problems in children (ages 8 to 10), and males, but not in adolescents (ages 15 to 17) or females. Since, the present study included 10- to 13-year-olds, an age group which was not assessed in Allen's study (2000), it is difficult to compare our results with theirs. However, our study seems to point out that further research is needed to investigate the importance or unimportance of the association between BRS and disruptive behaviors.

Since we previously found (Dietrich et al submitted) main effects indicating that Externalizing Problems, referring to a broad dimension of aggressive and delinquent behaviors was meant, were associated with autonomic measures it may seem surprising that we did not find any main effects for OD and CD Problems separately. The contrasting findings between the present study and our previous one can probably largely be explained by methodological differences. We used the new CBCL/YSR DSM-IV scales OD Problems and CD Problems instead of the 'old' scales Aggressive Behavior and Delinquent Behavior. These two scales together constitute the Externalizing Problems scale we used in our previous study. The DSM-IV scales OD an CD Problems we used in the present study contain similar, but also different items than the Aggressive Behavior and the Delinquent Behavior scales. This may have yielded different results. In addition, we specifically adjusted for Anxiety Problems and not for the broad dimension on internalizing problems, including the scales 'Anxious/Depressed', 'Withdrawn/Depressed', and 'Somatic complaints', which may also have yielded different results. Finally, the effect sizes of the significant effects in our previous study were small, and may have disappeared because the smaller concepts of OD and CD Problems were investigated separately, instead of the larger concept Externalizing Problems.

Apart from the possible explanations mentioned above, it is also possible that autonomic nervous system functioning in itself does not constitute a risk factor for OD or CD Problems, but that, in combination with other factors, such as socio-economic status, parental rearing practices, early adversities, or adverse peer relationships, autonomic nervous system functioning may become more important. This is not entirely unlikely, given the growing knowledge about the importance of interactions between biological/individual factors and environmental influences (Moffit et al 2005; Rutter and Silberg 2002).

According to the fearlessness-theory (Raine 1993, 1996; Zuckerman and Neeb 1979) individuals who score low on anxiety and high on disruptive problems have the highest chance of low arousal levels (Raine 1993). In accordance with this theory, we found that the more low-anxious/high-disruptive children were, the lower their HR was. However, HRV LF in standing posture, which is predominantly sympathetically mediated, became higher, instead of lower, if children were more low-anxious/high-disruptive. This is in contrast with the fearlessness-theory because when HR decreases, vagal activity is likely to increase and sympathetic activity to decrease (Guyton 1986). In short, evidence for the fearlessness-theory was not very strong.

BRS in supine posture would mainly reflect vagal activity, but what BRS in standing posture indicates is not so straight forward. BRS could be called the balance function of the autonomic nervous system. If a rise in BP is perceived by the baroreceptors, HR will decrease to compensate for the higher BP. If the receptors detect a drop in BP, HR will increase to restore BP levels (Allen et al 2000; Kirchheim 1976). If basal HR is low, as is found in children who display disruptive problems, one could argue that the receptors are less

sensitive, and therefore BRS would be reduced (Virtanen et al 2003). On the other hand, HR in the present study was, like in Allen's study (2000) inversely related to BRS, in both the supine ($r=-.52$, $p<.001$) and standing position ($r=-.67$, $p<.001$). Combining the low HR we found with these correlations, a higher BRS was to be expected. Unfortunately, this finding does not give us any information on the role of the fearlessness-theory in the general population.

The findings should be interpreted against the limitations of our study. First, data were not collected in a laboratory situation, but in schools. Although this resulted in a less standardized way of collecting the data, it may also have been a strength of this study, because children were in a familiar environment, which is less stressful than a laboratory. Collection of cardiovascular measures in a lab would probably have resulted in higher reliability of the data. This indicates that the findings of the present study may represent an underestimation of the associations between autonomic nervous system functioning and disruptive behaviors. Second, although the autonomic measures we used in the present study have been widely used as indices of vagal and/or sympathetic activity of the autonomic nervous system, it is difficult to attribute the mediation of these indices to only one branch of the autonomic nervous system.

We conclude that, despite evidence from previous studies, the fearlessness-theory may not be as important as is currently presumed in explaining the occurrence of disruptive behaviors in children and adolescents. The fearlessness-theory was supported by some of the findings, but contradicted by other findings, and effect sizes arguing for and against the theory were small. The findings of the present study may not be as many of us, clinicians or researchers, wish. They indicate that we may be further away than we would like from solving the numerous gaps in our knowledge that exist regarding the biological background of disruptive behavior problems. Of course, it can be argued that a number of limitations are responsible for our relative lack of findings in the 'right' direction. However, the findings may also reflect reality, and were derived from a very large representative sample from the general population, from which thorough and sophisticated measures of autonomic activity were obtained. This underscores the importance of our findings, and the need for considering the present study as a valuable source for future theory building.

Chapter 6

Does autonomic nervous system functioning predict future disruptive behaviors in adolescents from the general population?

Frouke Sondeijker
Robert Ferdinand
Andrea Dietrich
Kirstin Greaves-Lord
Tineke Oldehinkel
Hans Ormel
Frank Verhulst

Submitted for publication

DOES AUTONOMIC NERVOUS SYSTEM FUNCTIONING PREDICT FUTURE DISRUPTIVE BEHAVIORS IN ADOLESCENTS FROM THE GENERAL POPULATION?

Early identification of disruptive behaviors is needed because of the burden such behaviors cause. Autonomic nervous system functioning has been proposed as a risk factor for disruptive behaviors in children and adolescents. Participants were 766 10- to 13-year-old boys and girls from the Dutch general population. Self-reports and parent-reports were used to assess disruptive behaviors at two assessment waves. Heart rate (HR) and variations in HR and blood pressure were measured with a sophisticated physiological recording technique at wave 1. Whether autonomic measures predicted disruptive problems two years later was analyzed by performing linear regression analyses. HR and baroreflex sensitivity (BRS) did not predict disruptive behavior problems. Low heart rate variability in the low frequency band (HRV LF) and low respiratory sinus arrhythmia (RSA) in standing position predicted parent-reported oppositional defiant problems. High RSA in supine posture predicted parent-reported and self-reported conduct problems. Basal HR and BRS cannot be used to detect young adolescents in the general population who are at risk for future disruptive behaviors. Although explained variances were small, HRV LF and RSA seem to indicate a certain risk.

Introduction

Early identification of children and adolescents at risk for disruptive behavior problems, such as oppositional defiant (OD) and conduct (CD) problems, is needed because of the burden such behaviors cause to individuals themselves, families, schools, and the community at large. Autonomic nervous system functioning, measured by heart rate (HR), has been proposed as a possible marker for the identification of children and adolescents at risk for disruptive behaviors (Ortiz and Raine, 2004).

According to the arousal theories (Raine, 1993,1996; Zuckerman and Neeb, 1979), children and adolescents who have a low HR, or in general who have low arousal levels, are at risk for disruptive behaviors. One possible explanation for the inverse association between arousal and disruptive behaviors is the fearlessness-theory (Raine, 1993,1996). According to this theory low arousal levels lead to a lack of fear. Because of their fearlessness, individuals with low arousal levels might be at risk for disruptive behavior problems. Another explanation is the sensation-seeking theory (Zuckerman and Neeb, 1979). In this theory it is suggested that individuals who exhibit disruptive behaviors do this in order to restore low arousal levels back to a higher level.

The finding that low resting HR is associated with future disruptive behaviors has often been replicated in clinical and general population samples (Farrington, 1997; Kriscunas, 2002; Raine, 2003; Raine et al., 1990; Wadsworth, 1976). Nevertheless, most of these studies were limited to boys. Although lower than in boys, the prevalence of disruptive behavior problems in girls is not negligible (Côté et al 2001; Tremblay et al 1992), and therefore girls should also be included in this area of research. The two prospective general population studies which concerned both males and females (Moffit et al., 2001; Raine et al., 1997) relied on only one informant, whereas it is known that differences between reports of different informants, e.g. parents and children, are the rule, rather than the exception (Andrews et al 1993; Edelbrock, et al 1986; Verhulst and van der Ende 1992).

Previous studies indicated that disruptive behaviors were not only related to HR (Pine et al 1996; Raine et al 1997; Rogeness et al 1990), but also to autonomic measures that reflect fluctuations in HR (Boyce et al 2001; Mezzacappa et al 1997; Pine et al 1998). HR fluctuations can be divided into fluctuations with different frequencies. Heart rate variations in the low-frequency band (HRV LF; generally 0.04-0.14 Hz) are primarily influenced by variations in blood pressure. HRV LF would predominantly reflect sympathetic activity of the ANS in standing posture, whereas in supine posture vagal effects would predominate. HRV measured in the high frequency band (HRV HF; 0.15-0.40 Hz), often called respiratory sinus arrhythmia (RSA), is primarily respiratory in origin, and would be vagally mediated (Mezzacappa et al 1997). In addition to HR, HRV LF, and RSA, baroreflex sensitivity (BRS), which plays a role in short-term blood pressure regulation, is a well-known indicator of autonomic regulation that has been associated with psychopathology (Allen et al 2000; Watkins et al 1999). Although, these measures have been associated to psychopathology in cross-sectional studies, they have not often been studied prospectively yet. We know of only one study that prospectively examined the association between disruptive behaviors and autonomic measures other than HR (Mezzacappa et a 1997). Mezzacappa et al. (1997) found that dampened RSA was associated with disruptive behaviors from childhood through adolescence. Because disruptive behaviors were assessed yearly from age 10 to age 15, and RSA only at age 15, it was not clear if lower RSA was a predictor or an outcome of disruptive behaviors. Furthermore, Mezzacappa's study concerned only boys.

We aimed to extend existing knowledge by examining whether autonomic nervous system functioning, assessed by HR, HRV LF, RSA and BRS, predicts disruptive behaviors in boys and girls from the general population. Another topic that has not been taken into account sufficiently in previous studies is the role of anxiety. According to the fearlessness-

theory, children and adolescents who score low on anxiety and high on disruptive problems, are most likely to experience low arousal levels. Therefore, in the present study all analyses were adjusted for Anxiety Problems.

Methods

Sample and procedure

The present study was part of the TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS is a prospective cohort study of Dutch young adolescents, who were 10 to 13 years old at the first assessment wave (wave 1), which took place in 2001-2002. They were re-assessed two years later in 2003-2004 (wave 2). The target sample consisted of young adolescents from five municipalities in the North of the Netherlands, including both urban and rural areas. Of all eligible individuals (N=2,935), 76.0% participated in the study (N=2,230, mean age 11.09 years, SD .55, 50.8% girls). Participants did not differ from those who refused with respect to the proportion of single parent families, the prevalence of teacher-rated problem behavior, several socio-demographic variables, and mental health outcomes (De Winter et al., 2005).

At wave 2, information was obtained from 2,149 (96.4%) of those who participated at wave 1 (mean age 13.56 years, SD .53, 51.0% girls). Two questionnaires were used at wave 1 and wave 2 to assess disruptive behaviors; the Child Behavior Checklist (CBCL) and the Youth-Self Report (YSR). The CBCL was available at both assessment waves for 1,765 individuals and the YSR for 1,941 individuals. Furthermore, at wave 1, autonomic nervous system functioning, assessed by HR, HRV LF, RSA, and BRS, was determined for 1,868 individuals, of whom 841 were excluded because their measurements were regarded unsuitable (e.g. adequate signal recording failed, or measurements were shorter than 100 seconds; Dietrich et al 2006). There were 1,027 boys and girls (47% vs 53%, mean age 11.0 years, SD=.50) for whom reliable HR, HRV LF, RSA, and BRS could be computed via measurements in supine and standing position. This resulted in 766 individuals for whom wave 1 and wave 2 CBCL's and YSR's, and reliable wave 1 autonomic measures were available.

To examine possible selective attrition a stepwise logistic regression analysis was performed with 'all information available' as a dependent variable and age, gender, social-economic-status (SES), HR in supine and standing posture, and wave 1 scores on the CBCL and YSR OD and CD Problems (see below) scales as predictors. Low SES predicted attrition, whereas the other predictors did not. The effect size of the entire model was very small (Cox and Snell R^2=.6%).

Written consent was obtained from the children's parents. The study was approved by the Central Dutch Medical Ethics Committee.

Questionnaires

Disruptive behaviors were assessed with the Child Behavior Checklist/4-18 (CBCL; Achenbach, 1991a), and the Youth Self-Report (YSR; Achenbach, 1991b).

