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HPA-axis activity and externalizing behavior problems in early adolescents from the general population: The role of comorbidity and gender The TRAILS study

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Gender;
General population

Summary

Contradictory findings on the relationship between hypothalamus–pituitary–adrenal (HPA)-axis activity and externalizing behavior problems could be due to studies not accounting for issues of comorbidity and gender. In a population-based cohort of 1768 (10- to 12-year-old) early adolescents, we used a person-oriented approach and a variable-oriented approach to investigate whether comorbidity with internalizing behavior problems and gender moderate the relationship between HPA-axis activity (cortisol awakening response and evening cortisol levels) and externalizing behavior problems. We found that: (1) in early adolescents with pure externalizing behavior problems, there was a particularly strong effect of gender, in that girls showed significantly higher total cortisol levels after awakening (AUC_G levels) and a significantly higher cortisol awakening response (AUC_I levels) than boys. (2) Girls with pure externalizing behavior problems showed a significantly higher cortisol awakening response (AUC_I levels) than girls without behavior problems or girls with comorbid internalizing behavior problems. This effect was absent in boys. (3) Externalizing behavior problems, in contrast to internalizing behavior problems, were associated with higher evening cortisol levels. This effect might, however, result from girls with externalizing behavior problems showing the highest evening cortisol

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levels. Overall, we were unable to find the expected relationships between comorbidity and HPA-axis activity, and found girls with pure externalizing behavior problems to form a distinct group with regard to their HPA-axis activity. There is need for prospective longitudinal studies of externalizing behavior problems in boys and girls in relation to their HPA-axis activity. It would be useful to consider how other risk factors such as life events and family and parenting factors as well as genetic risks affect the complex relationship between externalizing behavior problems and HPA-axis activity.

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1. Introduction

The hypothalamus–pituitary–adrenal (HPA)-axis is a central component of the body's neuroendocrine response to stress, with cortisol as its major end product (Tsigos and Chrousos, 2002). 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 externalizing behavior problems. According to the stimulation-seeking theory, low arousal represents an unpleasant condition which may lead to stimulus-seeking behavior to attain higher and more pleasant levels of arousal (Zuckerman, 1979; Raine, 1996). Several studies on the relationship between HPA-axis activity and externalizing behavior problems have shown that children or early adolescents (aged 7 to 12) with externalizing behavior problems have low levels of cortisol (both basal and in response to stressors) (Ryan, 1998). However, other studies did not find a relationship between externalizing behavior problems and low basal cortisol levels (Dabbs et al., 1991; Schulz et al., 1997; Klimes-Dougan et al., 2001; Sondejker et al., 2007).

Relatively few studies on the relationship between HPA-axis activity and externalizing behavior problems have measured cortisol levels in response to awakening. The increase in cortisol levels in about half an hour after awakening, the cortisol awakening response (CAR), can serve as a reliable marker of HPA-axis activity (Pruessner et al., 1997). There is evidence that the CAR is genetically influenced (Wüst et al., 2000a) and associated with chronic stress (Wüst et al., 2000a, b; Pruessner et al., 2003b; Schlotz et al., 2004). In contrast, afternoon and evening basal cortisol levels are more environmentally influenced (Wüst et al., 2000a; Bartels et al., 2003; Schreiber et al., 2006) and hence susceptible to environmental stressors. Consequently, the CAR and evening basal cortisol levels appear to reflect independent characteristics of HPA-axis activity (Rosmalen et al., 2005).

This paper focuses on the role of gender and comorbidity as potential explanations for the inconsistent results on the relationship between externalizing behavior problems and HPA-axis activity. Gender is thought to be associated with HPA-axis activity, in that girls show higher basal cortisol levels (Klimes-Dougan et al., 2001; Rosmalen et al., 2005) and a higher CAR (Pruessner et al., 1997; Wüst et al., 2000b; Rosmalen et al., 2005) than boys. An association between gender and HPA-axis activity does not, however, exclude the possibility that gender acts as a moderator in the relationship between HPA-axis activity and externalizing behavior problems (Baron and Kenny, 1986). As a consequence of the

large amount of studies in clinical or high-risk samples, studies concerning externalizing behavior problems have largely been conducted with boys. Thus, in samples consisting of predominantly boys, these studies may have mistakenly concluded that externalizing behavior problems are associated with low HPA-axis activity. So far, few studies have examined the moderating effect of gender on the relationship between HPA-axis activity and externalizing behavior problems. These studies concluded that low cortisol may be a biological marker for *male* externalizing behavior problems in particular (Shirtcliff et al., 2005; Loney et al., 2006).

