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Blunted HPA axis response to stress is related to a persistent Dysregulation Profile in youth

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ABSTRACT

The Child Behavior Checklist Dysregulation Profile (DP) in youth has been shown to be a predictor of psychopathology later in life. We examined the activity of the hypothalamic pituitary adrenal (HPA) axis in youth with remitted, new, persistent, and no DP. Data from 489 youth (47% boys) participating in a Dutch longitudinal general population study were included (Wave 1 mean age = 11.5, Wave 2 = 14.2). Wave 2 diurnal cortisol patterns and levels in response to a laboratory stress paradigm were compared in youth with DP at Wave 1 only, Wave 2 only, both Waves, and neither Wave. Youth with the DP at Wave 2 only or at both time points showed blunted cortisol responses to stress relative to the other two groups. There were no group or sex differences in diurnal cortisol activity. More research is needed to determine how the association between DP symptoms and HPA axis functioning changes over time.

1. Introduction

With increasing emphasis on the need for prevention of psychiatric disorders (Beardslee, Chien, & Bell, 2011; O'Connell, Boat, & Warner, 2009), there has been a call for research identifying risk in youth in order to prevent debilitating psychopathology later in life. The Dysregulation Profile (DP), assessed using a widely used parent-report questionnaire measure called the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001), has been shown to be a particularly strong predictor of poor mental health outcomes later in life (Althoff, Verhulst, Rettew, Hudziak, & van der Ende, 2010; Biederman et al., 2009; Holtmann et al., 2011; Meyer et al., 2009). The DP, which consists of clinically elevated scores on the aggressive behavior, anxious-depressed, and attention problems scales of the CBCL, was originally identified by Biederman et al. (1995) as a profile common among children with bipolar disorder. As research on the DP has advanced, however, it has become clear that the profile is predictive of not only bipolar disorder, but also many other serious and debilitating emotional and behavioral problems, such as substance use, major depression, personality disorders, and suicidality (Althoff et al., 2010; Biederman et al., 2009; Holtmann et al., 2011; Meyer et al., 2009). Recently, Althoff et al. (2010) showed that the DP (measured in childhood) predicted anxiety disorders, mood disorders, substance use disorders, disruptive behavior disorders, and major depressive disorder in adulthood, 14 years later.

Based on the literature, the DP appears to be best described as a profile reflective of problems in regulating behavior, attention, and emotion (hence the name Dysregulation Profile). Therefore, children with this profile are likely to have difficulties in multiple areas of functioning and may be particularly at risk for co-occurring disorders later in life. Because of its clear clinical relevance and the ease with which it can be measured, the DP may be an excellent identifier of populations in need of preventive interventions to ameliorate existing psychopathology, and to prevent even more severe problems in the long-term.

To fully understand the etiology of the DP, and to ultimately design effective treatment and prevention protocols, it is necessary to study the biological processes that may differentiate youth with the DP from youth with other psychopathology and from healthy youth. However, the biological correlates of the DP have not yet been sufficiently examined. Holtmann, Zepf, and colleagues (Holtmann, Duketis, Goth, Poustka, & Boelte, 2010; Zepf, Wockel, Poustka, & Holtmann, 2008) found elevated thyroid stimulating hormone (TSH) levels and evidence of dysfunction in the serotonin system among youth with the DP. However, a more recent study failed to find any association between indicators of thyroid function and the DP in youth (Zepf et al., 2011). These studies have led the way in attempting to understand the function or dysfunction of biological systems related to the regulation of mood and stress among youth with the DP. However, more research is

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clearly needed to identify biomarkers and examine the etiology of this important identifier of severe psychopathology and long-term impairment.

One of the most widely studied biological systems in the development of psychiatric disorders is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis regulates the response and adaptation to changes, including stressors, in the environment. When exposed to stress, the central nervous system is activated, and corticotropin releasing hormone (CRH), adrenal corticotrophic hormone (ACTH), and cortisol are released in the brain. The increased cortisol levels elicit the inhibition of the HPA axis, and once the stressor is gone, cortisol levels return to their baseline levels (Jacobson & Sapolsky, 1991).

Variations in HPA axis activity, usually assessed using repeated measurements of salivary cortisol during a normal day or during a laboratory stress task, have been found in clinical and healthy populations (Chida & Hamer, 2008; Chida & Steptoe, 2009). Individuals with psychopathology such as depression, anxiety, aggression, substance use, and other emotional and behavioral problems often display maladaptive cortisol responses, such as cortisol levels that do not sufficiently increase in response to a stressor, or that do not recover after the removal of a stressor (Burke, Davis, Otte, & Mohr, 2005; Chida & Hamer, 2008; Greaves-Lord, Ferdinand, Oldehinkel, Sondeijker, Ormel, & Verhulst, 2007; Greaves-Lord, Huizink, Oldehinkel, Ormel, Verhulst, & Ferdinand, 2009). HPA-axis responsivity to stress is influenced by many different factors, including the severity of psychopathology (Burke et al., 2005; Chida & Hamer, 2008; Kudielka, Hellhammer, & Wust, 2009). For example, in healthy subjects, there is evidence that individuals with emotion regulation deficits show *increased* cortisol levels in response to a stressor compared to those without such deficits (Lam, Dickerson, Zoccola, & Zaldivar, 2009; Quirin, Kuhl, & Dusing, 2011). In contrast, patients with more severe impairment of emotion regulation abilities (e.g., those with bipolar or borderline personality disorder) show *blunted* HPA-axis responding to stress (Nater et al., 2010; Steen et al., 2011). In other words, cortisol levels do not adequately increase following a stressor for those with severely impaired emotion regulation. This blunted cortisol response indicates a maladaptive response to stress, which can contribute to more severe levels of psychopathology over time (Burke et al., 2005). Given that the DP appears to predict severe adult psychopathology, we were interested in determining whether youth with the DP would also display alterations in HPA-axis functioning, such as blunted cortisol responses to stress.

