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Critical review

Adolescence, stress and cortisol in autism spectrum disorders

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Abstract

Adolescence, the transition between childhood and adulthood, is a period of remarkable physiological, psychological and social change. A variety of physiological changes coincide with the dynamic transition, which is evident in the regulation and responsivity of the limbic–hypothalamic–pituitary–adrenocortical axis. Specifically, elevations in diurnal basal cortisol levels have been reported as well as higher cortisol in response to perceived stressors. Although this enhanced responsivity may help prepare the individual to adapt to increased demands and new challenges, it may also mark a time of increased vulnerability in populations already prone to enhanced physiological arousal and poor adaption to change, such as autism. To date, most studies investigating the integrity of the limbic–hypothalamic–pituitary–adrenocortical axis in children with autism spectrum disorders have shown more variable diurnal regulation and a pattern of enhanced responsivity to stress. There is also evidence of more marked reactivity over development suggesting that adolescence may be a time of increased risk for enhanced physiological arousal and social stress.

Conclusion

The following critical review briefly summarizes the literature to date on autism, adolescence and salivary cortisol. The current summary suggests that enhanced study of the interplay between social functioning and stress during the adolescent period in autism spectrum disorders is warranted.

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Introduction

Adolescence is a time of remarkable physiological, psychological and social changes in both typical and atypical populations. Due to the many changes that define it, adolescence has often been described as a time of 'storm and stress'[1]. During this developmental period, pubertal maturation contributes to significant changes in morphology, cognition, emotion regulation and physiological stress responsivity[2,3]. In typical development, adolescence is a time of increased awareness and interest in both peer and romantic relationships[4]. It also represents a time of dramatic rise in psychopathology and depression, which have been associated with dysregulation of stress systems, such as the hypothalamic–pituitary–adrenocortical (HPA) axis[3].

Although frequently used interchangeably, adolescence and puberty represent distinct maturational phenomena. Adolescence, strictly defined, is the developmental transition of juvenile social and cognitive processes to their adult versions. Puberty refers to biological maturation, particularly that of sexual systems and the physiological effects of resultant changes to the endocrine system[5]. The interplay between these two systems is, however, critical for appropriate and complete development into adulthood[6]. In this critical review, we aim to discuss the stresses on adolescents regarding social functioning.

Discussion

All work has been conducted in accordance with the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

HPA axis, stress and anxiety

The HPA axis is involved in the regulation of several biological processes and interactions, including physiological response to stress[7]. Cortisol is the primary stress hormone in humans and is released from the adrenal cortices following activation of the HPA axis in response to extreme physiological or psychological stress[7,8]. Cortisol has a normal circadian rhythm with a peak early in the morning followed by a sharp increase referred to as the cortisol awakening response (CAR); cortisol levels consequently decline throughout the day and the levels are lowest in the evening. The system can be activated by both actual and perceived threat. With regards to the latter, there exist four primary psychological determinants that induce a stress response, which include conditions of novelty, unpredictability, uncontrollability and social evaluative threat[9,10], the response to each of which varies based on environmental, idiosyncratic and developmental factors.

Stress and anxiety are common responses to the environment and both are frequently adaptive mechanisms to everyday life. If stress or anxiety are experienced in an excessive and uncontrollable manner, however, they can become pathological[11]. For the purpose of this review, anxiety encompasses the anticipatory and apprehensive cognitive activity related to events for which a person is exposed. Stress

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refers to the physiological reactivity in response to events, including activation of primary stress systems, such as the HPA axis. Although these states are highly correlated to each other in many circumstances, they are not synonymous and disjunction between the two does occur. Children with autism, for example, show a lack of correspondence between stress and anxiety in various circumstances[12].

Adolescence and the HPA axis

A variety of physiological changes coincide with the dynamic transition from childhood to adolescence, including the regulation and responsivity of the HPA axis. Characterization of physiological change in this system across the adolescent transition in typical and atypical development is important for characterizing developmental variation[13] as well as marking the end of childhood and the beginning of adult biological responses[14].