Whereas externalizing behavior problems are thought to be inversely related with basal cortisol levels, internalizing behavior problems are thought to be positively related with basal cortisol levels (Ryan, 1998; Goodyer et al., 2001). The hypothesis of additive effects would predict higher than expected basal cortisol levels in the comorbid condition compared to the pure externalizing condition. McBurnett et al. (1991) showed that comorbid externalizing and internalizing behavior problems lead to higher cortisol levels than pure externalizing behavior problems in a sample that included boys only. However, later studies that investigated mixed-gender samples could not replicate this finding (Oosterlaan et al., 2005; Shirtcliff et al., 2005), which may indicate a gender-specific effect of comorbidity. As an alternative to the hypothesis of additive effects, comorbidity might be characterized by unique characteristics not found in pure conditions. Comorbidity between externalizing and internalizing behavior problems, which occurs more frequently than chance would predict (Boylan et al., 2007), has shown to be more heterogeneous in terms of clinical presentation and in etiology when compared to pure externalizing behavior problems. Since pure externalizing behavior problems are more genetically influenced than comorbid externalizing and internalizing behavior problems (Gjone and Stevenson, 1997), pure externalizing behavior problems may be more strongly related to the genetically influenced CAR than comorbid externalizing and internalizing problems. Comorbidity probably results from a combination of genetic and environmental risk factors (Gjone and Stevenson, 1997; Boylan et al., 2007) and may be related to both the genetically influenced CAR and to the environmentally influenced evening cortisol levels.

The purpose of the present study is to disentangle main effects of externalizing behavior problems and gender on HPA-axis activity from possible moderating effects of gender and comorbidity in a population-based cohort of 10- to 12-year-old early adolescents. To analyze the effects of comorbidity, we will follow both a person-

oriented and a variable-oriented approach to data analysis. In the person-oriented approach, comorbidity is considered as unique to the individual, whereas in the variable-oriented approach, comorbidity is considered as an aggregation of externalizing and internalizing behavior problems. In this way, both approaches may provide different information that can be complementary (Ormel et al., 2005; von Eye et al., 2006). The first hypothesis is that the potential inverse relationship between externalizing behavior problems and total cortisol levels after awakening is specific for boys. Second, we hypothesize that comorbid externalizing and internalizing behavior problems lead to higher total cortisol levels after awakening than pure externalizing behavior problems. The third hypothesis is that pure externalizing behavior problems are more strongly related to the CAR than comorbid externalizing and internalizing problems; in addition, we hypothesize that comorbid behavior problems are related to evening cortisol levels as well.

2. Methods

2.1. Sample

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch (early) adolescents, with the aim to chart and explain the development of mental health from early adolescence into adulthood, both at the level of psychopathology and the levels of underlying vulnerability and environmental risk. Early adolescents will be measured biennially at least until they are 25 years old. The present study involves data from the first (T1) assessment wave of TRAILS, which ran from March 2001 to July 2002. If both parents and early adolescents agreed to participate, parental written informed consent was obtained after the procedures had been fully explained. Of all early adolescents approached for enrollment in the study ($N = 3145$), 76.0% ($N = 2230$, mean age = 11.09, S.D. = 0.56, 50.8% girls) early adolescents participated in the study. Responders and non-responders did not differ with respect to the prevalence of teacher-rated behavior problems, nor regarding associations between sociodemographic variables and mental health outcomes. Detailed information about sample selection and analyses of non-response bias has been reported elsewhere (de Winter et al., 2005).

2.2. Procedure

Well-trained interviewers visited one of the parents or guardians (preferably the mother, 95.6%) at their homes to administer an interview covering a wide range of topics, including developmental history and somatic health, parental psychopathology and care utilization. In addition to the interview, the parent was asked to fill out some questionnaires concerning the child's mental health and behavior. Early adolescents filled out questionnaires at school, in the classroom, under the supervision of one or more TRAILS assistants. Besides, intelligence and a number of biological and neurocognitive parameters were assessed individually (at school, except for saliva samples, which were collected at home). Teachers were asked to fill out a

brief questionnaire for all TRAILS-participants in their class. Measures that were used in the present study are described more extensively below.

2.3. Measures

2.3.1. Behavioral problems

Behavioral problems were assessed with the Child Behavior Checklist (CBCL) (Achenbach, 1991a; Verhulst et al., 1996) and the Youth Self-Report (YSR) (Achenbach, 1991b; Verhulst et al., 1997). The CBCL is a measure of parent-reported emotional and behavioral problems in 4- to 18-year-old children and the YSR is a self-report questionnaire that was modeled on the CBCL. The CBCL and the YSR contain 113 and 112 items, respectively. These items are rated as 0 (not true), 1 (somewhat or sometimes true) or 2 (very true or often true). Both the CBCL and the YSR contain two broadband scales: one for internalizing behavior problems and one for externalizing behavior problems. For each of the two broadband scales, we used the mean of the standardized CBCL and YSR scores. The composite scores on externalizing and internalizing behavior problems were analyzed and compared using a person-oriented approach and a variable-oriented approach.