The Child Behavior Checklist (CBCL) is a parent questionnaire for assessing problems in 4- to 18-year-olds. The Youth Self-Report (YSR) is a self-report questionnaire that was modeled on the CBCL. The questionnaires contain respectively 113 and 112 items on behavioral or emotional problems in the past six months. The response format is 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The good reliability and validity of the American version of the CBCL and YSR were confirmed for the Dutch translations (De Groot et al., 1994; Verhulst et al., 1996; Verhulst et al., 1997). The original empirical syndrome scales for the CBCL and the YSR were based on multivariate statistical analysis on data from large samples. To fit more closely to the clinical-diagnostic approach,

represented by the DSM (APA, 1994), new DSM-IV scales were constructed for the CBCL and its derivatives (Achenbach and Dumenci, 2001; Achenbach et al., 2003). In the present study we used the DSM-IV scales Anxiety Problems, Oppositional Defiant (OD) Problems, and Conduct (CD) Problems. A confirmatory factor analyses proved the good fit of these scales (Sondeijker et al., 2005).

Autonomic measures

HR and blood pressure (BP) measurements took place in a quiet room at school, one child at a time. First, participants were asked to lie down and not to move or talk. While supine, the procedure was explained to them, a cuff was fixed around the middle phalanx of the third finger of the right hand to non-invasively measure spontaneous fluctuations in continuous beat-to-beat systolic finger BP using the Portapres device (FMS Finapres Medical Systems BV, Amsterdam, the Netherlands). A three-lead electrocardiogram was applied to register HR. Recordings did not start until participants had a few minutes of supine rest and signals were stabilized. Then, HR and BP signals were registered for 4 minutes in supine position during spontaneous breathing, followed by 2 minutes in standing position, again after signals had stabilized. Recordings were digitized (sample rate 100Hz, using a DAS-12 data acquisition card for notebooks, Keithley Instruments, Cleveland, Ohio, USA) and stored on hard disk for off-line analysis. Internal reliability of the data has been reported in a previous study (Dietrich et al., 2006).

HR was calculated as 60,000/mean interbeat-interval (IBI), expressed in beats per minute (bpm). Calculation of HRV LF, RSA, and BRS was performed by spectral analysis in the CARSPAN software program using the transfer function technique as previously described (Robbe et al., 1987). CARSPAN allows for discrete Fourier transformation of non-equidistant systolic BP and IBI-series. The analyzed time series were corrected for artifacts.

HR fluctuations can be divided in fluctuations with different frequencies. HR variations in the low-frequency band (LF; generally .04-.14 Hz) are primarily influenced by variations in BP. HRV LF is described in literature as predominantly sympathetically mediated in standing posture, whereas in supine posture vagal effects would predominate. HRV measured in the high frequency band (HF; .15-.40 Hz), often called respiratory sinus arrhythmia (RSA), is described as primarily respiratory in origin, and vagally mediated (Mezzacappa et al., 1997).

BRS, a well-known indicator of autonomic regulation that has been associated with psychopathology previously (Allen et al., 2000; Watkins et al., 1999), reflects both vagal and sympathetic influences. However, BRS in supine posture would primarily reflect vagal control, because sympathetic influences are minimal in resting condition (Allen et al., 2000; Pomeranz et al., 1985). BRS was defined as the mean modulus between systolic BP and IBI in the .07-.14 Hz frequency band (ms/mmHg) with a coherence of more than .3. A coherence level of .3 was comparable to the frequently used level of .5 (Dietrich et al., 2006).

Statistical analyses

To investigate whether autonomic measures predicted future disruptive behaviors, regression analyses were performed with the CBCL scale OD Problems at wave 2 as the dependent variable and wave 1 HR in supine posture as an independent variable. To adjust for possible effects of gender, age, and anxiety, these variables were added to the model as independent variables. In order to examine the direction of the associations, we corrected for wave 1 CBCL scale OD Problems. Similar analyses were conducted with supine measures of HRV LF, RSA, and BRS as independent variables. Similar analyses as for OD Problems were performed with wave 2 scores on the CBCL scale CD Problems, YSR scale OD Problems,

and YSR scale CD Problems as dependent variable. All analyses were repeated for the autonomic measures in standing posture.

Preliminary analyses indicated that there were no significant main effects or interactions for Body Mass Index and pubertal stage. Hence, these factors were not considered in further analyses.

Results

Results of the linear regression analyses with wave 2 CBCL scales OD Problems and CD Problems as dependent variables and autonomic measures as predictors are presented in Table 6-1.

Table 6-1. Standardized betas and effect sizes for associations between CBCL OD and CD Problems scores and autonomic measures.

	CBCL OD Problems			CBCL CD Problems		
	ß	p	R^2	ß	p	R^2
HR supine	.017	.57	-	-.033	.26	-
HR standing	.030	.30	-	-.024	.40	-
HRV supine	-.035	.23	-	.016	.57	-
HRV standing	-.065	.03	.4%	-.026	.36	-
RSA supine	.000	.99	-	.060	.04	.4%
RSA standing	-.057	.05	.3%	-.001	.98	-
BRS supine	-.011	.70	-	.050	.08	-
BRS standing	-.046	.11	-	-.010	.72	-

Note. Betas are standardized betas. Effect sizes (R^2) are reported for significant effects only. CBCL = Child Behavior Checklist; OD = Oppositional Defiant; CD = Conduct Disorder; HR = heart rate; HRV = Heart rate variability; RSA = respiratory sinus arrhythmia; BRS = baroreflex sensitivity.

HRV LF in standing posture, a predominantly sympathetic measure, predicted parent-reported OD Problems. The lower HRV LF was in 10- to 13-year-olds, the more OD Problems were present two years later (explained variance = .4%). RSA in standing posture, described as a largely vagally mediated measure, also predicted parent reported OD Problems. The lower RSA in 10- to 13-year-olds, the higher parent reported OD Problems scores were two years later (explained variance = .3%). RSA in supine posture, which is described as an index for vagal activity, predicted parent-reported CD Problems. The higher RSA was in 10- to 13-year-olds, the more CD Problems were present two years later (explained variance = .4%).

In Table 6-2 the results of the linear regression analyses with wave 2 YSR scales OD Problems and CD Problems as dependent variables and the autonomic measures as predictors are presented.

Table 6-2. Standardized betas and effect sizes for associations between YSR OD and CD Problems scores and autonomic measures.

	YSR OD Problems			YSR CD Problems		
	ß	p	R^2	ß	p	R^2
HR supine	.016	.63	-	-.023	.49	-
HR standing	.045	.18	-	-.018	.58	-
HRV supine	-.016	.64	-	.057	.09	-
HRV standing	-.050	.14	-	-.016	.63	-
RSA supine	.014	.67	-	.067	.04	.4%
RSA standing	-.044	.19	-	.004	.90	-
BRS supine	-.018	.59	-	.019	.57	-
BRS standing	-.050	.14	-	-.013	.70	-

Note. Betas are standardized betas. Effect sizes (R^2) are reported for significant effects only. YSR = Youth Self Report; OD = Oppositional Defiant; CD = Conduct Disorder; HR = heart rate; HRV = Heart rate variability; RSA = respiratory sinus arrhythmia; BRS = baroreflex sensitivity.

The autonomic measures HR, HRV LF, RSA, and BRS did not predict self-reported OD Problems. However, a higher RSA in supine posture in 10- to 13-year-olds, predicted self reported CD Problems two years later (explained variance = .4%).

Discussion

According to previous studies low resting HR is a predictor for disruptive behavior problems (Farrington, 1997; Kriscunas, 2002; Moffit et al., 2001; Raine, 2003; Raine et al., 1997; Raine et al., 1990; Wadsworth, 1976). Associations between other measures of autonomic nervous system activity such as HRV LF, RSA, and BRS and disruptive behaviors have been investigated in cross-sectional studies (Allen at al., 2000; Mezzacappa et al., 1997), but seldom longitudinally. In the present prospective study, which concerned both males and females, used parent-reports and self-reports, and besides HR also used HRV LF, RSA, and BRS as measures for autonomic nervous system activity, HR did not predict OD or CD Problems. In our previous, cross-sectional study HR was also not directly associated with OD or CD Problems. However, lower HR in supine posture was associated with lower scores on the interaction variable YSR CD Problems x Anxiety Problems (explained variance = .6%); lower HR in standing posture was associated with lower scores on the interaction variable YSR OD Problems x Anxiety Problems (explained variance = .3%); and lower HR in standing posture was associated with lower scores on the interaction variable YSR CD Problems x Anxiety Problems (explained variance = 1.2%). In this prospective study we also found a number of other predictors than HR.

OD Problems

Low HRV LF in standing position predicted parent-reported OD Problems. Since HRV LF in standing posture would mainly reflect sympathetic activity, this finding might indicate that reduced sympathetic activity predicts OD Problems two years later. Reductions in HR in children with disruptive behaviors can arise from enhanced vagal activation or from reduced sympathetic activation (Guyton, 1986). Hence, reduced activity in the sympathetic branch of the autonomic nervous system is what we expected to find based on the arousal theories

(Raine, 1993, 1996; Zuckerman and Neeb, 1979). That we did not find reduced HR in combination with reduced sympathetic activation, could indicate that there is some kind of parasympathetic antithesis.

Low RSA in standing posture, that would predominantly reflect vagal activity, predicted OD Problems as well. In other words, besides reduces sympathetic activity, diminished vagal activity also predicted OD Problems. Theoretically, diminished vagal activity is associated with an increase in HR instead of a decrease. Probably this is the antithesis we were looking for. Because sympathetic and vagal activity have opposite effects on HR (Guyton, 1986), the combination of decreased sympathetic and decreased parasympathetic activity in those who were at risk for future OD Problems may have resulted in heart rates that were similar to heart rates in those who were not at risk for OD Problems. Although a similar HR, different sympathetic and parasympathetic activity, and thereby a different physiological balance, maybe present already in individuals at risk.

The finding that both sympathetic and vagal activity are decreased in adolescents at risk for parent-reported OD Problems, may indicate that both the branches of the autonomic nervous system are dampened equally in these individuals. Hypothetically, this could, for example, be due to stressful conditions in pre- or postnatal life, or to genetic factors (Van Goozen et al., 2000). However, if such factors would play a role in individuals at risk for OD Problems, decreased BRS values which would indicate decreased flexibility in the regulation of the autonomic nervous system, might also be expected (Virtanen et al., 2003). Since we did not find significant lower BRS values in adolescents at risk for OD Problems, a theory of general damage to the autonomic nervous system is not tenable.

CD Problems

High RSA in supine posture predicted parent-reported and self-reported future CD Problems, indicating increased vagal activity in adolescents at risk. Increased vagal activity results in a lower HR (Guyton, 1986; Mezzacappa et al., 1997), which is often found in children and adolescents with CD Problems (Ortiz and Raine, 2004). Therefore, this finding is in accordance with previous evidence (Raine, 1993,1996; Zuckerman and Neeb, 1979). It remains unclear why decreased HR did not predict CD problems. Perhaps, changes in activity of one of the branches of the autonomic nervous system have to be persistent before influencing baseline HR. Another possibility would be that there is a sympathetic antithesis that we did not include in our analysis, for example blood pressure variability in the low frequency band (BPV LF; Zhong et al, 2005) or pre-ejection period (PEP; Boyce et al, 2001; Schachinger et al, 2001).

OD versus CD Problems

In contrast with numerous previous studies (Farrington, 1997; Kriscunas, 2002; Moffit et al., 2001; Raine, 2003; Raine et al., 1997; Raine et al., 1990; Wadsworth, 1976), HR does not seem to be a good predictor for both OD and CD Problems in the general Dutch population. The same can be said of BRS. Our findings regarding HR, which like BRS is a balance measure of the ANS, and disruptive behaviors were not in accordance with the meta-analysis from Ortiz and Raine (2004). Based on their meta-analysis, these authors concluded that HR is the best replicated biological correlate of antisocial behavior in children and adolescents. It is hard to offer a reasonable explanation for the differences between our findings and theirs, especially because Ortiz and Raine (2004) demonstrated that the association between HR and disruptive problems was not moderated by gender, age, method of recording, use of a psychiatric control group, recruitment source, concurrent versus prospective nature of testing, and source of behavioral rating.

