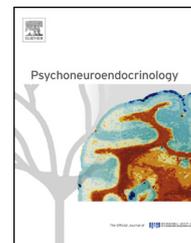




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Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety

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Summary Children and adolescents with autism spectrum disorder (ASD) have much higher rates of anxiety disorders relative to their typically developing peers. However, there have been few attempts to investigate what physiological parameters may be associated with this elevated rate of anxiety. Therefore, this study investigated the physiological correlates of anxiety in ASD, with a focus on whether measures of heart rate and cortisol responsiveness to psychosocial stress differentiate those participants with ASD with and without a co-occurring anxiety disorder. A total of 75 male participants aged 10–16 years with normal intellectual ability underwent a psychosocial stress test. The participants included healthy controls ($n = 23$), ASD only (ASD; $n = 20$) and ASD with a comorbid anxiety disorder (ASDanx; $n = 32$). Heart rate, heart rate variability and salivary cortisol were compared by fitting a piecewise regression model to examine baseline levels and change over time within and between the rest, stress and recovery phases of the stress test. The ASDanx group had different response patterns from both the ASD and control groups. The ASDanx

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group was characterized by a blunted cortisol and heart rate response to psychosocial stress. Furthermore, in the ASDanx group, reduced heart rate and cortisol responsiveness were significantly related to increased anxiety symptoms. This is the first study to report a possible physiological basis for co-occurring anxiety disorders in children and adolescents with ASD. It is possible that a non-adaptive physiological response to psychosocial stress may be related to the high prevalence of co-occurring anxiety disorders in people with ASD.

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1. Introduction

Autism spectrum disorder (ASD) is characterized by persistent deficits in social communication/interaction and restricted interests and repetitive behaviors, which present in early childhood. Children and adolescents with ASD also suffer from higher rates of co-occurring anxiety disorders (prevalence ~40%, [Van Steensel et al., 2011](#)) compared to their typically developing peers (prevalence ~3–8%, [Costello et al., 2003](#); [Merikangas et al., 2010](#)). Similarly, studies using questionnaire measures have identified elevated reports of anxiety symptoms in those with ASD ([Gadow et al., 2005](#); [Sukhodolsky et al., 2008](#)). However, there has been little research examining why people with ASD have such high rates of anxiety, or what physiological mechanisms may underlie these co-occurring anxiety disorders.

The diagnosis of pediatric anxiety disorders typically relies heavily on the self-report of internalizing symptoms ([Schniering et al., 2000](#)). These can be difficult for many individuals with an ASD to report due to difficulties understanding and labeling emotions ([Losh and Capps, 2006](#)). Therefore, in addition to providing information on potential physiological mechanisms, establishing the biological correlates of anxiety in ASD may eventually provide an additional marker of anxiety diagnoses that is not reliant on self-report assessments.

2. Physiology of anxiety and stress

Anxiety disorders are a group of conditions characterized by excessive and unpleasant worries or fearfulness that have a negative impact on a person's life. Anxiety is described with respect to three elements: cognitions, behaviors and physiological changes. When people are anxious they experience changes in one or more of these elements ([Lang, 1985](#)). The physiological stress response, on which this paper is focused, in part constitutes the physiological component of anxiety. However, stress is not a unique response to anxiety; rather anxiety is one of many external pressures on a biological system that is designed to maintain balance via the mechanisms described below.

The autonomic nervous system (ANS) and hypothalamic—pituitary—adrenal (HPA)-axis are both part of a dynamic stress response system that is vital in generating adaptive responses to both physiological and psychological threat, and are involved in the well-defined “fight-or-flight” response. Under threat, the body responds with the activation of the ANS, specifically in the sympathetic branch, to heighten arousal and prepare the person to deal with the stressor. Parasympathetic control is also exerted by the nucleus ambiguus and dorsal motor nucleus of the vagus nerve

([Ulrich-Lai and Herman, 2009](#)), acting on the sinoatrial node of the heart, and limiting the duration of the arousal state ([Kolman et al., 1976](#)). Synchronously, corticotrophin releasing hormone (CRH), the initial secretagogue of the HPA-axis, is released from the hypothalamus. This then induces the release of adrenocorticotropin releasing hormone (ACTH) from the pituitary gland and finally cortisol from the adrenals. While acute exposure to stress is associated with the potentiation of the HPA-axis and an increase in cortisol, chronic exposure to stress hormones leads to compensatory down-regulation, and a resulting blunted cortisol response or “hypocortisolemia” ([Miller et al., 2007](#)), which has been associated with both adverse childhood events ([Danese and McEwen, 2012](#)) and post-traumatic stress disorder (PTSD; [Yehuda and Seckl, 2011](#)).

3. The HPA-axis and ANS in ASD and anxiety disorders

Given the biological overlap between anxiety and stress ([Shin and Liberzon, 2010](#)) and the previous use of stress markers such as cortisol ([Van West et al., 2008](#)) and heart rate (HR) ([Schmitz et al., 2011](#)) to examine anxiety in childhood, markers of HPA-axis and ANS function are potential target measures of anxiety in ASD. However, it is currently unclear whether ASD specific differences in HPA-axis or ANS function are significantly associated with the increased rates of anxiety observed in this population.

The most common task used to elicit a stress response and to compare normal stress physiology with psychopathology related differences is a psychosocial stress test (PST) ([Kirschbaum et al., 1993](#)). This typically consists of a baseline period, followed by preparing and giving a speech, and then completing an arithmetic task under observation.

Studies using various adaptations of the PST in an ASD population have reported mixed results, but most point toward a significantly blunted increase in cortisol in response to the social stressor in people with ASD compared to controls ([Corbett et al., 2012](#); [Jansen et al., 2006](#); [Lanni et al., 2012](#); [Levine et al., 2012](#)). In non-ASD children with an anxiety disorder, the pattern is more inconsistent. A number of studies including participants with social phobia have reported variable findings including: cortisol hyper-responsiveness in pre-pubertal anxious children compared to controls ([Van West et al., 2008](#)); a non-significant trend for a blunted response in similarly aged anxious children with social phobia ([Krämer et al., 2012](#)); and no significant group difference in adolescent girls with social phobia compared to healthy controls ([Martel et al., 1999](#)). However, the social stressor response pattern in adults with both social phobia ([Beaton et al., 2006](#); [Furlan et al., 2001](#)) and panic disorder

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