



The role of anxiety in cortisol stress response and cortisol recovery in boys with oppositional defiant disorder/conduct disorder



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ABSTRACT

Children with antisocial and aggressive behaviors have been found to show abnormal neurobiological responses to stress, specifically impaired cortisol stress reactivity. The role of individual characteristics, such as comorbid anxiety, in the stress response is far less studied. Furthermore, this study extended previous studies in that not only baseline and reactivity to a psychosocial stressor were examined, but also recovery from a stressor. These three phases of cortisol could be impacted differentially in boys with oppositional defiant disorder/conduct disorder (ODD/CD) with (+ANX) and without anxiety (–ANX). The results revealed that cortisol patterns in response to psychosocial stress were different for boys with ODD/CD + ANX ($n = 32$), ODD/CD – ANX ($n = 22$) and non-clinical controls (NC) ($n = 34$), with age range of 7.8–12.9 years. The ODD/CD – ANX group showed lower overall cortisol levels than the NC group. When considering the three phases of cortisol separately, the ODD/CD – ANX group had lower baseline cortisol levels relative to the other groups, whereas the ODD/CD + ANX showed an impaired cortisol recovery response. Within those with ODD/CD, callous-unemotional traits were predictive of high baseline cortisol levels. Also, anxiety predicted high baseline and recovery cortisol levels, whereas a high number of CD symptoms predicted reduced cortisol stress reactivity. These results clearly indicate that comorbid anxiety is an important factor in explaining differences in stress response profiles in boys with ODD/CD; although boys with CD/ODD are generally characterized by an impaired cortisol stress response, we found that those with comorbid anxiety showed impaired cortisol recovery, whereas those without anxiety showed reduced baseline cortisol levels.

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1. Introduction

There is increasing evidence that neurobiological deficits play a key role in aggressive and antisocial behavior in children (van Goozen et al., 2007). It is argued that stress regulating mechanisms, such as the hypothalamic-pituitary-adrenal (HPA) axis, are important in explaining individual differences in aggressive and antisocial behavior. The end product, cortisol, has received much attention because of its vital role in enabling adaptive responses to stress, in order to survive and cope with danger (Sapolsky, 1998).

Studies have reported mixed findings concerning the relationship between aggressive and antisocial behavior and cortisol (Alink et al., 2008; van Goozen et al., 2007). Inconsistencies in findings might be explained by methodological differences, such as different populations (community versus clinical, age, male/female), sampling of cortisol (plasma, urine, saliva) and time of the day, informant (self-, parent- or teacher-report) and type of stressor. However, another explanation might be found in the notion that children with aggressive and antisocial behavior form a heterogeneous group (Stadler, 2010), and that individual differences in levels of emotional problems vary greatly (Schoorl et al., 2015).

Nevertheless, studies on primary school-aged children with aggression problems have generally found normal cortisol baselines but reduced cortisol stress reactivity to stress, compared to controls (Snoek et al., 2004; van Goozen et al., 1998; van Goozen

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et al., 2000). This blunted cortisol stress reactivity has been associated with fearlessness and deficient emotion regulation (van Goozen, 2015), which may be an important mechanism driving behavioral problems in children with oppositional defiant disorder (ODD) or conduct disorder (CD) (Burke, 2012; Cavanagh et al., 2014). Interestingly, studies on ODD/CD and anxiety show different results; cortisol levels were higher in anxious children with CD (McBurnett et al., 1991) and higher cortisol stress reactivity was found in boys with ODD (van Goozen et al., 1998) and ODD/CD (van Goozen et al., 2000) with relatively high levels of anxiety compared to low anxious boys. Thus not all children with ODD/CD have low cortisol levels and comorbid anxiety might be an important factor contributing to variability in cortisol responses within ODD/CD samples.

Because in previous studies variation in callous-unemotional (CU) traits has been considered a relevant factor contributing to variability in cortisol responses (Hawes et al., 2009), this was also included in the present manuscript. CU traits have been related to lower baseline cortisol as well as blunted cortisol response to stress (Loney et al., 2006; Stadler et al., 2011). However, two other studies did not find a relation between baseline cortisol and CU traits (Feilhauer et al., 2013; Poustka et al., 2010).