Still, on he other hand, HRV LF and RSA predicted OD and CD Problems. The debate regarding whether it is useful to discern OD Problems and CD Problems in a general population sample is unresolved (Rey et al., 1988; Werry et al., 1987). Remarkably, in the present study, a different physiological balance was present in children at risk for OD Problems than in children at risk for CD Problems. This could imply that, based on autonomic nervous system functioning, it is useful to distinguish OD and CD Problems because they might have a different etiology.

Multiple Informants

In the present study parent-reports and self-reports were used to measure OD and CD Problems because it is known that differences between reports of different informants are the rule rather than the exception (Andrews et al., 1993; Rubio-Stipec et al., 2003). The findings for CD Problems were similar for parent-reports and self-reports, whereas for OD Problems only parent-reports seemed to be important. Since our results indicated that analyses based on parent-reports might yield different results than analyses based on self-reports, we conclude that, although it is not common, it is important to use multiple informants in this kind of research.

Limitations

First, data were not collected in a laboratory situation, but in schools. This resulted in a less standardized way of collecting the data, but may also have been a strength of this study, because children were in a familiar environment, which is less stressful than a laboratory. On the other hand, collection of cardiovascular measures in a lab would probably have resulted in higher reliability of the data. This indicates that the findings of the present study may represent an underestimation of the associations between autonomic nervous system functioning and disruptive behaviors. Nevertheless, Ortiz and Raine (2004) postulated that method of recording does not moderate the relationship between HR and disruptive behaviors. Second, although the autonomic measures we used in the present study have been described as indices of vagal or sympathetic activity, it is not entirely correct to assume a one-to-one relation between HRV LF or RSA and activity of only one single branch of the autonomic nervous system (Salomon et al., 2000). In future research we should therefore focus more on combinations of autonomic measures that can give us information about physiological balance (Van Roon et al, 2004). Third, we can not rule out the problem of multiple testing. However, using several measures for autonomic nervous system activity, and not only HR, shed more light on the relation between autonomic functioning and future disruptive problems. If we had not used all these other measures, we would not have been able to find out that while their HR was equal, the physiological balance in children at risk for disruptive problems is different from those not at risk.

Practical implications

Based on our results we conclude that basal HR and BRS can not be used to detect young Dutch adolescents who are at risk for future disruptive behaviors in the general population. Further, although HRV LF and RSA seem to indicate a certain risk, explained variances were small, which indicates that these measures will presumably not be useful predictors in real life either.

Apart from the possible explanations mentioned above, it is also possible that autonomic nervous system functioning in itself is not a predictor for OD or CD Problems, but that, in combination with other factors, such as socio-economic status, parental rearing practices, early adversities, or adverse peer relationships, diminished autonomic nervous system functioning may become more important. This is not entirely unlikely, given the

growing knowledge about the importance of interactions between biological/individual factors and environmental influences (Moffit et al., 2005; Rutter and Silberg, 2002).

Chapter 7

General discussion

GENERAL DISCUSSION

In this thesis it was investigated whether distinct constructs of ADH Problems, OD Problems, and CD Problems should be used to describe disruptive behaviors in young adolescents from the general population. Furthermore, it was examined whether neuroendocrine and autonomic measures are associated with disruptive behaviors in young adolescents. In the current chapter the main findings and conclusions of the study will be presented and discussed.

Discerning ADH, OD, and CD Problems

The question was raised whether it is useful to distinguish ADH, OD, and CD Problems (APA 1994) from one another. Results of latent class analyses indicated that discerning these separate types of disruptive behaviors is not useful from a taxonomic perspective. These findings contrasted with studies that assessed differences in biological correlates of ADH, OD, and CD Problems (Herpertz et al 2001). Hence, while at the level of observable behaviors, ADH, OD, and CD problems did not seem to be useful as separate constructs, differences at a biological level may still be present.

Although not very convincing because of the small effect sizes, some biological differences between ADH, OD, and CD Problems were found in the present study as well. With regard to HPA-axis functioning, it was found that cortisol levels were associated with ADH Problems and not with OD or CD Problems. This might indicate that, despite high comorbidity rates between attention problems and aggressive or delinquent behaviors (Angold et al 1999), the biological antecedents or consequences of these different types of behavior problems may not be similar. Based on the associations that were found between ANS activity and disruptive behaviors, it can be speculated that there are differences in psychophysiological balance between OD and CD Problems. For instance, OD problems were associated with lower RSA, whereas CD Problems were associated with higher RSA. This could imply that, based on ANS functioning, it is useful to distinguish OD and CD Problems because they might have a different etiology.

Predicting future disruptive behaviors

Theoretically, low levels of arousal of the central nervous system (Chrousos and Gold 1998; Van Goozen et al 2000) would predispose to disruptive behaviors. According to the stimulation-seeking theory (Eysenck 1964; Quay 1965; Raine 1993; Zuckerman and Neeb 1979), low arousal represents an unpleasant physiological condition. To attain a higher, more pleasant level of arousal, individuals would seek stimulation by becoming aggressive or delinquent. According to the fearlessness theory, a low tendency to become aroused in response to fearful stimuli would result in a higher likelihood to become disruptive (Raine 1993).

Previous studies indicated that HPA-axis activity and ANS activity may be associated with future disruptive behavior problems in children and adolescents (e.g. Vanyukov et al 1993; Van Goozen et al 1998; Mc Burnett et al 2000; Pajer et al 2001; Shoal et al 2003; Van de Wiel et al 2004; Scerbo and Kolko 1994; Ortiz and Raine 2004; Mezzacappa et al 1997; Allen et al 2000). However, the findings of the present thesis indicated that HPA-axis activity and ANS functioning are only weak predictors of future disruptive behaviors in adolescents from the Dutch general population, if at all. The effect sizes of all our findings were small (explained variance between .3% and 2.6%).

Low HPA-axis activity in the sample as a whole did not predict future disruptive behaviors. However, in those with high levels of disruptive behaviors at the first assessment wave of the study, low morning cortisol levels predicted future behavior problems as

indicated by self-reports. Hence, the results suggest that low HPA-axis activity is not a good predictor for disruptive behaviors, but could be valuable to identify those with a poor prognosis, once disruptive behaviors are present in pre-adolescence. These findings corroborated results of some previous studies (McBurnett et al 2000; Shoal et al 2003). Low cortisol levels predicted a poor prognosis, only in case disruptive problems were already present. This might imply that low HPA-axis activity is a consequence of persistent behavior problems, instead of a cause (Gunnar & Vazquez 2001). This may also explain why, in referred samples, associations between HPA-axis activity and disruptive behaviors are being found more often.

It has been put forward that ANS activity, measured by heart rate (HR), can be used to identify children and adolescents at risk for disruptive behaviors (Ortiz and Raine 2004). The finding that low resting HR is associated with future disruptive behaviors has been replicated a number of times in clinical and general population samples (Farrington 1997; Kriscunas 2002; Raine 2003; Raine et al 1990; Wadsworth 1976). In contrast to these studies, the findings of the present thesis suggested that HR is not a good predictor for disruptive problems in the general Dutch population. Some previous studies indicated that BRS, another measure that reflects the balance between sympathetic and vagal activity, might be a valuable predictor of future disruptive behaviors (Allen et al 2000; Watkins et al 1999). This, however, was not confirmed by the present study as well. On the contrary, HRV LF and RSA did seem to indicate a certain risk for future disruptive problems. Nevertheless, explained variances were small.

Limitations

Since, limitations of this study were extensively discussed in chapters 2 to 6, they will not be repeated in this general discussion.

Implications and suggestions for future research

Much is already known about disruptive behaviors in children and adolescents. Disruptive behavior problems are common, have a negative impact on families, schools, and communities, predict delinquency and substance abuse in adulthood (e.g., Fergusson et al 1997; Frick et al 1993; Loeber 1982; Moffitt et al 1996, 2002; Nagin and Tremblay 1999; Robbins 1966), and although it is clear that disruptive behaviors are influenced by familial, situational, and societal factors, increasing evidence suggests that genetic and other biological processes are involved in the development of disruptive problems (Brunner et al 1993; Caspi et al 2002; Coccaro et al 1996; Kruesi et al 1992). The present study provided some information regarding the role of biological systems that become active in case of stressful experiences and disruptive behaviors. Unfortunately, effect sizes were generally small, which indicated that practical applications of the knowledge yielded by the present study are limited. The measures used to assess HPA-axis and ANS activity in the present study are not useful to identify those who are at risk for disruptive behaviors. However, this thesis contributes to existing knowledge about disruptive behaviors in a way that we did not expect in advance. The findings indicated that the arousal theories, which are widely used dogmas, may be valuable in clinical or high risk groups, but not at the level of the general population. Based on the results some suggestions for future research can be formulated. Considering the limited number of significant findings and the small effect sizes, it can be questioned whether the HPA-axis and the ANS, should be included in future research as independent predictors. First, the way these two systems interact among each other and the way this might put children at risk for disruptive behavior problems might deserve more attention (Bauer et al2002). Furthermore, it is possible that studying the activity of the HPA-axis or ANS, in combination with other factors, such as socio-economic status, parental rearing practices, early adversities,

or adverse peer relationships, might yield more powerful predictors of disruptive behaviors. This is not unlikely, given the expanding knowledge about the importance of interactions between biological factors and environmental influences (Moffit et al 2005; Rutter and Silberg 2002). Hence, future research studying interactive models is needed.

References

References

Aardal E, Holm AC (1995). Cortisol in saliva - Reference ranges and relation to cortisol in serum. *European Journal of Clinical Chemistry and Clinical Biochemistry, 33,* 927-932.

Abikoff H, Klein RG (1992). Attention-deficit hyperactivity and conduct disorder: comorbidity and implications for treatment. *Journal of Consulting and Clinical Psychology, 60*, 881-892

Achenbach TM (1991a). *Manual for the Child Behavior Checklist/4-18 and 1991 Child Profile.* Burlington, Vermont: University of Vermont, Department of Psychiatry.

Achenbach TM (1991b). *Manual for the Youth Self-Report and 1991 Profiles*. Burlington, VT: University of Vermont Department of Psychiatry.

Achenbach TM, Dumenci L (2001). Advances in empirically based assessment: Revised cross-informant syndromes and new DSM-oriented scales for the CBCL, YSR, and TRF: Comment on Lengua, Sadowski, Friedrich, and Fisher (2001). *Journal of Consulting and Clinical Psychology, 69*, 699-702.

Achenbach TM, Dumenci L, Rescorla LA (2003). DSM-oriented and empirically based approaches to constructing scales from the same item pools. *Journal of Clinical Child and Adolescent Psychology, 32*, 328-340.

Allen MT, Matthews KA, Kenyon KL (2000). The relationships of resting baroreflex sensitivity, heart rate variability and measures of impulse control in children and adolescents. *International Journal of Psychophysiology, 37*, 185-194.

Andrews VC, Garrison CZ, Jackson KL, Addy CL, McKeown RE (1993). Mother-adolescent agreement on the symptoms and diagnoses of adolescent depression and conduct disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*, 731-738.

Angold A, Costello EJ, Erkanli A (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*, 57-87.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.* Washington D.C.: American Psychiatric Association.

Barkley RA, DuPaul GJ, McMurray MB (1991). Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics, 87,* 519-531.

Bartels M, de Geus EJ, Kirschbaum C, Sluyter C, Boomsma DI (2003). Heritability of daytime cortisol levels in children. *Behavioral Genetics, 33*, 421-433.

Bauer AM, Quas JA, Boyce WT (2002). Associations between physiological reactivity and children's behavior: advantages of a multisystem approach. *Developmental and Behavioral Pediatrics, 23,* 102-112.

Beauchaine TP, Katkin ES, Strassberg Z, Snarr J. (2001). Disinhibitory psychopathology in male adolescents: discriminating conduct disorder from attention-deficit/hyperactivity disorder through concurrent assessment of multiple autonomic states. *Journal of Abnormal Psychology*, *110*, 610-624.

Berkson J (1946). Limitations of the application of fourfold table analysis to hospital data. *Biometrics, 2,* 47-53.

Boyce WT, Quas J, Alkon A, Smider NA, Essex MJ, Kupfer DJ (2001). Autonomic reactivity and psychopathology in middle childhood. *British Journal of Psychiatry*, *179*, 144-150.

Brooks-Gunn J, Warren MP, Rosso J, Gargiulo J (1987). Validity of self-report measures of girls' pubertal status. *Child Development, 58*,829-841.

Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA (1993). Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science*, *262*, 578-580.

Burgess LH, Handa RJ (1992). Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats. *Endocrinology*, *131*, 1261-1269.