Although HPA-axis responses have not yet been examined in youth with the DP, we turn to existing research on some of the DP sub-components for hypothesis formation. Research on the association between some of the sub-components of the DP and HPA-axis responding have been inconsistent. For example, studies have found positive, negative, and no association between HPA-axis responses in samples of youth with aggressive behavior (Cappadocia, Desrocher, Pepler, & Schroeder, 2009) and attention problems (Hastings, Fortier, Utendale, Simard, & Robaey, 2009; Ma, Chen, Chen, Liu, & Wang, 2011; Stadler et al., 2011; van West, Claes, & Deboutte, 2009). Some have hypothesized that a reason for this inconsistency could be the frequent lack of measurement of common co-occurring problems such as anxiety, depression, and emotional dysregulation within these samples (Cappadocia et al., 2009; Hastings et al., 2009; Stadler et al., 2011) or to the vulnerability of salivary cortisol measurements to be influenced by extraneous factors (Hellhammer, Wust, & Kudielka, 2009). Males and females also show differential cortisol levels even in the absence of psychopathology, with males typically displaying more pronounced responses to stress but a lower cortisol awakening response compared to females (Kudielka et al., 2009; Marsman, Swinkels, Rosmalen, Oldehinkel, Ormel, & Buitelaar, 2008). Thus, sex differences are critical to consider when examining HPA-axis functioning in youth.

Because the DP is a precursor to severe, long-lasting psychopathology, it is likely that stable high levels of these symptoms are associated with HPA axis dysfunction, especially in response to stress. In particular, it is important to know how different levels of severity and stability of the DP relate to HPA axis activity. Furthermore, despite clear sex differences in HPA axis functioning and in the development of psychopathology (Kudielka et al., 2009; Marsman et al., 2008; Nolen-Hoeksema & Girgus, 1994; Zahn-Waxler, Shirtcliff, & Marceau, 2008), the role of sex in the relation between psychopathology and HPA axis functioning has been relatively understudied (Zahn-Waxler et al., 2008).

In this investigation, we aimed to determine (1) whether differences in DP severity and stability were related to differences in HPA axis activity, both diurnally and in response to stress, and (2) whether these effects differed between boys and girls. Because the DP has been indicative of severe and pervasive psychopathology, we hypothesized that youth with stable high levels of DP symptoms rather than unstable DP symptoms would display blunted cortisol both diurnally and in response to stress. Further, we hypothesized that this effect would be moderated by the sex of subjects (Steen et al., 2011). We expected that the cortisol response would be more blunted for girls with the DP as compared to boys, consistent with previous findings on sex differences (Kudielka et al., 2009).

2. Methods

2.1. Participants

The sample for this study is part of a larger sample that participated in a longitudinal general population study (Tick, van der Ende, & Verhulst, 2007). For this larger study, 2567 children and adolescents were randomly drawn from municipal registers of 35 representative municipalities, including urban and rural areas, in the Dutch province of South Holland. At the first measurement (Wave 1), between December 2003 and April 2005, 1710 of the 2286 eligible families participated. For details on the initial data collection, see (Tick et al., 2007; Tick, van der Ende, & Verhulst, 2008). Approximately three years later, between January 2006 and March 2009, 1161 individuals were invited to participate in Wave 2 of the study if (1) they were born between January 1st 1988 and August 31st 1997, (2) they participated at Wave 1, and (3) they gave permission to be contacted for follow-up research. One hundred seventy one individuals refused or were unable to participate, resulting in 990 children and adolescents between 8 and 20 years old who participated at Wave 2. Of these 990 children and adolescents, 489 had complete Wave 1 and Wave 2 CBCL data, participated in Wave 2 cortisol assessment procedures, and were thus included in the current study. Fig. 1 describes participation and attrition for the current study. These participants did not differ from those without Wave 2 cortisol data on sex ($\chi^2(1) = 1.86$ ns), but those without Wave 2 cortisol data were slightly older at Wave 1 (mean age = 12.4) compared to those with Wave 2 cortisol data (mean age = 11.4; $F(1, 1705) = 33.19$, $p < .001$, $\eta^2 = .02$). Subjects who participated in the assessment of cortisol response to stress had mothers ($F(1, 1681) = 20.00$, $p < .001$, $\eta^2 = .01$) and fathers ($F(1, 1562) = 6.86$, $p < .01$, $\eta^2 = .004$) with higher-level jobs than those who did not participate. Written informed consent was obtained from all participating youth and their parents. The Medical Ethics Committee of the Erasmus Medical Center approved the study. For the current study, the mean age of participants at Wave 1 was 11.5 years (SD = 2.7, range = 6–16), and mean age at Wave 2 was 14.2 years (SD = 3.6, range = 8–20). Forty-seven percent of the sample was male.

2.2. Measures and procedure

2.2.1. Diurnal and stress-related cortisol levels at Wave 2

At Wave 2, salivary cortisol samples were taken at ten time points in total by passively drooling into a test tube, a reliable and stress-free approach (Kirschbaum & Hellhammer, 1994).

2.2.2. Diurnal cortisol levels

Four tubes for assessment of salivary cortisol levels on a normal day were sent to the participants by mail prior to the stress procedure. Detailed written and verbal instructions were given on the time (a normal day) and manner of sample collections, and to preserve the tubes in the freezer until the testing day. Instructions included asking participants to refrain from consuming caffeine or chocolate on the day of, ingesting dairy products 1 h prior, and eating 30 min prior to saliva collection. Participants were instructed to provide the first sample directly upon awakening, the second 30 min afterwards, the third at 12 p.m. and the fourth at 8 p.m.