In the person-oriented approach, our large sample size allowed us to set a strict cut-off (P50) for creating a "supernormal" Control group. The 84th percentile for externalizing and internalizing behavior problems was used as a cut-off to assign adolescents into the groups with behavior problems. For both dimensions, the 84th percentile has been identified as the "borderline range" cut-off discriminating between adaptive and maladaptive behavior (Achenbach and Rescorla, 2001). Early adolescents were assigned to one of the following groups: (1) Control group (externalizing <P50 and internalizing <P50), (2) Pure EXT group (externalizing \geq P84 and internalizing <P84), (3) Pure INT group (externalizing <P84 and internalizing \geq P84), and (4) Comorbid group (externalizing \geq P84 and internalizing \geq P84).

In the variable-oriented approach, we adopted the framework described by Essex et al. (2006) and used a severity measure ($\text{severity} = [E+I]/2$) as an index for comorbidity and a directionality measure ($\text{directionality} = [E-I]/2$) for determining whether the possible behavior problems are mainly externalizing or internalizing, where E indicates the standardized externalizing behavior problems and I indicates the standardized internalizing behavior problems.

2.3.2. Cortisol

TRAILS participants collected cortisol samples (saliva) at home, using the Salivette sampling device (Sarstedt, Rommelsdorfer Str., D-51588 Nümbrecht, Germany), which was handed to the parent at the parent interview, accompanied by a verbal and a written instruction. The Salivette tube consists of a plastic sampling vessel with a suspended insert containing a sterile neutral cotton wool swab that has to be chewed for about 45 s and then returned to the insert. Participants were instructed to collect three saliva samples: the first sample shortly after waking up (still lying in bed), the second sample 30 min later, and the third

sample at 2000 h. Both the sampling and the preceding day should be normal (school) days, without special events or stressful circumstances. Since the in TRAILS participating schools started at approximately the same time, the sampling-time variation of the morning samples among the early adolescents is expected to be limited and the estimated corresponding times are 0700h for the first sample ($Cort_{0700}$) and 0730h for the second sample ($Cort_{0730}$). Participants were instructed not to collect saliva when they were ill, had a cold, had a headache, or were menstruating. Furthermore, they were requested not to take any medication, if possible. Any deviations from this protocol, either in terms of sampling times or in terms of other requirements, were indicated 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. Participants who did not return the salivettes within a couple of months were sent a reminder letter. In total, we received saliva samples of 1768 early adolescents (79.3% of all TRAILS participants). Non-responders did not differ from responders in terms of gender (48.4% male vs. 49.4% male for non-responders vs. responders, respectively, χ^2 (df = 1) = 0.132; $p = 0.716$) or pubertal development (average Tanner score = 1.92 vs. 1.86, $t = -1.394$; $p = 0.164$); non-responders were slightly older (11.16 years vs. 11.08 years, $t = -3.084$; $p < 0.01$) and had a higher mean BMI (18.50 kg/m² vs. 17.92 kg/m², $t = -3.224$; $p < 0.01$) (Rosmalen et al., 2005).

The saliva samples were stored at -20°C until analysis. Previous studies suggest that salivary cortisol levels are stable for prolonged periods of time at -20°C (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. Procedures of determination of cortisol levels are described more extensively elsewhere (Rosmalen et al., 2005).

2.4. Statistical analyses

We excluded 22 early adolescents because they used corticosteroid-containing medication. For each time point, single cortisol samples with values that were above 3 S.D. of the mean of the particular time point were excluded from the analysis in order to reduce the impact of outliers ($Cort_{0700}$ 21 excluded, 1666 valid measurements in the final dataset; $Cort_{0730}$ 11 excluded, 1683 valid measurements in the final dataset; $Cort_{2000}$ 18 excluded, 1689 valid measurements in the final dataset). After this exclusion, cortisol levels followed a normal distribution ($Cort_{0700}$ skewness = 0.700, kurtosis = 0.632; $Cort_{0730}$ skewness = 0.426, kurtosis = 0.239; $Cort_{2000}$ skewness = 1.217, kurtosis = 2.014).