Calogero AE, Bernardini R, Gold PW, Chrousos GP (1988). Regulation of rat hypothalamic corticotropin-releasing hormone secretion in vitro: potential clinical implications. *Advances in Experimental Medicine and Biology, 245*, 167-181.

Caspi A, McClay J, Moffit TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297,* 851-854.

Chrousos GP, Gold PW (1998). EDITORIAL: A Healthy Body in a Healthy Mind—and Vice Versa—The Damaging Power of "Uncontrollable" Stress. *Journal of Clinical Endocrinology and Metabolism, 83*, 1842-1845.

Coccaro EF, Kavoussi RJ, Sheline YI, Lish JD, Csernansky JG (1996). Impulsive aggression in personality disorder correlates with tritiated paroxetine binding in the platelet. *Archives of General Psychiatry, 53*, 531-536.

Coie J, Dodge K (1998). Aggression and antisocial behavior.

Cole PM, Zahn-Waxler C, Fox NA, Usher BA, Welsh JD (1996). Individual differences in emotion regulation and behavior problems in preschool children. *Journal of Abnormal Psychology*, *105*, 518-529.

Côté S, Tremblay RE, Nagin DS, Zoccolillo M, Vitaro F (2002). Childhood behavioral profiles leading to adolescent conduct disorder: risk trajectories for boys and girls. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*, 1086-1094.

Côté S, Zoccolillo M, Tremblay RE, Nagin DS, Vitaro F (2001). Predicting girls' conduct disorder in adolescence from childhood trajectories of disruptive behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry, 40***,** 678-684.

Cupps TR, Fauci AS (1982). Corticosteroid-mediated immunoregulation in man. *Immunology Review*, *65*, 133-155.

Dabbs JM, Jurkovic GJ, Frady RL (1991). Salivary testosterone and cortisol among late adolescent male offenders. *Journal of Abnormal Child Psychology, 19*, 469-478.

Dayton CM, Macready GB (1988). Concomitant variable latent class models. *Journal of the American Statistical Association, 83*, 173-178.

Deater-Deckard K, Dodge KA, Bates JE, Pettit GS (1998). Multiple risk factors in the development of externalizing behavior problems: Group and individual differences. *Development and Psychopathology, 10*, 469-493.

De Boeck G, Alsop D, Wood C (2001). Cortisol effects on aerobic and anaerobic metabolism, nitrogen excretion, and whole-body composition in juvenile rainbow trout. *Physiological and Biochemical Zoology, 74*, 858-868.

De Groot A, Koot HM, Verhulst FC (1994). The cross-cultural generalizability of the CBCL cross-informant syndromes. *Psychological Assessment, 6*, 225-230.

De Groot A, Koot HM, Verhulst FC (1996). Cross-cultural generalizability of the Youth Self-Report and Teacher's Report Form cross-informant syndromes. *Journal of Abnormal Child Psychology, 24*, 651-664.

De Winter AF, Oldehinkel AJ, Veenstra R, Brunnekreef JA, Verhulst FC, Ormel J (2005). Evaluation of nonresponse bias in mental health determinants and outcomes in a large sample of preadolescents. *European Journal of Epidemiology, 2*, 173-181.

Dietrich A, Riese H, Van Roon AM, Van Engelen K, Neeleman J, Rosmalen JGM (2006). Spontaneous baroreflex sensitivity in (pre)adolescents. *Journal of Hypertension*, *24*, 345-352.

Dorn L, Susman E, Nottelman E, Inoff-Germain E, Chrousos G. (1990). Perceptions of puberty: Adolescent, parent, and health care personnel. *Developmental Psychopathology, 26*, 322-329.

Edelbrock C, Costello AJ, Dulcan MK, Conover NC, Kala R (1986). Parent-child agreement on child psychiatric symptoms assessed via structured interview. *Journal of Child Psychology and Psychiatry, 27*, 181-190.

Eysenck H (1964). *Crime and Personality*. London: Methuen.

Farrington DP (1993). Childhood origins of teenage antisocial behavior and adult social dysfunction. *Journal of the Royal Society for Medicine, 86,* 13-17.

Farrington DP (1997). *The relationship between low resting heart rate and violence.* In: Raine A, Brennan P, Farrington DP, Mednick SA, eds. Biosocial bases of violence, New York: Plenum, 89-106.

Fergusson DM, Horwood LJ, Lynsky MT (1994). Structure of DSM-III-R criteria for disruptive childhood behaviors: confirmatory factor models. *Journal of the American Academy for Child and Adolescent Psychiatry, 33,* 1145-1157.

Fergusson DM, Lynskey M, Horwood LJ (1997). Attentional difficulties in middle childhood and psychosocial outcomes in young adulthood. *Journal of Child Psychology and Psychiatry, 38*, 633-644.

Freeman D, Garety PA, Bebbington PE, Smith B, Rollinson R, Fowler D, Kuipers E, Ray K, Dunn G (2005). Psychological investigation of the structure of paranoia in a non-clinical population. *British Journal of Psychiatry, 186,* 427-435.

Frick PJ (2001). Effective interventions for children and adolescents with conduct disorder. *Canadian Journal of Psychiatry, 46,* 597-608.

Frick PJ, Lahey BB, Loeber R, Tannenbaum L, Van Horn Y, Christ MAG, et al (1993). Oppositional defiant disorder and conduct disorder: A meta-analytic review of factor analyses and cross-validation in a clinic sample. *Clinical Psychology Review*, *13*, 319-340.

Gunnar MR, Morison SJ, Chisholm K, Schuder M (2001). Salivary cortisol levels in children adopted from Romanian orphanages. *Development and Psychopathology, 13*, 611-628.

Gunnar MR, Vazquez DM (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology, 13*, 515-538.

Guyton AC (1986). *Arterial pressure regulation: Rapid pressure controle by nervous reflexes and other mechanisms*. In: Guyton AC, eds. Textbook of medical physiology. Philadelphia: WB Saunders Company; 244-256.

Handa RJ, Burgess LH, Kerr JE, O'Keefe JA (1994). Gonadal steroid hormone receptors and sex differences in the hypothalamo-pituitary-adrenal axis. *Hormonal Behavior, 28*, 464-476.

Herpertz SC, Wenning B, Mueller B, Qunaibi M, Sass H, Herpertz-Dahlmann B (2001). Psychophysiological responses in ADHD children with and without conduct disorder – implications for adult antisocial behavior. *Journal of the American Academy for Child and Adolescent Psychiatry, 40,* 1222-1230.

Hinshaw SP (2002). Process, mechanism, and explanation related to externalizing behavior in developmental psychopathology. *Journal of Abnormal Child Psychology, 30*, 431-446.

Hudziak JJ, Heath AC, Madden PF, Reich W, Slutske W, Bierut LJ, Neuman RJ, Todd RD (1998). Latent class and factor analysis of DSM-IV ADHD: a twin study of female adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 848-857.

Jacobson L, Sapolsky R (1991). The Role of the Hippocampus in Feedback-Regulation of the Hypothalamic-Pituitary-Adrenocortical Axis. *Endocrine Reviews*, *12*, 118-134.

Jansen LMC, Gispen-de Wied CC, Jansen MA, Van der Gaag RJ, Matthys W, Van England H (1999). Pituitary adrenal reactivity in a child psychiatric population: salivary cortisol response to stressors. *Eu ropean Neuropsychopharmacology, 9,* 67-75.

Kadesjo B, Gillberg C (2001). The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry, 42*, 487-492.

Kamath MV, Fallen EL (1993). Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. *Critical Reviews in Biomedical Engineering, 21*, 245-311.

Kariyawasam SH, Zaw F, Handley SL (2003). Reduced salivary cortisol in children with comorbid attention deficit hyperactivity disorder and oppositional defiant disorder. *Neuroendocrinology Letters, 23*, 45-48.

Kass RE, Wasserman L (1995). A reference Bayesian test for nested hypotheses and its relationship to the Schwarz criterion. *Journal of the American Statistical Association, 90*, 928-634.

Keiss W, Meidert A, Dressendorfer K, Schriever K, Kessler U, Konig A, Schwarz H, Strasburger C (1995). Salivary cortisol levels throughout childhood and adolescence: Relation with age, pubertal stage, and weight. *Pediatric Research, 37*, 502-506.

King JA, Barkley RA, Barrett S (1998). Attention-deficit hyperactivity disorder and the stress response. *Biological Psychiatry, 44***,** 72-74.

Kirchheim HR (1976). Systemic arterial baroreceptor reflexes. *Physiological Review*, *56*, 100-177.

Kirschbaum C, Hellhammer DH (1994). Salivary cortisol in psychoneuroendocrine research: recent developments and applications. *Psychoneuroendocrinology, 19*, 313-333.

Klein RG, Abikoff H, Klass E, Ganeles D, Seese LM, Pollack S (1997). Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. *Archives of General Psychiatry*, *54*, 1073-1080.

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

Kolko DJ, Bokstein OG, Barron J (1999). Methylphenidate and behavior modification in children with ADHD and comorbid ODD or CD: main and incremental effects across settings. *Journal of the American Academy for Child and Adolescent Psychiatry, 38,* 578-586.

Kovac I, Merette C, Legault L, Dongier M, Palmour RM (2002). Evidence in an international sample of alcohol-dependent subjects of subgroups with specific symptom patterns of antisocial personality disorder. *Alcoholism: Clinical and Experimental Research, 26*, 1088-1096.

Kriscunas M (2002). *Teenage lower resting heart rate predicts antisocial adult behavior*. Department of Psychology, University of Southern California, Los Angeles, CA 90089.

Kruesi MJ, Hibbs ED, Zahn TP, Keysor CS, Hamburger SD, Bartko JJ, Rapoport JL (1992). A 2-year prospective follow-up study of children and adolescents with disruptive behavior disorders. Prediction by cerebrospinal fluid 5-hydroxyindoleacetic acid, homovanillic acid, and autonomic measures? *Archives of General Psychiatry, 49,* 429-435.

Lahey BB, Hart EL, Pliszka S, Applegate B, McBurnett K (1993). Neurophysiological correlates of conduct disorder: a rationale and a review of research. *Journal of Clinical Child Psychology, 22*, 141-153.

Lahey BB, Loeber R, Burke J, Rathouz PJ (2002). Adolescent outcomes of childhood conduct disorder among clinic- referred boys: Predictors of improvement. *Journal of Abnormal Child Psychology, 30*, 333-348.

Lahey BB, Loeber R, Quay HC, Frick PJ, Grimm J (1992). Oppositional defiant and conduct disorders: issues to be resolved for DSM-IV. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*, 539-546.

Leadbeater BJ, Kuperminc GP, Blatt SJ, Hertzog C (1999). A multivariate model of gender differences in adolescents' internalizing and externalizing problems. *Developmental Psychology, 35*, 1268-1282.

Loeber R (1982). The stability of antisocial and delinquent child behavior: A review. *Child Development, 53*, 1421-1446.

Loeber R, Green SM, Keenan K, Lahey BB (1995). Which boys will fare worse? Early predictors of the onset of conduct disorder in a six-year longitudinal study. *Journal of the American Academy of Child Adolescent Psychiatry, 34*, 499-509.

Loeber R, Keenan K (1994). Interaction between conduct disorder and its comorbid conditions: Effects of age and gender. *Clinical Psychology Review, 14*, 497-523.

Loeber R, Schmaling KB (1985). Empirical evidence for overt and covert patterns of antisocial conduct problems: a meta-analysis. *Journal of Abnormal Child Psychology, 13*, 337-353.

Loeber R, Stouthamer-Loeber M (1998). Development of juvenile aggression and violence. Some common misconceptions and controversies. *American Psychology, 53*, 242-259.

Maughan B, Rutter M (1998). Continuities and discontinuities in antisocial behavior from childhood to adult life. *Advances in Clinical Child Psychology, 20,* 1-47.

McBurnett K, Lahey BB (1994). Psychophysiological and neuroendocrine correlates of conduct disorder and antisocial behavior in children and adolescents. In: Fowles DC, Sutker P, Goodman S (Ed.), *Progress in Experimental Personality and Psychopathology Research.* New York, Springer Publishing Co, pp 199-232.

McBurnett K, Lahey BB, Capasso L, Loeber R (1996). Aggressive symptoms and salivary cortisol in clinic-referred boys with conduct disorder. *Understanding Aggressive Behavior in Children, 794*, 169-178.