The HPA axis, by nature, is adaptive to environmental change; yet, there is an underlying trait-like diurnal fluctuation. During the critical developmental adolescent period, there is an apparent maturation of the circadian rhythm revealing higher basal cortisol levels in older adolescents[14–16]. A recent longitudinal study assessing the stability and individual variability of HPA axis maturation in 357 youth studied at four assessments (aged 9–15 years) revealed flatter circadian rhythms and higher cortisol values as youth matured based on chronological age and physical development[17]. Gender differences have also been identified. For example, compared to male adolescents across development, females often show higher cortisol levels and more robust circadian rhythms[17] and symptoms of anxiety and depression have been linked with enhanced cortisol reactivity in girls[14].

Changes in normative stress responsivity during the adolescent transition have been documented. The puberty-HPA stress hypothesis proposes enhanced stress reactivity with the emergence of sexual maturation[14]. Investigation of 82 healthy children and adolescents showed developmental differences based on several physiological indices of arousal[18]. Similarly, in a large cohort of children and adolescents aged 9–17 years, biological reactivity (i.e. cortisol) increased in anticipation of a social stressor based on both age and puberty[19]. This finding was especially notable during the mid-adolescence to advanced stages of pubertal development. It has been proposed that the anticipatory rise in cortisol may be associated with changes in cognitive processes that may in turn contribute to more worry prior to social evaluation[20]. The enhanced responsivity may help prepare the individual to adapt to increased demands and new challenges. However, it may also mark a time of increased vulnerability in populations already prone to enhanced physiological arousal and poor adaption to change such as autism[18].

Adolescence and autism

Adolescence poses a number of serious challenges in typical development provoking anxiety and stress as youth place new importance on peer relationships and begin to develop romantic relationships[21]. Peer rejection in adolescents is a major contributor to anxiety[22], and impairments in social skills inherent to autism spectrum disorders (ASD) become increasingly more apparent in adolescence due to the enhanced complexity and demand for competence during this period of time[23]. As a result, children with ASD often develop significant social anxiety directly related to their social impairments[24]. In addition to anxiety resulting from altered interactions related to social ability, greater awareness of their impairments may also be a significant contributing factor to anxiety[23]. Thus, these and other findings have fostered growing attention on the co-occurrence of anxiety in adolescents with ASD.

It has been estimated that between 11% and 84% of children with ASD experience anxiety that impairs everyday function[25] and 42–55% have a co-morbid anxiety disorder[26,27]. Furthermore, anxiety symptoms impact many areas of functioning, including restless behaviour and sleep difficulties[28]. Therefore, addressing anxiety in ASD is a major concern. Additionally, stress and anxiety have been shown to be significant contributors to specific difficulties, such as loneliness and social withdrawal that may compound already inhibited social abilities. Risk of psychopathologies, already frequently associated with adolescence, such as depression, are also elevated in children with ASD[29] and there is evidence that anxiety may arise or even worsen during adolescence[30,31]. As such, it is important to address underlying causes of stress and anxiety in children with ASD, while remaining mindful of differences from typically developing children. For example, it has been shown that compared with their typically developing peers, children with ASD experience elevated stress and anxiety in both social and non-social contexts, and that repeated exposure to stressors often amplifies the physiological stress response as opposed to attenuating it[32,33]. This altered vulnerability to dysregulated arousal emphasizes the importance of judicious application of interventions shown to be effective for anxiety treatment in ASD, such as cognitive behavioural therapy[34,35].

The overall trajectory of autism symptoms and resultant behaviours over maturation is the subject of conflicting reports. An early study suggested deterioration of symptom profile during the onset of puberty[36]. Similarly, behavioural decompensation requiring intervention was reported in a series of case reports[37]. Although there are various physi-

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ological changes potentially contributing to a worsening of symptom presentation, it has been suggested that sex hormones acting on DNA methylation at the *RELN* promoter may be an important factor[38]. Conflicting with these findings, other studies have found that autism symptoms and maladaptive behaviours tend to decrease in participants aged 10 years and above over long periods of time[39].

Another study following 242 subjects over 4.5 years found the greatest improvement in autism symptoms and maladaptive behaviour during puberty, with overall symptom trajectory decaying after exit from high school[40]. It is important to note that reductions in disability-related services have been proposed as a possible explanation for this trajectory. Taken together, it is clear that significant work remains in establishing a framework for understanding changes in overall autism symptom profiles, behaviour and mood during adolescence.