With regard to the morning cortisol levels we used Area Under the Curve (AUC) measures. The computation of the AUC is a frequently used method in endocrinological research to assess the overall secretion over a specific time

period (area under the curve with respect to ground, AUC_G), and to estimate circadian changes over a specific time period (area under the curve with respect to increase, AUC_I) (Pruessner et al., 2003a). Pruessner et al. (2003a) recommend employing both formulas when analyzing datasets with repeated measures. We used the following formulas for calculating the (1) total cortisol after awakening: $AUC_G = (Cort_{0730} - Cort_{0700}) \times 0.5/2 + Cort_{0700} \times 0.5$, and (2) cortisol awakening response (CAR): $AUC_I = (Cort_{0730} - Cort_{0700}) \times 0.5/2$. The former correlates 0.71 with $Cort_{0700}$ and 0.86 with $Cort_{0730}$ and the latter is in this design mathematically equal to one-quarter of the difference between awakening level and level 30 min later (Rosmalen et al., 2005). According to their conceptual meaning, findings with respect to AUC_G levels will be interpreted in line with previous studies on basal cortisol samples and findings with respect to AUC_I levels will be interpreted in line with previous studies on the CAR. Furthermore, we used $Cort_{2000}$ levels for our interest in basal cortisol levels in the evening.

In a previous study on the present sample, gender and the quadratic effect of sampling month were identified as potential confounders in the relationship between HPA-axis activity and psychopathology. Age, pubertal development, and BMI appeared not to be related to HPA-axis activity (Rosmalen et al., 2005).

In the person-oriented approach, a two-way analysis of covariance (ANCOVA) was performed on AUC_G levels, AUC_I levels, and evening cortisol levels, with group (four levels: Control, Pure EXT, Pure INT, Comorbid) and gender (two levels) as factors, and the quadratic effect of sampling month as covariate. When a main effect of group was found, planned contrasts were examined: Control group vs. Pure EXT group, Control group vs. Comorbid group, and Pure EXT group vs. Comorbid group. When an interaction effect between group and gender was found, we performed a one-way ANCOVA in each of the groups, with gender as factor, and quadratic effect of sampling month as covariate and a one-way ANCOVA in both genders, with group as factor, and quadratic effect of sampling month as covariate. Again, when a significant main effect of group was observed in one of the genders, planned contrasts as described above were examined.

In the variable-oriented approach, three stepwise multiple regression analyses were performed and AUC_G , AUC_I , and evening cortisol levels. In the first step, the potential confounders gender and the quadratic effect of sampling month were entered into the model. In the second step, severity, directionality, and the interaction terms between these factors and gender were entered. When an interaction effect between severity (or directionality) and gender was found, we performed a multiple regression analysis for boys and girls separately, with the quadratic effect of sampling month entered in the first step and severity (or directionality) entered in the second step.

3. Results

3.1. Person-oriented approach

Table 1 shows age, gender, and mean standardized scores for externalizing and internalizing behavior problems for the Control, Pure EXT, Pure INT, and Comorbid group. Age differed significantly among the four groups ($p < 0.05$),

though differences were small. As we expected, groups had dissimilar gender distributions ($p < 0.001$). The Comorbid group showed more severe internalizing behavior problems than the Pure INT group ($p < 0.001$) and more severe externalizing behavior problems than the Pure EXT group ($p < 0.001$).

3.1.1. AUC_G levels

Table 2 shows the results of the two-way analyses of covariance. As expected, we found a main effect of gender ($F(1,902) = 17.0$, $p < 0.001$) and a main quadratic effect of sampling month ($F(1,902) = 10.2$, $p < 0.01$) on AUC_G levels (Table 2). In addition, the interaction effect of group \times gender approached significance ($F(3,902) = 2.4$, $p = 0.062$). This trend and the effects of gender and sampling month accounted for 2.5% of the adjusted variance.

Analyses for boys and girls separately revealed no main effects of group. In contrast, analyses for the separate groups revealed a main effect of gender in the Pure EXT group ($F(1,140) = 11.7$, $p < 0.01$) (adjusted $R^2 = 7.3\%$), but not in the Control group, the Pure INT group, and the

Comorbid group. In the Pure EXT group, girls showed significantly higher AUC_G levels than boys (Figure 1A).

3.1.2. AUC_I levels

We found the expected main effect of gender ($F(1,902) = 4.5$, $p < 0.05$). In addition, we found a significant main effect of group ($F(3,902) = 2.9$, $p < 0.05$) and a significant interaction effect of group \times gender ($F(3,902) = 3.5$, $p < 0.05$). These effects accounted for 0.8% of the adjusted variance.

With respect to the main effect of group, planned contrasts revealed that the Pure EXT group showed significantly higher AUC_I levels compared to both the Control group ($p < 0.01$) and the Comorbid group ($p < 0.05$) (Figure 1B). In addition, the Control group did not differ from the Comorbid group.

With respect to the interaction effect of group \times gender, analyses for boys and girls separately revealed a significant main effect of group in girls only ($F(3,457) = 3.5$, $p < 0.05$) (adjusted $R^2 = 2.1\%$). Planned contrasts revealed that girls from the Pure EXT group showed significantly higher AUC_I

Table 1 Age, gender, and mean of the standardized CBCL and YSR scores on internalizing and externalizing behavior problems, for the Control, Pure EXT, Pure INT, and Comorbid group.