McBurnett K, Lahey BB, Rathouz PJ, Loeber R (2000). Low salivary cortisol and persistent aggression in boys referred for disruptive behavior. *Archives of General Psychiatry, 57*, 38-43.

McBurnett K, Pfiffner LJ, Capasso L, Lahey BB, Loeber R (1997). *Children's aggression and DSM-III-R symptoms predicted by parent psychopathology, parenting practices, cortisol, and SES*. In: Raine A, Brennan PA, Farrington DP, Mednick SA (Eds). Biological Bases of Violence. Plenum Press, New York, 345-348.

McCabe KM, Hough R, Wood PA, Yeh M (2001). Childhood and adolescence onset conduct disorder: A test of the developmental taxonomy. *Journal of Abnormal Child Psychology, 29*, 305-316.

McCutcheon AL (1987). *Latent class analysis* (Vol. 64). Newbury Park: SAGE Publications.

Mezzacappa E, Tremblay RE, Kindlon D, Saul JP, Arseneault L, Seguin J, Pihl RO, Earls F (1997). Anxiety, antisocial behavior, and heart rate regulation in adolescent males. *Journal of Child Psychology and Psychiatry, 38*, 457-469.

Moffitt TE (1993). Adolescence-limited and life-course-persistent antisocial behavior: A developmental taxonomy. *Psychological Review, 100*, 674-701.

Moffit TE, Caspi A (2001). Childhood predictors differentiate life-course persistent and adolescent-limited antisocial pathways among males and females. *Development and Psychopathology*, *13*, 355-375.

Moffitt TE, Caspi A, Dickson N, Silva P, Stanton W (1996). Childhood-onset versus adolescents-onset antisocial conduct problems in males: natural history from ages 3 to 18 years. *Development and Psychopathology, 8*, 399-424.

Moffitt TE, Caspi A, Harrington H, Milne BJ (2002). Males on the life-course-persistent and adolescence-limited antisocial pathways: follow-up at age 26 years. *Developmental Psychopathology, 14*, 179-207.

Moffit TE, Caspi A, Rutter M (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry, 62*, 473-481.

Moffitt TE, Silva PA (1988). Neuropsychological deficit and self-reported delinquency in an unselected birth cohort. *Journal of the American Academy of Child and Adolescent Psychiatry, 27*, 233-240.

Moss HB, Vanyukov MM, Martin CS (1995). Salivary cortisol responses and the risk for substance abuse in prepubertal boys. *Biological Psychiatry, 38*, 547-555.

Muthén LK, Muthén BO (2000). *Mplus. Statistical Analyses with Latent Variables. User's Guide* (Version 2). Los Angeles: Muthén & Muthén.

Nagin D, Tremblay RE (1999). Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. *Child Development, 70*, 1181-1196.

Netherton C, Goodyer I, Tamplin A, Herbert J (2004). Salivary cortisol and dehydroepiandrosterone in relation to puberty and gender. *Psychoneuroendocrinology, 29*, 125-140.

Oosterlaan J, Geurts HM, Knol DL, Sergeant JA (2005). Low basal salivary cortisol is associated with teacher-reported symptoms of conduct disorder. *Psychiatry Research, 134*, 1-10.

Ortiz J, Raine A (2004). Heart rate level and antisocial behavior in children and adolescents: a meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 154-162.

Pajer K, Gardner W, Rubin RT, Perel J, Neal S (2001). Decreased cortisol levels in adolescent girls with conduct disorder. *Archives of General Psychiatry, 58*, 297-302.

Pelham WE, Hoza B, Pillow DR, Gnagy EM, Kipp HL, Greiner AR, et al (2002). Effects of methylphenidate and expectancy on children with ADHD: behavior, academic performance, and attributions in a summer treatment program and regular classroom settings. *Journal of Consulting and Clinical Psychology, 70,* 320-335.

Pine DS, Wasserman GA, Coplan J, Fried J, Sloan R, Myers M, Greenhill L, Shaffer D, Parsons B (1996). Serotonergic and cardiac correlates of aggression in children. *Annals of the New York Academy of Sciences, 794*, 391-393.

Pine DS, Wasserman GA, Miller L, Coplan JD, Bagiella E, Kovelenku P, Myers MM, Sloan RP (1998). Heart period variability and psychopathology in urban boys at risk for delinquency. *Psychophysiology*, *35*, 521-529.

Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, et al. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *American Journal of Physiology*, *248*, 151-153.

Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*, 916-931.

Pruessner JC, Wolf OT, Hellhammer DH, Buske, Kirschbaum A, vonAuer K, Jobst S, Kaspers F, Kirschbaum C (1997). Free cortisol levels after awakening: A reliable biological marker for the assessment of adrenocortical activity. *Life Sciences, 61*, 2539-2549.

Quay HC (1965). Psychopathic Personality as Pathological Stimulation-Seeking. *American Journal of Psychiatry, 122*, 180-183.

Raine A (1993). *The psychopathology of crime: Criminal behavior as a clinical disorder.* San Diego: Academic Press.

Raine A (1996). Autonomic nervous system factors underlying disinhibited, antisocial, and violent behavior. Biosocial perspectives and treatment implications. *Annals of the New York Academy of Sciences, 794*, 46-59.

Raine A (2002). Annotation: the role of prefrontal deficits, low autonomic arousal, and early health factors in the development of antisocial and aggressive behavior in children. *Journal of Child Psychology and Psychiatry, 43*, 417-434.

Raine A (2003). *Resting heart rate and life-course persistent antisocial behavior*. Department of Psychology, University of Southern California, Los Angeles, CA 90089.

Raine A, Venables PH, Mednick SA(1997). Low resting heart rate at age 3 years predisposes to aggression at age 11 years: evidence from the Mauritius Child Health Project. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 1457-1464.

Raine A, Venables PH, Williams M (1990). Relationships between central and autonomic measures of arousal at age 15 years and criminality at age 24 years. *Archives of General Psychiatry*, *47*, 1003-1007.

Rask E, Walker B, Soderberg S, Livingstone D, Eliasson M, Johnson O, Andrew R, Olsson T (2002). Tissue-specific changes in peripheral cortisol metabolism on obese women: Increased adipose 11B-hydroxysteroid dehydrogenase type 1 activity. *Journal of Clinical Endocrinology and Metabolism, 87,* 3330-3336.

Rey JM, Bashir MR, Richards IN, Plapp JM, Stewart GW (1988). Oppositional disorder: fact or fiction? *Journal of the American Academy of Child and Adolescent Psychiatry, 27,* 157-162.

Robbe HW, Mulder LJ, Ruddel H, Langewitz WA, Veldman JB, Mulder G (1987). Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension, 10,* 538-543.

Robbins L (1966). *Deviant children grown up.* Baltimore: Williams & Wilkins.

Rogeness GA, Cepeda C, Macedo CA, Fischer C, Harris WR (1990). Differences in heart rate and blood pressure in children with conduct disorder, major depression, and separation anxiety. *Psychiatry Research*, *33*, 199-206.

Rosmalen JGM, Oldehinkel AJ, Ormel J, De Winter AF, Buitelaar JK, Verhulst FC (2005). Determinants of salivary cortisol levels in 10-12 year old children; a population-based study of individual differences. *Psychoneuroendocrinology, 5,* 483-495.

Roy BN, Reid RL, Van Vugt DA (1999). The effects of estrogen and progesterone on corticotropin-releasing hormone and arginine vasopressin messenger ribonucleic acid levels in the paraventricular nucleus and supraoptic nucleus of the rhesus monkey. *Endocrinology, 140*, 2191-2198.

Rubio-Stipec M, Fitzmaurice G, Murphy J, Walker A (2003). The use of multiple informants in identifying the risk factors of depressive and disruptive disorders. *Social Psychiatry and Psychiatric Epidemiology*, *35*, 51-58.

Rutter M, Giller H, Hagell A (1998). *Antisocial behavior by young people.* Cambridge: Cambridge Uneversity Press.

Rutter M, Silberg J (2002). Gene-environment interplay in relation to emotional and behavioral disturbance. *Annual Review of Psychology, 53*, 463-490.

Salomon K, Matthews KA, Allen MT (2000). Patterns of sympathetic and parasympathetic activity in a sample of children and adolescents. *Psychophysiology*, *37*, 842-849.

Sapolsky RM, Krey LC, McEwen BS (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews, 7,* 284-301.

Sapolsky RM, Romero LM, Munck AU, (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21,* 55-89.

Sayal K (2004). The role of parental burden in child mental health service use: longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry, 43,* 1328-1333.

Scerbo AS, Kolko DJ (1994). Salivary testosterone and cortisol in disruptive children: relationship to aggressive, hyperactive, and internalizing behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry, 33*, 1174-1184.

Schachar R, Wachsmuth R (1990). Hyperactivity and parental psychopathology. *Journal of Child Psychology and Psychiatry, 31,* 381-392.

Schulz KP, Halperin JM, Newcorn JH, Sharma V, Gabriel S (1997). Plasma cortisol and aggression in boys with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 605-609.

Seckl JR, Meaney MJ (2004). Glucocorticoid Programming. *New York Academy of Science, 1032*, 63-84.

Shoal GD, Giancola PR, Kirillova GP (2003). Salivary cortisol, personality, and aggressive behavior in adolescent boys: a 5-year longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*, 1101-1107.

Snoek H, Van Goozen SHM, Matthys W, Sigling HO, Koppeschaar HPF, Westenberg HGM, Van Engeland H (2002). Serotonergic functioning in children with oppositional defiant disorder: a sumatriptan challenge study. *Biological Psychiatry, 51*, 319-325.

Sondeijker FE, Ferdinand RF, Oldehinkel AJ, Veenstra R, De Winter AF, Ormel J, Verhulst FC (2005). Classes of adolescents with disruptive behaviors in a general population sample. *Social Psychiatry and Psychiatric Epidemiology, 40*, 931-938.

Sondeijker FE, Ferdinand RF, Oldehinkel AJ, Veenstra R, Tiemeier H, Ormel J, Verhulst FC (2006). Disruptive behaviors and HPA-axis activity in young adolescent boys and girls from the general population. *Journal of Psychiatric Research.*

Stoff DM, Pasatiempo AP, Yeung J, Cooper TB, Bridger WH, Rabinovich H (1992). Neuroendocrine responses to challenge with DL-fenfluramine and aggression in disruptive behavior disorders of children and adolescents. *Psychiatry Research, 43*, 263-276.

Tanner J (1962). *Growth at adolescence: With a general consideration of the effects of heredity and environmental factors upon growth and maturation from birth to maturity.* Oxford: Blackwell Scientific Publications.

Tremblay RE, Masse B, Perron D, Leblanc M, Schwartzman AE, Ledingham JE (1992). Early disruptive behavior, poor school achievement, delinquent behavior, and delinquent personality: longitudinal analyses. *Journal of Consulting and Clinical Psychology, 60*, 64-72.

Vamvakopoulos NC, Chrousos GP (1993). Evidence of direct estrogenic regulation of human corticotropin-releasing hormone gene expression. Potential implications for the sexual dimophism of the stress response and immune/inflammatory reaction. *Journal of Clinical Investigation, 92*, 1896-1902.

Van der Ende J, Verhulst FC (2005). Informant, gender and age differences in ratings of adolescent problem behavior. *European Child and Adolescent Psychiatry, 14,* 117-126.

Van de Wiel NM, van Goozen SH, Matthys W, Snoek H, van Engeland H (2004). Cortisol and treatment effect in children with disruptive behavior disorders: a preliminary study. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*, 1011-1018.

Van Lier PA, Verhulst FC, Van der Ende J, Crijnen AA (2003). Classes of disruptive behavior in a sample of young elementary school children. *Journal of Child Psychology and Psychiatry, 44,* 377-387.

Van Goozen SH, Matthys W, Cohen-Kettenis PT, Buitelaar JK, van Engeland H (2000). Hypothalamic-pituitary-adrenal axis and autonomic nervous system activity in disruptive children and matched controls. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*, 1438-1445.

Van Goozen SH, Matthys W, Cohen-Kettenis PT, Gispen-de Wied C, Wiegant VM, van Engeland H (1998). Salivary cortisol and cardiovascular activity during stress in oppositional-defiant disorder boys and normal controls. *Biological Psychiatry, 43*, 531-539.

Van Roon AM, Mulder LJM, Althaus M, Mulder G (2004). Introducing a baroreflexmodel for studying cardiovascular effects of mental workload. *Psychophysiology, 41*, 961-981.

