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Cortisol levels at baseline and under stress in adolescent males with attention-deficit hyperactivity disorder, with or without comorbid conduct disorder

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ABSTRACT

Reported findings on cortisol reactivity to stress in young people with ADHD are very variable. This inconsistency may be explained by high rates of comorbidity with Conduct Disorder (CD). The present study examined cortisol responses to a psychosocial stressor in a large sample of adolescent males with ADHD ($n=202$), with or without a comorbid diagnosis of Conduct Disorder (CD). Associations between stress reactivity and callous-unemotional traits and internalizing symptoms were also assessed. The ADHD only (n=95) and ADHD+CD (n=107) groups did not differ in baseline cortisol, but the ADHD+CD group showed significantly reduced cortisol stress reactivity relative to the ADHD only group. Regression analyses indicated that ADHD symptom severity predicted reduced baseline cortisol, whereas CD symptom severity predicted increased baseline cortisol (ADHD $\beta=-0.24$, CD $\beta=0.16$, $R=0.26$) and reduced cortisol stress reactivity ($\beta=-0.17$, $R=0.17$). Callous-unemotional traits and internalizing symptoms were not significantly related to baseline or stress-induced cortisol. Impaired cortisol reactivity is hypothesised to reflect fearlessness and is associated with deficient emotion regulation and inhibition of aggressive and antisocial behaviour. Consequently, it may partly explain the greater severity of problems seen in those with comorbid ADHD and CD.

1. Introduction

The Hypothalamic-Pituitary-Adrenal (HPA) axis plays a critical role in mediating physiological responses to stress, enabling organisms to adapt to environmental changes (Marquez et al., 2006). The regulation of the HPA axis, with cortisol as its end product, appears to be dysfunctional in several psychiatric disorders (Tsigos and Chrousos, 2002). Research interest in HPA axis activity in Attention-Deficit/Hyperactivity Disorder (ADHD) has focused on the theoretical notion of under-arousal and the putative need in those with ADHD to increase their levels of arousal to avoid boredom (Zuckerman, 1994; Stadler et al., 2011). Reduced baseline cortisol levels or a blunted cortisol response to psychological stress have been found in children with ADHD compared with healthy controls (Blomqvist et al., 2007; Ma et al., 2011; Isaksson et al., 2012). However, other studies found positive associations between ADHD symptoms and cortisol in population-based samples (e.g., Palma et al., 2012) or comparable cortisol levels in children with and without ADHD (e.g., Snoek et al., 2004; Cakaloz et al., 2005; Freitag et al., 2009; Palma et al., 2012). These mixed results could be due to variations within ADHD samples, especially in relation to comorbid disorders, sample size and hormone measurement techniques (see Fairchild (2012), for a review).

Adolescents with ADHD are a heterogeneous population, with 30–50% of children with ADHD in clinical settings also meeting criteria for Conduct Disorder (CD; Biederman et al., 1991). There is clear and much more consistent evidence that HPA axis activity is altered in those with CD and Oppositional Defiant Disorder (ODD; Van Goozen, et al., 2000; Kariyawasam et al., 2002; Oosterlaan et al., 2005; Van Goozen, et al., 2007; Fairchild et al., 2008). It has been hypothesised that blunted cortisol reactivity reflects fearlessness and is associated with deficient emotion regulation and

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inhibition of antisocial behaviour (Van Goozen et al., 2007). However, previous studies on cortisol secretion in children with ADHD have not always controlled for comorbid disruptive behaviour disorders (DBDs) such as CD or ODD (e.g., Blomqvist et al., 2007). Consequently, the first aim of this study was to investigate adolescent boys with ADHD and compare those with or without a comorbid diagnosis of CD in terms of baseline cortisol and cortisol stress reactivity.

Studies that did assess and control for comorbid DBDs have still obtained mixed results. Some studies found lower baseline cortisol levels in children with ADHD and comorbid ODD/CD, but not in children with non-comorbid ADHD (Cakaloz et al., 2005; Freitag et al., 2009), whereas others found reduced baseline cortisol levels in non-comorbid ADHD (Van West et al., 2009; Ma et al., 2011) and one study found no effect of DBD comorbidity within an ADHD sample (Isaksson et al., 2012).

This may be due to differences between studies in cortisol measurement techniques or saliva collection protocols. The HPA axis is a dynamic system that not only responds to psychological and physical stress, but also exhibits a marked diurnal rhythm (Kirschbaum and Hellhammer, 1989). Therefore studies that have only assessed cortisol at one (e.g., Ma et al., 2011) or two (Cakaloz et al., 2005) time point may be difficult to interpret, especially if they have not controlled for time of awakening or time of sample collection. Furthermore, some research has relied on participants collecting cortisol samples themselves (e.g., Freitag et al., 2009; Isaksson et al., 2012), which requires participants keeping to a strict timescale and carefully following collection protocols. Problems with adherence to a saliva collection protocol might be particularly pronounced in young people with ADHD who have difficulties with concentration, organisation and being forgetful; this could lead to both false positive and false negative findings (Kudielka et al., 2004).