	%/ $M \pm S.D.$				Statistical test value	p -Value
	Control ($n = 546$)	Pure EXT ($n = 144$)	Pure INT ($n = 153$)	Comorbid ($n = 92$)		
Demographic characteristics						
Age (years)	11.1 \pm 0.5	11.2 \pm 0.5	11.0 \pm 0.6	11.1 \pm 0.6	$F(3,931) = 3.7$	0.011
Gender (% boys)	45.1	78.5	34.0	53.3	$\chi = 67.9$, $df = 3$	< 0.001
Behavior problems						
Internalizing above p84			1.34 \pm 0.5	1.66 \pm 0.8	$t(234) = -4.1$	< 0.001
Externalizing above p84		1.33 \pm 0.4		1.60 \pm 0.6	$t(243) = -4.2$	< 0.001

Table 2 ANCOVA results for the effect of group, gender, and the interaction effect of group \times gender on AUC_G levels, AUC_I levels, and $Cort_{2000}$ levels, with quadratic effect of sampling month as covariate.

	AUC_G			AUC_I				$Cort_{2000}$				
	df	F	p	Adj. R^2	df	F	p	Adj. R^2	df	F	P	Adj. R^2
Model				2.5%				0.8%				4.5%
Factors												
Group	3	1.3	0.270		3	2.9	0.035*		3	0.8	0.487	
Gender	1	17.0	< 0.001**		1	4.5	0.034*		1	1.0	0.311	
Group \times gender	3	2.4	0.062		3	3.5	0.015*		3	0.5	0.655	
Covariate												
sampling month	1	10.2	< 0.01**		1	1.4	0.236		1	47.0	< 0.001**	
Error	902				902				936			

*Significant at the 0.05 level.

**Significant at the 0.01 level.

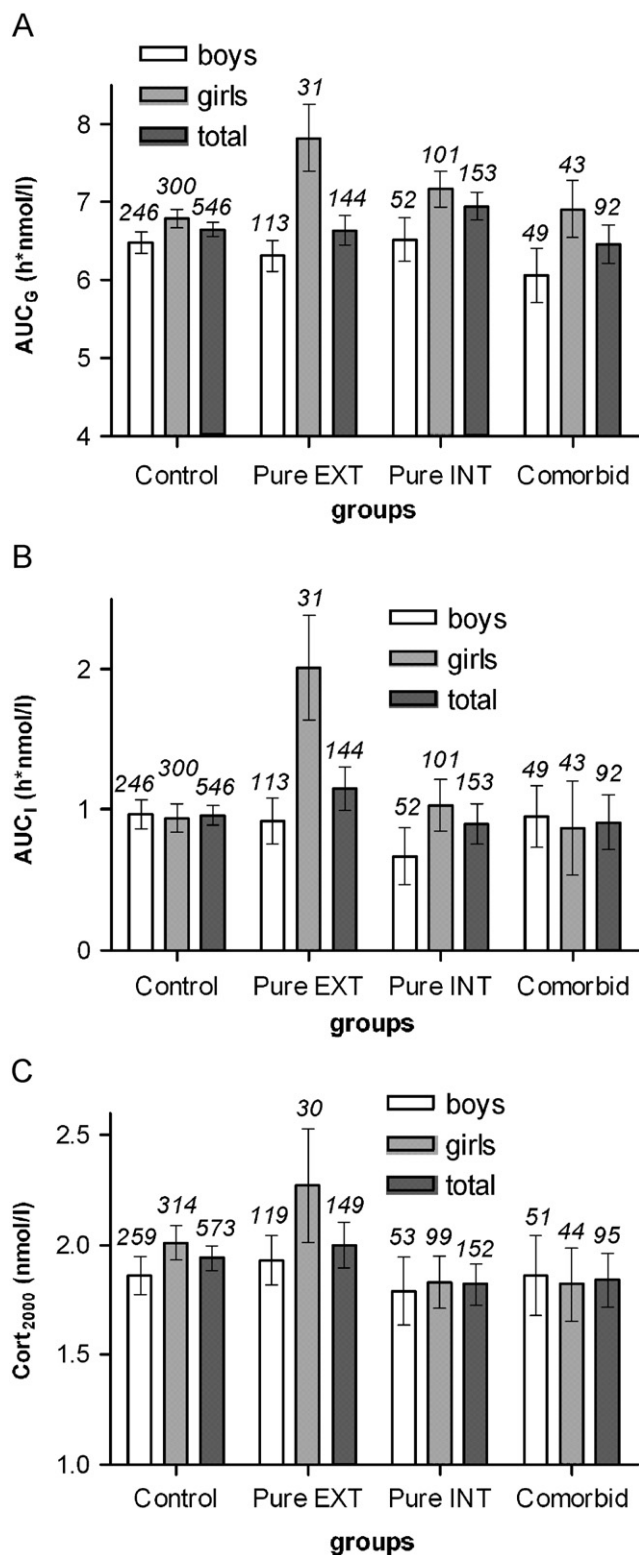


Figure 1 Error bars showing the mean and 95% confidence intervals for AUC_G levels, AUC_I levels, and $Cort_{2000}$ levels for the total group and by gender.

levels compared to girls from both the Control group ($p < 0.01$) and the Comorbid group ($p < 0.01$) (Figure 1B). The Control group did not differ from the Comorbid group.