Vanyukov MM, Moss HB, Plail JA, Blackson T, Mezzich AC, Tarter RE (1993). Antisocial symptoms in preadolescent boys and in their parents: associations with cortisol. *Psychiatry Research, 46*, 9-17.

Verhulst FC, Achenbach TM (1995). Empirically based assessment and taxonomy of psychopathology: cross-cultural applications. A review. *European Child and Adolescent Psychiatry, 4*, 61-76.

Verhulst FC, Dekker MC, van der Ende J (1997). Parent, teacher and self-reports as predictors of signs of disturbance in adolescents: whose information carries the most weight? *Acta Psychiatrica Scandinavia, 96*, 75-81.

Verhulst FC, Van der Ende J (1992). Agreement between parents' reports and adolescents' self-reports of problem behavior. *Journal of Child Psychology and Psychiatry, 33*, 1011-1023.

Verhulst FC, Van der Ende J (1993). "Comorbidity" in an epidemiological sample: a longitudinal perspective. *Journal of Child Psychology and Psychiatry, 34*, 767-783.

Verhulst FC, Van der Ende J, Koot HM (1997). *Handleiding voor de Youth Self-Report (YSR) [Manual for the Youth Self-Report (YSR)]*. Rotterdam: Erasmus University/Department of Child and Adolescent Psychiatry, Sophia Children's Hospital.

Verhulst FC, Van der Ende J, Koot JM (1996). *Handleiding voor de Child Behavior Checklist/4-18* (CBCL) *[Manual for the Child Behavior Checklist (CBCL)]*. Rotterdam: Erasmus University/Department of Child and Adolescent Psychiatry, Sophia Children's Hospital.

Virtanen R, Jula A, Salminen JK, Voipio-Pullki LM, Helenius A, Kuusela T, et al (2003). Anxiety and hostility are associated with reduced baroreflex sensitivity and increased beat-to-beat blood pressure variability. *Psychosomatic Medicine*, *65*, 751-756.

Vuong QH (1989). Likelihood ratio test for model selection and non-nested hypotheses. *Econometrica, 57,* 307-333.

Wadsworth MEJ (1976). Delinquency, pulse rates, and early emotional deprivation. *British Journal of Criminology, 16,* 245-256.

Wadsworth ME, Hudziak JJ, Heath AC, Achenbach TM (2001). Latent class analysis of Child Behavior Checklist Anxiety/Depression in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*, 106-114.

Watkins LL, Grossman P, Krishnan R, Blumenthal JA(1999). Anxiety reduces baroreflex cardiac control in older adults with major depression. Psychosomatic Medicine, *61*, 334-340.

Weicker H, Werle E (1991). Interaction between hormones and the immune system. *International Journal of Sports Medicine, 12*, 30-37.

Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L (1971). Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *Journal of Clinical Endocrinology and Metabolism, 33*, 14-22.

Werry JS, Reeves JC, Elkind GS (1987). Attention deficit, conduct, oppositional, and anxiety disorders in children: I. A review of research on differentiating characteristics. *Journal of the American Academy for Child and Adolescent Psychiatry, 26,* 133-143.

Wust S, Wolf J, Hellhammer DH, Federenko I, Schommer N, Kirschbaum C (2000). The cortisol awakening response - normal values and confounds. *Noise and Health*, *2*, 79-88.

Zoccolillo M (1993). Gender and the development of conduct disorder. *Development and Psychopathology, 5*, 65-78.

Zuckerman M, Neeb M (1979). Sensation seeking and psychopathology. *Psychiatry Research*, *1*, 255-264.

Summary

Summary

The objective of the present thesis was to obtain more knowledge regarding disruptive behaviors, by examining taxonomic, neuroendocrine and autonomic aspects of disruptive behaviors in young adolescents from the general population. In *Chapter 1*, the background and the main aims of the current thesis were outlined. Disruptive behavior problems, such as Attention Deficit Hyperactivity (ADH) Problems, Oppositional Defiant (OD) Problems, and Conduct (CD) Problems, are common in children and adolescents, have a negative impact on various aspects of the child's life and on families, schools, and communities. Furthermore, disruptive behavior problems tend to persist. Therefore, research aimed at identifying early risk factors is needed. The main aims of the thesis were: (1) to examine whether the existing distinction between ADH, OD, and CD Problems represented the best way to identify homogeneous groups of individuals with disruptive behaviors, (2) to determine whether high levels of disruptive behaviors were associated with low basal Hypothalamus Pituitary Adrenal (HPA) -axis activity, as is suggested in previous studies, (3) to investigate whether low salivary cortisol levels predicted future disruptive behavior problems and to examine whether low HPA-axis activity predicted the persistence of such problems, (4) to determine whether measures for autonomic nervous system (ANS) activity are good indicators of OD and CD Problems, (5) to investigate whether ANS functioning, assessed by heart rate (HR), Heart rate variability in the low frequency band (HRV LF), respiratory sinus arrhythmia (RSA) and baroreflex sensitivity (BRS), predicted future disruptive behaviors. To answer these questions the first two assessment waves of TRAILS, a prospective cohort study of Dutch young adolescents initially aged 10-12 years, were used.

In *Chapter 2*, we examined which classes of preadolescents with symptoms of ADH Problems, OD Problems, and CD Problems could be identified in the general population. Three groups of adolescents were revealed; the first characterized by high scores on ADH, OD, and CD items, a second by high probabilities of ADH and OD symptoms, and a third with low scores on all items. Because classes of preadolescents with symptoms of only one type of disruptive behavior problems were not found, it might be questioned how useful it is to distinguish between ADH, OD, and CD Problems in studies that address behavior problems in young adolescents from the general population.

In *Chapter 3*, we investigated to what extent HPA-axis functioning is associated with disruptive behaviors in pre-adolescents from the general population. We concluded that, although studies in high risk groups of mainly boys found evidence for an association between low basal HPA-axis activity and high levels of disruptive behavior problems, this association could hardly be confirmed in a large representative population sample of boys and girls. This casted doubt on the usefulness of cortisol measurements to estimate risk for behavior problems, and on a putative important role for HPA-axis functioning in the etiology of disruptive behavior problems.

In *Chapter 4*, it was investigated whether low HPA-axis activity predicted future disruptive behaviors. The results suggested that low HPA-axis activity is not a good predictor for disruptive behaviors in the general population, and is of limited value to identify those with a poor prognosis, once disruptive behaviors are present in pre-adolescence.

In *Chapter 5*, we aimed to gain more insight in the association between autonomic functioning and OD or CD problems. By themselves, OD or CD Problems were not associated with any of the autonomic measures we used. However, there were some interaction effects with anxiety. Nevertheless, because of the small effect sizes we concluded that in children and adolescents from the general population autonomic measures are poor indicators of OD and CD Problems.

In *Chapter 6*, we examined whether autonomic nervous system activity, which has been proposed as a risk factor for disruptive behaviors in children and adolescents, predicted future disruptive problems. HR and BRS were not associated with disruptive behaviors, whereas low HRV LF and RSA seemed to indicate a certain risk for disruptive problems. However, explained variances were small, which indicated that these measures will presumably not be useful predictors in real life.

In *Chapter 7*, the main findings and conclusions of this thesis were presented and discussed in two parts. The first part was about the taxonomy of disruptive behavior problems; the second part was about associations between physiological stress-systems and disruptive behavior problems. Latent class analyses, as described in chapter 2, indicated that it may not be useful to discriminate between ADH, OD, and CD Problems. However, some evidence indicated that, if HPA-axis and ANS activity are taken into account, it may be of some value to make such distinctions. Cortisol levels were associated with ADH Problems and not with OD or CD Problems. Furthermore, a different physiological balance, measured by ANS activity, was present in children at risk for OD Problems versus children at risk for CD Problems. Replication of these findings should certainly be tested in future studies, given the small effect sizes.

We concluded that HPA-axis and ANS activity were only weak predictors for future disruptive behaviors in adolescents from the Dutch general population. The findings indicated that the arousal theories, which are widely used dogmas, may be valuable in clinical or high risk groups, but not at the level of the general population.

Samenvatting

Samenvatting

Het doel van dit proefschrift was om meer kennis te vergaren over gedragsproblemen door de taxonomie onder de loep te nemen en neuro-endocrine en autonome aspecten van gedragsproblemen te onderzoeken in jonge adolescenten uit de normale bevolking. In *Hoofdstuk 1* werd de achtergrond van de studie besproken en werden de hoofdvragen uiteen gezet. Gedragsproblemen, waaronder aandachtstekort problemen (ADH problemen), oppositioneel opstandig gedrag (OD problemen) en antisociaal gedrag (CD problemen) worden verstaan, komen veel voor in kinderen en adolescenten. Dit soort problemen hebben een negatieve invloed op verschillende aspecten van het leven van het kind, maar beïnvloeden ook families, scholen en gemeenten. Vaak persisteren gedragsproblemen tot in de volwassenheid. Om deze redenen is het van belang onderzoek te doen naar mogelijke risicofactoren van gedragsproblemen. De hoofdvragen van dit proefschrift waren: (1) onderzoeken of het bestaande onderscheid tussen ADH, OD en CD problemen de beste manier is om homogene groepen van kinderen met gedragsproblemen de identificeren in de normale bevolking, (2) onderzoeken of er een verband bestaat tussen gedragsproblemen en lage Hypothalamus Hypofyse Bijnier (HPA)-as activiteit, zoals wordt gesuggereerd in eerder onderzoek, (3) onderzoeken of lage cortisol waarden gedragsproblemen twee jaar later voorspellen en onderzoeken of lage cortisol waarden de persistentie van gedragsproblemen voorspellen, (4) onderzoeken of maten voor activiteit van het autonome zenuwstelsel (AZS) goede indicatoren zijn voor OD en CD problemen, (5) onderzoeken of activiteit van het AZS, gemeten middels hartslag, hartslagvariabiliteit in de hoge en lage frequentieband en baroreflex sensitiviteit, toekomstige gedragsproblemen kan voorspellen. Om deze vragen te beantwoorden is er gebruik gemaakt van de eerste twee metingen van TRAILS. TRAILS staat voor TRacking Adolescent's Individual Lives Survey en is een prospectieve cohort studie onder jonge Nederlandse adolescenten, die bij aanvang van het onderzoek tussen de 10 en 12 jaar oud waren.

In *Hoofdstuk 2* hebben we onderzocht welke groepen adolescenten met symptomen van ADH, OD en CD problemen we konden onderscheiden in de normale bevolking. Drie groepen kwamen naar voren: de eerste gekarakteriseerd door hoge scores op alle drie de probleemgebieden, de tweede gekenmerkt door hoge scores op ADH en OD problemen en een derde groep die werd gekenmerkt door lage scores op ADH, OD en CD problemen. Omdat er geen groepen werden gevonden met hoge scores op bijvoorbeeld alleen de aandachtstekort problemen, kan men zich afvragen hoe zinvol het is onderscheid te maken tussen ADH, OD en CD problemen in studies naar gedragsproblemen in de normale bevolking.

In *Hoofdstuk 3* hebben we onderzocht of HPA-as functioneren geassocieerd was aan gedragsproblemen in jonge adolescenten uit de normale bevolking. Onze conclusie luidde dat, hoewel studies in hoogrisico of klinische groepen voornamelijk bestaand uit jongens bewijs vonden voor een associatie tussen lage HPA-as activiteit en gedragsproblemen, deze associatie nauwelijks kan worden bevestigd in een grote representatieve populatie uit de normale bevolking bestaande uit zowel jongens als meisjes. Dit deed ons twijfelen aan de bruikbaarheid van cortisol metingen om het risico op gedragsproblemen te bepalen. De mogelijk belangrijke rol van HPA-as functioneren voor de etiologie van gedragsproblemen kan eveneens in twijfel worden getrokken.

In *Hoofdstuk 4* hebben we onderzocht of HPA-as activiteit toekomstige gedragsproblemen kon voorspellen. De resultaten toonden aan dat HPA-as activiteit geen goede voorspeller was voor gedragsproblemen in de normale bevolking. Wel waren er aanwijzingen dat diegenen met een slechte prognose, als er eenmaal gedragsproblemen aanwezig waren in de adolescentie, konden worden geïdentificeerd.