Even when cortisol reactivity to a stressor has been investigated, there are inconsistent findings. Reduced cortisol reactivity to stress has been found in children with ADHD and comorbid DBD compared to children with ADHD alone (Hastings et al., 2009; Snoek et al., 2004). Other studies found associations between ADHD symptoms and reduced cortisol stress reactivity after controlling for comorbid DBD (Van West et al., 2009; Pesonen et al., 2011). However, the choice of stressor is important. For example, some previous studies have used inadequate or relatively weak stressors, such as cognitive tests (e.g., Yang et al., 2007). The present study used an established psychosocial stress induction protocol that elicited feelings of anger, failure and negative social evaluation (e.g., Van Goozen et al., 2000; Snoek et al., 2004; Fairchild et al., 2008), and involved collecting eight cortisol samples under strict experimental conditions.

When analysing the effects of CD, it is also important to assess the effects of anxiety/depression symptoms as it is increasingly recognised that comorbidity between externalizing and internalizing problems is common (Lahey and Waldman, 2012). Anxiety or depressive symptoms are frequently reported to be associated with *increased* cortisol activity or reactivity (Knight et al., 2010). Thus patterns of cortisol reactivity in ADHD can be further complicated by patterns of comorbid emotional symptoms as well as conduct disorder (e.g., Hastings et al., 2009).

Another potentially important source of heterogeneity that is closely related to conduct disorder, is variation in callous-unemotional (CU) traits. These traits identify those at greater risk for severe antisocial behaviour (Lahey and Waldman, 2012) and reduced responsiveness to treatment (Hawes et al., 2014). The importance of such traits has been acknowledged by including limited prosocial emotions as a specifier for CD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). CU traits have been linked to lower baseline cortisol levels and a blunted cortisol response to stress (O'Leary et al., 2007). However, the impact of CU traits on cortisol activity has been predominantly investigated in non-clinical samples free of psychiatric disorders (Loney et al., 2006). An exception to this was a study that reported reduced cortisol responses to stress in participants with ADHD and high levels of CU traits – with over half of the participants having a comorbid DBD diagnosis – compared to those with ADHD with low levels of CU traits (Stadler et al., 2011). This finding now needs to be replicated in a larger clinical sample of adolescents with ADHD (the sample size in the latter study was N = 36).

Previous research has also focused on heterogeneity in cortisol reactivity between ADHD subtypes. Maldonado et al. (2009) observed reduced overall cortisol levels in hyperactive/impulsive children compared with inattentive ADHD children during a psychosocial stress induction procedure. However, their stress procedure was conducted in the morning and failed to induce an increase in cortisol. Van West et al. (2009) reported blunted cortisol responses in combined ADHD children when compared with a group of inattentive children. However, this group also had higher DBD symptoms. Hastings et al. (2009) controlled for comorbid disorders and found that ADHD subtypes were not differentially associated with baseline or reactive cortisol levels. However, comorbid DBD predicted decreased cortisol reactivity in boys with inattentive and hyperactive subtypes of ADHD, but not in boys with combined subtype of ADHD. This study did not focus on ADHD subtype classifications because previous publications (e.g. Willcutt et al., 2012) have demonstrated that these subtypes are not definitive or stable over time. Instead we examined the role of symptom severity within each dimension on cortisol.

The present study aimed to assess cortisol levels at baseline (pre-stress samples taken under experimental conditions) and in response to stress (area under curve with respect to increase; Pruessner et al., 2003) in a sample of adolescent males with ADHD, and explore the contributions of Conduct disorder diagnosis, ADHD severity, CD symptom severity, CU traits and internalizing symptoms. To our knowledge, this is the largest study of experimentally-induced stress reactivity in an ADHD or CD sample.

2. Methods

2.1. Sample

Participants were recruited from Child and Adolescent Mental Health Services and Community Child Health Clinics in Wales. Children in the sample were males of British Caucasian origin (also being recruited for a genetics study; Van Goozen et al., 2015) and had a clinical diagnosis of ADHD. Those with any known clinical or research diagnosis of schizophrenia, bipolar disorder, Autistic Spectrum Disorder (ASD), Tourette's syndrome, or with an IQ < 70, epilepsy, brain damage or any other neurological or genetic disorder were excluded from the study. In total, 202 adolescent males with ADHD (mean age = 13.95 years, sd = 1.82; age range 10–17 years) took part in the present study. No participants were stimulant naïve but participants who were currently being prescribed stimulant medication were asked to come off their medication at least 24 h prior to testing.

Ethical approval was obtained from the Wales Multicentre Research Ethics Committee. Informed written consent was obtained from all parents and adolescents aged over 16 years whereas written assent was obtained from adolescents below age 16 years.