Analyses for the separate groups revealed a main effect of gender in the Pure EXT group ($F(1,140) = 9.1$, $p < 0.01$) (adjusted $R^2 = 5.1\%$), but not in the Control group, the Pure INT group, and the Comorbid group. In the Pure EXT group, girls showed significantly higher AUC_I levels than boys (Figure 1B).

3.1.3. $Cort_{2000}$ levels

We found the expected main quadratic effect of sampling month ($F(1,936) = 47.0$, $p < 0.001$), but no main effect of group or an interaction effect of group \times gender. The effect of sampling month accounted for 4.5% of the adjusted variance.

3.2. Variable-oriented approach

3.2.1. AUC_G levels

Table 3 shows the results of the multiple regression analyses. As already shown in the person-oriented approach, gender ($\beta = -0.102$, $p < 0.001$) and the quadratic effect of sampling month ($\beta = 0.113$, $p < 0.001$) significantly predicted AUC_G levels. The interaction effect of severity \times gender approached significance ($\beta = -0.044$, $p = 0.081$). The addition of the interaction effect increased the adjusted R^2 from 2.3% to 2.4%. Analyses for boys and girls separately revealed that the effect of severity on AUC_G levels approached significance in girls ($\beta = 0.065$, $p = 0.071$), but not in boys. In girls, the addition of the effect of severity increased the adjusted R^2 from 0.9% to 1.1%.

3.2.2. AUC_I levels

The quadratic effect of sampling month significantly predicted AUC_I levels ($\beta = 0.071$, $p < 0.01$). Besides, the interaction effect of severity \times gender approached significance ($\beta = -0.045$, $p = 0.078$). The addition of the interaction effect increased the adjusted R^2 from 0.5% to 0.6%. As also reported for AUC_G levels, the effect of severity on AUC_I levels approached significance in girls ($\beta = 0.069$, $p = 0.052$), but not in boys. In girls, the addition of the effect of severity increased the adjusted R^2 from 1.6% to 1.8%.

3.2.3. $Cort_{2000}$ levels

Besides being affected by the quadratic effect of sampling month ($\beta = 0.202$, $p < 0.001$), evening cortisol levels were also affected by directionality ($\beta = 0.056$, $p < 0.05$). The addition of the effect of directionality did not increase the adjusted R^2 (retained 4.1%). The positive beta coefficient indicates that externalizing behavior problems, in contrast to internalizing behavior problems, are associated with higher evening cortisol levels.

4. Discussion

This study was designed to disentangle main effects of externalizing behavior problems and gender on HPA-axis activity from possible moderating effects of gender and comorbidity in a population-based cohort of 10- to 12-year-old early adolescents. We followed a person-oriented approach and a variable-oriented approach, as both approaches may provide

Table 3 Stepwise multiple regression results for the effect of severity, severity \times gender, directionality, and directionality \times gender on AUC_G levels, AUC_I levels, and Cort₂₀₀₀ levels, the covariates gender and quadratic effect of sampling month included in the first step.

Cortisol measures	Step 1	Beta	p-Value	Adj. R ² (%)	Step 2 (CBCL predictors)	Beta	p-Value	Adj. R ² (%)
AUC _G	Gender	-0.102	0.000**	2.3	Severity	0.024	0.340	-
	Sampling month	0.113	0.000**	2.3	Severity \times gender	-0.044	0.081	2.4
					Directionality	-0.009	0.734	-
					Directionality \times gender	-0.036	0.158	-
AUC _I	Gender	-0.038	0.134	-	Severity	0.029	0.257	-
	Sampling month	0.071	0.005**	0.5	Severity \times gender	-0.045	0.078	0.6
					Directionality	0.017	0.517	-
					Directionality \times gender	-0.005	0.847	-
Cort ₂₀₀₀	Gender	-0.029	0.229	-	Severity	0.002	0.927	-
	Sampling month	0.202	0.000**	4.1	Severity \times gender	-0.002	0.931	-
					Directionality	0.056	0.031*	4.1
					Directionality \times gender	-0.020	0.412	-

Adjusted R² are reported for significant effects and effects that approached significance.

*Significant at the 0.05 level.

**Significant at the 0.01 level.

different information that can be complementary (Ormel et al., 2005; von Eye et al., 2006).