In addition to child factors that may contribute to variability, it may also be relevant to distinguish several phases of stress responses, which could be impacted differentially in these children. The degree to which children are able to regulate stress is not only evident in a blunted or sharpened cortisol response to stress, but also in their ability to recover from stress. The ability to recover after a stressor is an important indicator of the quality of an individual's emotion regulation (Freeman, 1939; Ji et al., 2016). Infants of mothers whose interactions with their infants were most disrupted, e.g. highly unresponsive, ineffective or inappropriate, did not recover from a stressor; their cortisol levels kept increasing after the stressor was gone (Crockett et al., 2013). Also, faster cortisol recovery after daily stressors was related to maternal sensitivity in infants, indicating that sensitive mothers helped their infants indirectly to regulate their cortisol response (Albers et al., 2008; Blair et al., 2008). Healthy individuals are able to rapidly down regulate emotions after a stressor has ended, as a means of adapting to environmental challenges without the severe biological cost of keeping stress levels high (Hastings et al., 2011). Recovery from stress is thus an important mechanism in behavioral adaptation. The aggressive and antisocial behavior that children suffering from ODD/CD show might be the result of impaired recovery. However, the literature examining cortisol recovery separate from cortisol response to stress in children with emotional and behavioral problems is sparse, and in relation to ODD/CD, to our knowledge, non-existent. Therefore, the aims of the study were to further investigate the role of anxiety within those with ODD/CD and to examine cortisol under baseline, stress and recovery conditions. To this end we included boys with ODD/CD with and without a comorbid anxiety disorder and also a sample of typically developing boys as controls.

2. Method

The current study was approved by the Medical Ethical Committee of Leiden University Medical Centre (LUMC). Prior to participation signed informed consent according to the declaration of Helsinki was obtained from the parents. Eleven boys with ODD/CD and two controls from the larger study were not able to produce saliva samples, missed one or more saliva sample or had one or two saliva samples that were inadequate for analyses, i.e. 3 SD above mean, and were excluded from the current study.

2.1. Participants

The ODD/CD group ($n=54$) was recruited at clinical health centers ($n=19$), special education schools ($n=26$) and regular elementary schools ($n=9$). All boys had an IQ over 70, were aged between 7.8 and 12.9, and had a diagnosis of ODD or CD on the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al., 2000). All boys met criteria for ODD diagnosis and 17 boys (32%) also met CD criteria. Other comorbid diagnoses were: attention deficit hyperactivity disorder (ADHD) ($n=38$, 70%), depression ($n=8$, 15%), and other disorders, e.g. eating or tic disorders ($n=15$, 28%), as based on the DISC-IV. Twenty-two boys (41%) used psychostimulants and two (4%) were on risperidone.

Using the DISC-IV boys with ODD/CD were divided into the ODD/CD + ANX group if they met criteria for a comorbid anxiety disorder ($n=32$). Boys in the ODD/CD + ANX group met criteria of one or more of the following anxiety disorder: separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, agoraphobia and specific phobia. If they did not meet criteria for any of these anxiety disorders they were included in the ODD/CD-ANX group ($n=22$).

The non-clinical control group (NC) ($n=34$) was recruited at regular elementary schools. All boys had an IQ over 70 and were aged between 8.0 and 12.7. None of them used medication or showed severe aggressive behaviors, expressed as a diagnosis of ODD or CD, a score outside the normal range ($T>60$) on the externalizing scale of the Child Behavior Checklist (CBCL/6–18) or Teacher Report Form (TRF/6–18) (Achenbach and Rescorla, 2001).

2.2. Recruitment

Boys referred through clinical centers were first screened with the CBCL (Achenbach and Rescorla, 2001). Those who scored above the borderline cut off point on the externalizing scale were subsequently administered the DISC-IV interview Module E (section on ODD and CD) (Shaffer et al., 2000). Only those children who met criteria of either ODD or CD were asked to take part in this study.

Special educational needs schools and regular elementary schools were selected based on their location, no further than one hour's drive from Leiden University. Headmasters were contacted by one of the researchers and if the headmaster agreed to take part, information brochures for parents and response-cards were distributed by the teachers to the children in their class.

Participating boys were asked to visit Leiden University for one day with one of their parents. During this day parents signed an informed consent, filled out questionnaires and completed the DISC-IV interview.

2.3. Measures

IQ was estimated using the Vocabulary and Block Design subtests of the Dutch version (Kort et al., 2005) of the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003). These subtests have been found to provide a good estimation of full scale IQ scores (Sattler, 1992).

Child psychopathology was assessed using the Dutch version of the DISC-IV interview (Ferdinand and van der Ende, 2002) with one of the parents. The DISC-IV is a highly structured diagnostic instrument (Shaffer et al., 2000) and was conducted by a clinical trained psychologist with experience. Diagnosis occurred after completion of the interview, at time of measuring symptoms this interviewer was 'blind' to diagnosis. Symptom scores and diagnoses are according to the DSM-IV criteria (DSM-5 had not been published at the start of this study).

CU traits were measured with the CU subscale of the Dutch version (De Wied et al., 2014) of the Antisocial Process Screening

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