In *Hoofdstuk 5* hebben we gepoogd meer inzicht te krijgen in de associatie tussen het functioneren van het autonome zenuwstelsel en gedragsproblemen. Zowel OD als CD problemen bleken niet geassocieerd te zijn met het functioneren van het AZS. Maar, keken we naar de interactie effecten met angst, dan leek er wel een verband te bestaan. Echter, de effect sizes van deze verbanden waren zo klein dat we kunnen concluderen dat ook autonome maten zwakke indicatoren zijn voor gedragsproblemen..

In *Hoofdstuk 6* hebben we onderzocht of activiteit van het AZS, volgens eerder onderzoek een risicofactor voor gedragsproblemen, toekomstige gedragsproblemen kon voorspellen. Hartslag en baroreflex sensitiviteit waren niet geassocieerd met gedragsproblemen, maar lage hartslagvariabiliteit in zowel de hoge als de lage frequentieband leek wel een voorspeller voor gedragsproblemen. Echter, de proportie verklaarde variantie was klein, wat betekent dat deze maten waarschijnlijk ook geen bruikbare voorspellers zijn.

In *Hoofdstuk 7* werden de belangrijkste bevindingen en conclusies van dit proefschrift gepresenteerd en bediscussieerd in twee delen. Het eerste deel betrof de taxonomie van gedragsproblemen en het tweede deel ging over het verband tussen de stresssystemen en gedragsproblemen. Middels latente klassen analyse, zoals beschreven in hoofdstuk 2, toonden we aan dat het wellicht niet zinvol is onderscheid te maken tussen ADH, OD en CD problemen in de normale bevolking. Hoewel zo'n onderscheid op gedragsniveau niet zinvol leek, deden enkele bevindingen ons vermoeden dat op een biologisch niveau het onderscheid tussen ADH, OD en CD problemen wel degelijk nuttig zou kunnen zijn. Cortisol waarden waren bijvoorbeeld geassocieerd met ADH problemen, maar niet met OD en CD problemen. Daarnaast leek er een andere fysiologische balans te zijn in kinderen met een verhoogd risico op OD problemen dan in kinderen met een verhoogd risico op CD problemen. Replicatie van deze bevindingen in toekomstig onderzoek is noodzakelijk, zeker gezien de kleine effect sizes van deze studie. Concluderend kunnen we stellen dat zowel HPA-as als AZS activiteit slechts zwakke voorspellers zijn voor toekomstige gedragsproblemen in adolescenten uit de normale bevolking. De bevindingen laten zien dat de 'arousal-theorieën', die kunnen worden omschreven als veelgebruikte dogma's, mogelijk waardevol zijn in klinische of hoogrisico groepen, maar niet van belang lijken in de normale bevolking.

Een woord van dank

Een woord van dank

Na drie jaar studeren aan de Katholieke Universiteit Brabant (tegenwoordig universiteit van Tilburg) besloot ik de uiterst gezellige studentenstad Tilburg te verlaten om stage te gaan lopen op de afdeling neuropsychologie en psychiatrie van het Academisch Ziekenhuis te Maastricht. Ik wist al snel wat ik wilde (dacht ik) namelijk klinisch werk. Het contact met kinderen en hun ouders, het puzzelen van wat is er precies met dit kind aan de hand en hoe kunnen we helpen, zien hoe een kind vooruitgang boekt tijdens een behandeling, dat was wat me aansprak, daar wilde ik in verder en het schrijven van die scriptie dat stelde ik het liefst zo lang mogelijk uit. Maar natuurlijk moest ik er toch een keer aan beginnen. Dr. Jos Hendriksen en dr. Petra Hurks, mijn scriptiebegeleiders, waren net als mijn begeleiders vanuit de universiteit, Dr. Max Feltzer en Prof.dr. Harry van der Vlugt, naast klinisch ook graag wetenschappelijk bezig. Hoewel ik het niet direct besefte, kan ik nu wel concluderen dat zij mijn interesse voor de onderzoekswereld geprikkeld hebben; dank daarvoor. Petra nadat ik een middagje met jou had zitten SPSS-en was het opeens allemaal niet zo moeilijk meer en kreeg ik er zelfs vertouwen in dat ook ik dit ooit wel onder de knie zou kunnen krijgen. Het schrijven van de scriptie ging me uiteindelijk veel makkelijker af dan ik had verwacht en ik had er zelfs plezier. Dit heeft er uiteindelijk toe geleid dat ik op een AIO-project in Rotterdam heb gesolliciteerd en zo ben ik bij TRAILS terecht gekomen.

TRAILS is een enorme studie naar de geestelijke gezondheid en sociale ontwikkeling van kindertijd tot volwassenheid. Het is een hele eer om te promoveren op een onderzoek waar zo veel mensen deel van uitmaken, maar het is onmogelijk om al die mensen persoonlijk te bedanken. Bij deze toch een kort woord aan jullie gericht. Alle kinderen, ouders, leerkrachten en natuurlijk de subsidiegevers die hebben bijgedragen aan de totstandkoming van TRAILS: hartelijk dank, zonder jullie had TRAILS nooit zo'n mooi en bijzonder project kunnen worden.

Tijdens mijn sollicitatiegesprek hoorde ik dat de dataverzameling van TRAILS plaatsvond in Noord-Nederland. Leuk! dacht ik toen nog, totdat ik hoorde dat ik naar Groningen moest verhuizen om een bijdrage te leveren aan deze dataverzameling. Ik dacht meteen aan wat ik tegen familie en vrienden had gezegd: "ik wil best op veel plekken in Nederland werken, maar Groningen en Friesland, dat nooit, dat is echt veel te ver van hier (lees Maastricht en omgeving)". Maar ja het project was helemaal wat ik wilde en Groningen was maar voor 8 maanden, daarna zou ik naar Rotterdam verhuizen om mijn proefschrift te gaan schrijven. Toen ik gebeld werd en hoorde dat de baan van mij was als ik hem wilde, kon ik niet anders dan alleen maar heel blij "ja!" zeggen en dat terwijl ik nog geen halve minuut wakker was. Theedrinken met vriendinnen werd ingeruild voor het zoeken naar woonruimte in Groningen. Het leek een onmogelijke opgave, maar zoals altijd kwam het ook nu net op tijd goed; mede door de inspanning van Andrea de Winter, projectleidster van TRAILS.

Ik had verwacht dat ik het erg moeilijk zou hebben in Groningen, zo ver weg van alles en iedereen, maar ik had fantastische collega's en leuke Chinese huisgenoten die heerlijk konden koken. Ik voelde me eigenlijk al heel snel thuis en mijn Limburgse vrienden zagen dit als dé kans om ook eens een kijkje te nemen in het noorden van het land waardoor mijn appartementje bijna elk weekend een hotel leek…ontzettend gezellig! Ook heb ik nog een aantal bijzondere herinneringen overgehouden aan mijn tijd in Groningen. Zo heb ik jou Tineke leren kennen als een hele vrolijke, gezellige, spontane (ik denk aan onze treinreis naar Fulda), maar ook wetenschappelijk ontzettend getalenteerde vrouw. Vooral je manier van kritiek geven vond ik heel prettig en ik had dan ook altijd veel aan je commentaar. Een andere persoon die voor mij in deze periode heel veel heeft betekend ben jij Agnes. Elke keer als het even tegenzat kon ik bij jou mijn hart luchten (ontplofte koelkast, gestolen portemonnee, het schrijven van nieuwsbrieven), maar we hebben ook veel lol gehad samen. Wat ik nooit zal

vergeten is die helemaal leuk versierde kamer toen ik jarig was. Je wist dat ik het voor het eerst in mijn leven niet zou gaan vieren omdat dat praktisch gewoon niet handig was, maar jij wilde het niet ongemerkt voorbij laten gaan. Je was echt het perfecte kamergenootje en nu een heel attente vriendin waar ik altijd terecht kan zelfs als ik een slaapplaats nodig heb. Ik hoop dat we elkaar ook in de toekomst regelmatig blijven zien. Verder waren er in Groningen veel mensen waar ik prettig mee heb samengewerkt, en hoewel ik jullie niet allemaal bij naam noem, hoop ik dat jullie toch weten dat ik het over jullie heb: "allemaal bedankt voor de geweldige tijd in Groningen".

Mijn verhuizing van Groningen naar Rotterdam verliep soepel. Vele handen maken licht werk zegt men en dat was ook zo dus iedereen die geholpen heeft wil ik bij deze bedanken. Tjaakje, jou wil ik nog even apart bedanken, want naast dat je een leuke, behulpzame collega was, heb ik met jou nog een aantal bijzondere avonturen beleefd. Natuurlijk de aangifte op het politiebureau, maar ook een ritje van Rotterdam naar Groningen in een hele grote (verhuis)bus en ik denk dat ik dat zonder jou echt niet gedurfd had, vooral het inparkeren was een hel. Ik hoorde dat je een nieuwe baan hebt, maar wie weet komen we elkaar nog wel een keertje tegen in Groningen.

In Rotterdam was het weer helemaal anders, nieuwe woonruimte, voor het eerst echt iets voor mezelf, nieuwe collega's en ten opzichte van Limburg en Groningen een ieder-voor-zich-cultuur waar ik erg aan moest wennen. In tegenstelling tot in de Rotterdamse binnenstad heerste er op de Westzeedijk, het domein van de AIO's, een picknickcultuur (uitspraak van Pol van Lier). Alle collega's en oud collega's van de Westzeedijk, ik heb een hele leuke tijd met jullie gehad. We konden met zijn allen heel hard werken, dan was het muisstil, maar op andere momenten hielden we niet op met kletsen en ook ik maakte me daar vaak schuldig aan moet ik bekennen (toch Esther?). Wat ik echt heel fijn vond is dat ik altijd bij iedereen terecht kon, als ik ff niet op een woord kwam in het Engels, als SPSS niet deed wat ik wilde, of als ik iets in een artikel niet snapte en wat uitleg nodig had….altijd stonden jullie voor me klaar en daar wil ik jullie nu op deze plek in mijn boekje graag voor bedanken.

In Rotterdam behoorde ik tot het AIO-groepje van Dr. Robert Ferdinand (die ik straks nog even apart zal noemen). Dit betekende elke dinsdagochtend van tien tot elf overleg in de screen en dat overleg was dan ook nog eens in het Engels. Het voelde in begin erg vreemd om in een groepje bestaande uit alleen Nederlands sprekende mensen Engels te praten. Toch heb ik er veel aan gehad en op een gegeven moment ga je zelfs in het Engels denken. Naast het beter leren presenteren in het Engels werden we ook wetenschappelijk aardig bijgeschoold over van alles en nog wat variërend van statistiek tot genetica en van hoe schrijf ik een subsidieaanvraag tot hoe beantwoord ik review commentaar. Het koste soms wat voorbereidingstijd maar je leerde er ontzettend veel van en daar heeft iedereen in deze groep aan bijgedragen. Ook hebben we met zijn allen twee studiedagen georganiseerd. Dat was echt supergaaf. En de studiereis naar Australië daarna minstens net zo te gek. Jongens jullie zijn allemaal goud waard en ik had deze tijd met jullie dan ook echt niet willen missen.

Dan is het nu tijd om de coauteurs van mijn artikelen te bedanken te beginnen met Dr. Robert Ferdinand. Robert, naast coauteur op mijn artikelen ben jij ook mijn copromotor en dagelijks begeleider. Zonder jou was dit proefschrift er niet gekomen en als het er al was gekomen dan nooit zo snel, want als ik je een artikel of stuk tekst toe stuurde dan had ik dat meestal binnen 24 uur weer terug voorzien van commentaar en nuttige tips. We hebben tijdens ons overleg een aantal malen discussies gevoerd, we waren het niet altijd eens, maar uiteindelijk werden de artikelen er wel beter van en dat is wat telt zo heb ik van jou geleerd! Robert, heel erg bedankt voor je tijd en voor alles wat jij me hebt bijgebracht. De volgende personen, Prof.dr. Frank Verhulst en Prof.dr. Hans Ormel, mijn beide promotoren, wil ik graag bedanken voor alle lieve en bemoedigende woorden als er weer niet uit mijn analyses kwam wat ik gehoopt had. Frank en Hans het is gelukt, het boekje is klaar, en ook nog binnen

de vier jaar die er voor stonden. Ik dank jullie voor jullie hulp en alle geboden mogelijkheden in Groningen en Rotterdam. Prof.dr. Tineke Oldehinkel (klinkt stoer toch), jou had ik al genoemd aan het begin van mij dankwoord, maar ook jij hebt bijgedragen aan het geboren worden van mijn kindje, dit proefschrift, in de periode dat ik in Groningen woonde en werkte als dagelijks begeleidster en later als coauteur, dank je voor alle gezellige maar o zo verhelderende gesprekken! Ook tegen alle andere mensen die mee hebben geschreven aan een of meer hoofdstukken van dit boekje (Dr. Andrea de Winter, Dr. Rene Veenstra, Dr. Henning Tiemeier, Dr. Judith Rosmalen, Andrea Dietrich, Kirstin Greaves-Lord) zou ik willen zeggen "super bedankt".