The first hypothesis was that the potential inverse relationship between externalizing behavior problems and total cortisol levels after awakening is specific for boys. In the person-oriented approach, we did not find the expected group effect on total cortisol after awakening (AUC_G levels) in boys, nor did we find the expected directionality \times gender effect on AUC_G levels in the variable-oriented approach. Hence, we were not able to replicate findings from previous studies that demonstrated an inverse relationship between externalizing behavior problems and cortisol levels in samples consisting of predominantly boys (van Goozen et al., 1998; McBurnett et al., 2000; Oosterlaan et al., 2005) or findings from studies on mixed-gender samples that concluded that low cortisol may be specific for *male* externalizing behavior problems (Shirtcliff et al., 2005; Loney et al., 2006). Our inability to replicate previous findings could be related to the fact that previous studies have largely been conducted on clinical or high-risk samples, whereas the present study was based on a large population-based sample. Early adolescents with more severe externalizing behavior problems are most likely to be found in clinical or high-risk samples rather than in population-based samples. Indeed, low basal cortisol levels were found to be specific for children and adolescents with more severe disruptive behavioral problems (van de Wiel et al., 2004). Moreover, we demonstrated that gender had a particularly strong effect in the Pure EXT group, in that girls from the Pure EXT group showed significantly higher AUC_G levels than boys from the Pure EXT group (Figure 1A). This finding provides some evidence that the relationship between

externalizing behavior problems and hypoactivity of the HPA-axis might be absent in mixed-gender samples.

Concerning our second hypothesis, we expected that comorbid externalizing and internalizing behavior problems lead to higher total cortisol levels after awakening (AUC_G levels) than pure externalizing behavior problems, an effect that might be specific for boys (McBurnett et al., 1991). In the person-oriented approach, we did not find a main effect of group nor did we find a main effect of group in boys and girls separately. In the variable-oriented approach, we found an indication that AUC_G levels increase with increasing severity of behavior problems in girls. However, considering the findings of the person-oriented approach, this effect is not likely due to the girls from the Comorbid group, but rather due to the girls from the Pure EXT group (Figure 1A). The fact that we did not find a direction \times gender effect underlines the importance of using a person-oriented approach, that is, pure externalizing behavior problems cannot be separated from the person, at least in girls. In short, there appears to be no evidence of an effect of comorbidity on AUC_G levels. Several previous studies were also not able to detect an effect of comorbidity (Oosterlaan et al., 2005; Shirtcliff et al., 2005), suggesting that in externalizing behavior problems, additional internalizing behavior problems do not lead to increased AUC_G levels. Apparently, the relationship between comorbidity and AUC_G levels is more complicated than we assumed, and cannot be explained in a straightforward way by the hypothesis of additive effects of externalizing behavior problems and internalizing behavior problems.

The first part of the third hypothesis was that pure externalizing behavior problems are more strongly related

to the genetically influenced CAR (AUC_I levels) than comorbidity, since pure externalizing behavior problems are thought to be more genetically influenced than comorbid externalizing and internalizing behavior problems (Gjone and Stevenson, 1997). In the person-oriented approach, we indeed found elevated AUC_I levels in the Pure EXT group compared to the Control group and the Comorbid group. Exploration of the gender \times group interaction effect revealed that these effects are gender-specific, as they appear in girls but not in boys. In addition, like in the AUC_G analyses, the variable-oriented approach revealed an indication that AUC_I levels increase with increasing severity of behavior problems in girls. Again, considering the findings of the person-oriented approach, this effect may be more due to girls from the Pure EXT group than to girls from the Comorbid group (Figure 1B). We will discuss these findings in girls in more detail later. We also expected that the Comorbid group would show higher AUC_I levels than the Control group. Both in the total group and in analyses for boys and girls separately, this was not the case. It could be that the comorbidity was more environmentally determined, rather than genetically determined, but this was not supported by the analyses on evening cortisol levels. The person-oriented analyses could not confirm the second part of the third hypothesis that comorbid externalizing and internalizing behavior problems are related to evening cortisol levels. In contrast, the variable-oriented approach provided evidence that externalizing behavior problems, in contrast to internalizing behavior problems, may be related to higher evening cortisol levels. Though we did not find a directionality \times gender effect, girls with externalizing behavior problems show the highest evening cortisol levels, possibly influencing the strength of this effect (Figure 1C). Moreover, we should not put undue weight on this directionality effect given that this finding did not contribute to an increase of the effect size.

To summarize so far, the key findings of the present study are two-fold. Firstly, we were not able to find the expected relationships between comorbidity and AUC_G levels, AUC_I levels, and evening cortisol levels. Secondly, girls with pure externalizing behavior problems form a distinct group, showing elevated AUC_G levels and AUC_I levels, and possibly influencing the directionality effect on evening cortisol levels. With regard to the former conclusion, as stated before, comorbidity should be considered as more than an addition of externalizing and internalizing behavior problems. Since comorbid externalizing and internalizing behavior problems are probably more clinically and etiologically heterogeneous than pure (externalizing) behavior problems (Gjone and Stevenson, 1997; Boylan et al., 2007), it could be that comorbidity is relatively insensitive to the effects of this single aspect of the neuroendocrine system. Planned contrasts support this explanation, revealing that the Comorbid group did not differ from the Control group with respect to AUC_G levels and AUC_I levels. With regard to the second key finding, there are indications that the CAR (both total levels and with respect to increase) in externalizing behavior problems is strongly dependent on gender. This gender effect was not previously found since previous researchers almost exclusively studied boys or did not test gender differences. However, our finding is not in line with the study by Pajer et al. (2001) showing low levels

of cortisol in girls with conduct disorder. Yet, differences in cortisol sampling (plasma vs. saliva) and operationalizing of behavior problems (conduct disorder vs. broadband externalizing) could account for these apparently contradictory findings. Moreover, the course of externalizing behavior problems could play a role. Moffitt and Caspi (2001) demonstrated that relatively few girls show a life-course-persistent pattern of externalizing behavior problems (ratio = 10 males:1 female) in comparison to girls with an adolescence-limited pattern (ratio = 1.5 males:1 female). Moreover, since males with a life-course-persistent pattern of externalizing behavior problems score worse on many risk factors compared to females with an adolescence-limited pattern, it could be hypothesized that elevated AUC_G and AUC_I levels are a particular risk factor for adolescence-limited patterns of externalizing behavior problems in females. However, this possibility needs to be further investigated in longitudinal research.

There are some potential limitations regarding the present study that need to be acknowledged. Firstly, home collection of saliva is much more susceptible to situational influences than collection of saliva in the more controlled conditions at the laboratory. Recent research suggests, however, that home assessment of cortisol in saliva provides the same results as the assessment under highly controlled laboratory conditions (Wilhelm et al., 2007). Secondly, it has been argued that the dichotomization of quantitative variables, such as the scores of CBCL and YSR, is statistically inferior, rarely defensible and often will yield misleading results (MacCallum et al., 2002). We believe that setting a cutoff at the 84th percentile of CBCL and YSR is justified by the important distinction between behavior problems which fall within and outside the clinical range, and which has been confirmed and validated in papers by Achenbach and others working on the CBCL family of rating scales (Achenbach, 1991a; Verhulst et al., 1996; Achenbach and Rescorla, 2001). In the person-oriented approach, the Comorbid group exhibited more severe externalizing behavior problems than the pure externalizing group. Note that our variable-oriented approach took account of this issue by differentiating between overall severity and direction of psychopathology (Essex et al., 2006). As previously discussed, severity of disruptive behavioral problems might be related to HPA-axis activity (van de Wiel et al., 2004). However, our results suggest that this bias does not lead to higher HPA-axis activity in the Comorbid group.

On the other hand, the strength of the study lies in the fact that our findings are based on a very large population-based sample. Moreover, we obtained samples which were not subject to selection bias (de Winter et al., 2005). In addition, few studies have investigated the relationship between HPA-axis activity and externalizing behavior problems in population-based samples, and of these studies, few considered the influence of gender and comorbidity. Another asset of our study is the use of both person-oriented and variable-oriented analyses which proved to be complementary and took maximal account of the type and distribution of the available data. Note that although our significant findings were mainly based on the person-oriented approach, the results of the variable-oriented approach could be reconciled with the results of the person-oriented approach.

We like to underline that many of our findings were trends and that the effect sizes of our significant findings are relatively weak compared to effect sizes in studies on clinical or high-risk samples. This could be due to subjects included in clinical or high-risk samples being characterized by overall much greater severity of externalizing behavior problems than subjects sampled from the general population, and in turn, this greater severity could explain the size of the effects (van de Wiel et al., 2004). The weak effect sizes could also be due to random measurement errors since we do not know the exact sampling times; hence true relationships may have been underestimated.

In summary, our results indicate that comorbidity and gender need to be considered in studies of HPA-axis activity in relation to externalizing behavior problems. Although we did not find the expected effects with respect to comorbidity, our findings indicate that pure externalizing behavior problems should be differentiated from comorbid behavior problems, especially in girls. Longitudinal research should examine whether the findings in girls with externalizing behavior problems are the result of an adolescent-limited pattern of externalizing behavior problems. Moreover, while comorbidity and gender clarified part of the complex relationship between HPA-axis activity and externalizing behavior problems, there are many other risk factors such as life events and family and parenting factors as well as genetic risks that should be included to study this complex relationship.

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Conflict of interest

None declared.

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