Één iemand heeft nog wel wat aandacht verdiend denk ik en dat is Kirstin Greaves-Lord. Kirstin, je bent ongeveer een jaar na mij ook als AIO bij TRIALS begonnen. We werden in Groningen aan elkaar voorgesteld, maar leerden elkaar pas echt kennen toen ook jij regelmatig in Rotterdam was.
We hebben vaak met elkaar gepraat over de data, over analyses en over hoe we bepaalde dingen nu het beste konden zeggen of opschrijven. We konden kritisch naar elkaar zijn op een directe maar toch leuke manier. Echter, in de vele uren die we inmiddels samen in de trein hebben doorgebracht waren de gespreksonderwerpen van een heel andere aard, veel persoonlijker. Ik waardeer je positieve, avontuurlijke kijk op het leven, maar ook je open- en eerlijkheid. De treinen reden sneller als we er samen in zaten, althans zo leek het. Kirstin, ik heb veel steun aan je gehad zowel zakelijk als privé en ik denk dat ik je naast collega ook wel vriendin mag noemen. We gaan zeker contact houden en er zullen nog vele theekransjes met gebak volgen als het aan mij ligt.

Er is nog een groep collega's die ik moet bedanken, namelijk degenen waarmee ik heb samengewerkt in het externaliserende team, dat tegenwoordig ontwikkelingsstoornissen team heet. Ik vond het leuk om mijn onderzoekswerkzaamheden te combineren met klinisch werk. Ik mocht van alles doen: intakes, adviesgesprekken, psychologisch onderzoek en zelfs behandelingen. De ervaring die ik bij jullie heb opgedaan pakt niemand me meer af. Al was het dan op een ander vlak, ook van jullie heb ik veel geleerd. Dank jullie wel! Agnes, nog een kort woord speciaal voor jou; je was een geweldige co-therapeut en ik vind het helemaal super dat je ook nog mijn hele proefschrift hebt gechecked op spelfouten…thanx and cu in amersfoort!

Nu is dan het moment daar dat ik een sprongetje ga maken van mijn zakelijke leven naar mijn privé leven. Familie en schoonfamilie, bedankt voor de interesse die jullie de afgelopen jaren getoond hebben in de vorderingen van mijn proefschrift, ik kon dat erg waarderen. Leuk dat jullie er ook op de grote dag allemaal bij zullen zijn!

Kim, ik ken je al een hele tijd en hoewel je een aantal jaren jonger bent dan ik, lijk je soms een stuk volwassener. Ik vind het heel bijzonder dat ons contact altijd is gebleven, waar ik ook heen ging. Ik kan met je lachen en met je huilen en ik weet wat ik aan je heb. Onze saunabezoekjes zijn heel gezellig en aan het eind van de dag heb ik altijd het idee dat ik een week op vakantie ben geweest…vooral het laatste jaar had ik dit echt nodig. Het leven was met name het afgelopen jaar voor mij niet altijd even makkelijk zoals je weet, maar op de momenten dat ik je nodig had was je er altijd, hoe druk je het ook had. Danke doa veur! Vera, jou ken ik ook vanuit Ulestraten en ook ons contact is gebleven. De periode dat je in Rotterdam in het ziekenhuis hebt gelegen was erg spannend, maar gelukkig is alles goed gekomen. Nu je in Schoonhoven woont hoop ik dat we elkaar weer wat vaker zullen zien (ja ik moet nog steeds langskomen, maar ja zo'n proefschrift schrijven doe je nu eenmaal niet in 40 uur per week). Jij ook bedankt voor alles! Dan Rob en Vero, jullie staan altijd voor me klaar en met altijd bedoel ik ook echt altijd. Rob zonder jou ben ik echt een computeranalfabeet. Ik ben blij dat jij computerproblemen als een uitdaging ervaart en niet als frustratie, dat geeft mij ook altijd weer rust. Vero nog even een paar woordjes speciaal voor

jou. Al die lieve kaartjes had ik niet willen missen. Ik weet dat je niet bij mijn promotie aanwezig kunt zijn door je stageperiode in Afrika, maar ik weet dat je aan me denkt en dat betekent heel veel voor me. Lieve Rob en Vero ik wil jullie bedanken voor alle hulp en steun en ik denk dat we snel weer een avondje Catannen moeten plannen.

Sjoerd, Karian, Cees, Mieke, Patrick, Jolien en Foppe ik ken jullie pas sinds Johan en ik een setje zijn, maar ik wil jullie niet meer kwijt. We zien elkaar niet heel vaak, maar als we elkaar zien is het altijd helemaal gezellig. Ik heb het idee dat we allemaal in een hele spannende levensfase zitten. Er zijn leuke dingen zoals samenwonen, huizen kopen, trouwen en gezinsuitbreiding, maar ook minder leuke dingen als het verliezen van een baan. Ik ben ervan overtuigd dat we samen de wereld aankunnen! En dat jaarlijkse weekendje weg met zijn allen, houden we erin als het aan mij ligt. Bedankt voor alle steun de afgelopen paar jaren.

Noortje jou ken ik van de studie in Tilburg en nu je net als ik in Rotterdam werkt, zien we elkaar weer wat vaker. Onze superlange lunches blijken toch altijd nog te kort om alles te bespreken, maar thuis zetten we onze gesprekken dan gewoon voort. Je bent heel belangrijk voor me geworden en gesprekken met jou (en Rick) zijn altijd heel verhelderend. Rick ook jou heb ik de laatste jaren beter leren kennen je bent iemand waar je op kunt bouwen, jij staat op moeilijke momenten altijd voor mij (en Johan) klaar en dan meestal ook nog met een overheerlijke maaltijd. Lieve Noortje en Rick bedankt dat jullie er altijd zijn!

San en Eef, jullie zijn een verhaal apart. Ik heb jullie leren kennen tijdens mijn stage periode in Maastricht. Jullie waren mijn huisgenootjes. Lief en leed hebben we gedeeld als 'butsmutsen'. Onze kerstdiners en picknicks zal ik nooit vergeten. Het leven is een beetje veranderd, we wonen allemaal in een andere provincie en hebben allemaal een druk leven, toch is het als we elkaar weer zien net als vroeger. Dat klinkt wel alsof we heel oud zijn geworden, maar wat ik bedoel te zeggen is dat onze vriendschap gewoon goed voelt. Jullie zijn dan ook niet voor niets mijn paranimfjes. Ik heb er vertrouwen in dat jullie me (zelfs zonder Droopy, want die zal er deze keer niet bij zijn) aan het lachen kunnen maken, zelfs als ik stijf sta van de zenuwen, maar ik weet dat jullie aan de andere kant ook echt met me mee zullen leven en na afloop in net zo'n feeststemming zullen zijn als ik en dat is wat ik nodig heb op deze grote dag!

Dan mijn zusje Saartje. Saar jouw woorden toen ik aan deze baan als AIO begon, zal ik nooit vergeten. Je zei namelijk: "een paar artikelen schrijven, daar heb je toch geen vier jaar voor nodig dat moet in één jaar kunnen". Inmiddels ben je zelf ook AIO en is je mening een beetje bijgesteld. Als ik ergens tegenop zag zei jij altijd, ach dat doe je toch gewoon even en hoewel ik het op het moment dat je het zei nooit geloofde, ging ik het toch proberen en meestal met succes. Promoveren in één jaar is niet gelukt, maar ik denk dat vier jaar ook voor jou een mooi streven is zussie. Dank je wel voor alle motiverende woorden.

Paps en mams, wie had dat gedacht hè, dat ik na een studie psychologie ook nog even ging promoveren. Maar ja, doctorandus betekent zij die nog doctor moet worden en ik heb van jullie geleerd dat je altijd moet afmaken waar je aan begint…dat heb ik bij deze gedaan! Ik was altijd te laat thuis, hing altijd op straat, was een echte puber en jullie zagen me zelden studeren. Moet moeilijk zijn geweest, zeker voor twee leerkrachten. Ik vond het leven altijd te kort om me slechts met één ding bezig te houden, ik wilde altijd alles tegelijk. En eigenlijk wil ik dat nog steeds, maar sinds ik van heel dichtbij heb gezien dat dat ook nadelige gevolgen kan hebben voor je gezondheid, heb ik geleerd om ook af en toe eens 'nee' te zeggen. Ondanks dat ik niet altijd even makkelijk was, zijn jullie me wel altijd blijven steunen en kan ik voor ouderlijk advies ook nu nog altijd bij jullie aankloppen. Eigenlijk zijn jullie gewoon superouders en ik denk dat jullie daar nu wel eens voor bedankt mogen worden. Dus pap en mam heel heel heel erg bedankt!

Als laatste wil ik natuurlijk jou bedanken lieve Johan. We hebben elkaar ontmoet tijdens onze stage in Maastricht en zijn elkaar toen weer even uit het oog verloren, maar toen

ik in Groningen woonde kwamen we elkaar weer tegen en er bloeide iets moois, zo mooi dat ik het ervoor over had om elk weekend van Groningen naar Maastricht te reizen en weer terug. Toen ik in Rotterdam ging wonen halveerde de reistijd en dat was lekker, maar toen jij een GZ-plek kreeg in Ede hebben we de grote stap genomen om te gaan samenwonen en dat beviel zo goed dat we zelfs een huisje hebben gekocht samen. Promoveren is leuk, maar soms ook erg frustrerend….denk aan tegenvallende resultaten, afgewezen artikelen en deadlines. Johan, je had eigenlijk wel genoeg aan je zelf: werken, studeren en uitzoeken wat jij nu echt wil in dit leven, maar je kreeg ook al mijn frustraties nog er bovenop. Een hele klus lijkt me, maar hij is geklaard! De afgelopen jaren was je mijn rustpunt na een dag hard werken, en mijn lieve knuffelbeer bij wie ik altijd mocht uithuilen. Tja wat kan ik zeggen: THANX en nu dit achter de rug is ben ik weer gezellig!

Hora est.
Frouke

Curriculum Vitae

Curriculum Vitae

Frouke Elisabeth Paulus Louise Sondeijker werd geboren op 8 april 1980 te Heerlen. In 1998 behaalde zij haar VWO-diploma aan het Stella Maris College te Meerssen. Vanaf september 1998 studeerde zij Psychologie aan de Katholieke Universiteit Brabant, afstudeerrichting kinder- en jeugdpsychologie, waar zij in augustus 2002 het doctoraal examen haalde. Zij liep zowel haar klinische als wetenschappelijke stage in het Academisch Ziekenhuis Maastricht. Haar afstudeerscriptie had als onderwerp 'Het effect van een multimodale behandeling op cognitief functioneren en tijdsbesef bij kinderen met ADHD', en werd begeleid door Dr. J. Hendriksen en Dr. P. Hurks. De klinische stage werd begeleid door Dr. J. Hendriksen en Drs. F. Dings en vanuit de universiteit waren Dr. M. Feltzer en Prof.dr. H. van der Vlugt betrokken.

Vanaf december 2002 tot december 2006 was ze assistent in opleiding (AIO/promovenda) verbonden aan de Erasmus Universiteit Rotterdam en deed zij binnen de afdeling kinder- en jeugdpsychiatrie van het Erasmus MC-Sophia (Hoofd: Prof.dr. F.C. Verhulst) onderzoek naar de neuro-endocrine en autonome risicofactoren van gedragsproblemen bij adolescenten uit de normale bevolking. Het onderzoek is onderdeel van een grote prospectieve longitudinale studie naar de geestelijke gezondheid en sociale ontwikkeling van kindertijd tot volwassenheid genaamd Tracking Adolescents' Individual Lives Survey (TRAILS) (Projectleiders: Prof.dr. F.C. Verhulst en Prof.dr. J. Ormel, en onder dagelijkse begeleiding van Dr. R.F. Ferdinand). De resultaten van het onderzoek staan beschreven in dit proefschrift. Ten tijde van het promotieonderzoek heeft ze een jaar lang ook klinische werkzaamheden verricht variërend van intake en adviesgesprekken tot diagnostisch onderzoek en behandeling.