HPA axis in autism

The majority of characterizations of diurnal fluctuations and reactivity of the HPA axis in ASD have been conducted in children. Whereas lower functioning children with autism have been shown to exhibit atypical diurnal regulation of the HPA axis[41], higher functioning children with ASD show a normal temporal placement of cortisol secretion[42–44]. However, the rhythm tends to be much more variable from day-to-day compared with that of typically developing children, especially the morning values[42,45]. Additionally, evening values are higher[45] and have been associated with increased stress related to poor response to changes throughout the day[45,46]. Children with autism also tend to show a more sluggish response to adrenocorticotropic hormone stimulation[43] and lower serum concentrations have also been reported[47].

Our ability to adapt to changing circumstances and novelty is in part modulated by the HPA axis and in particular the CAR. Developmental factors may play a role in the CAR as suggested by studies examining the presence and frequency of the CAR in children and adolescents with ASD. Brosnan et al.[48] examined the presence of the CAR in a group of 20 adolescent males with Asperger syndrome and 18 typically developing control youth aged between 11 and 16 years. All participants showed a normal diurnal decline of cortisol; however, the CAR was absent in a majority of the youth with Asperger syndrome. The authors speculated that poor response to changes in individuals with Asperger syndrome may be due to refractory HPA axis; specifically, the CAR. More recently, Zinke et al.[49] investigated the CAR in a group of 15 high-functioning children with autism compared with 25 typically developing children aged 6–12 years and showed similar cortisol levels and frequency of the CAR between the groups. Taken together, developmental changes occurring between childhood and adolescents may be contributing to the observed differences. Distinctions in the diagnostic categories (i.e. Asperger syndrome versus HFA) or level of severity may also be playing a role.

Regarding response to stress, higher cortisol levels have been reported in children with ASD in response to non-social stimuli, including exposure to medical procedures such as phlebotomy[50] and exposure to a magnetic resonance imaging environment[42,45]. Social scenarios also result in activation of the HPA axis and subsequently higher cortisol during school integration[44], social interaction with peers in a playground[33,51] and engagement with unfamiliar children[52]. However, not all social stressors are salient for youth with ASD. It has been shown that a widely recognized social evaluative stressor, the Trier Social Stress Test – Child Version[53], failed to provoke a stress response in participants with ASD, whereas typically developing peers show increased physiological arousal across various indices[12,51,54,55]. These findings underscore the importance of "perceived" threat and suggest that children with ASD do not interpret some aspects of social evaluation, such as public speaking tasks, to be socially threatening.

Although the precise neuroendocrine mechanisms are yet to be determined, the findings to date implicate a pattern of increased arousal to acute stress rather than persistent hyperarousal in many children with ASD[42,56]. Although frequent perturbation of the stress system can be deleterious to the physical and mental health of the individual, the acute reactivity to stimuli (rather than a chronic state of arousal) suggests that it may be responsive to intervention. In fact, there is evidence that stress reactivity can be modified in response to treatment in youth with ASD. Cortisol levels in children and adolescents appear sensitive to intervention as demonstrated by reductions in the CAR following introduction of a service dog[57]. Additionally, lower cortisol levels have been reported in children aged 7–18 years following a theatre-based intervention designed to improve social interaction skills and reduce stress when engaging with typically developing peers[58].

It has been shown that age is a critical moderating factor in the activation of the limbic–hypothalamic–pituitary–adrenocortical (LHPA) axis in children with ASD. For example, older children with ASD show higher levels of cortisol compared with younger children with ASD as well as their typically developing peers during play[51,59]. The aforementioned studies have shown an interaction between diagnosis and age resulting in significantly higher stress responses in older school-age youth who engage in play with peers. As this study utilized a naturalistic playground paradigm, it likely parallels what is frequently experienced during daily recreational activities in

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the school environment. Importantly, heightened reactivity was diminished in the younger cohort, implying less awareness of and experience with negative social encounters[24]. Importantly, because cortisol levels are moderated by age, they may also to some degree reflect underlying maturational factors related to developmental, social and physiological changes.

To date, the majority of the research on the circadian rhythms and responsiveness to stress of cortisol has been conducted in children with autism with relatively few studies investigating adolescents and adults[60–62]. Furthermore, these limited studies utilized different methodologies (e.g. blood samples versus saliva). Moreover, developmental considerations as well as distinctions between age and puberty have not been part of the investigations. Considering the literature on the LHPA axis in typical development[17,18,63] and the emerging literature in autism[33,51], it may be predicted that stress reactivity, especially in response to social functioning, might be even more challenging for adolescents on the autism spectrum. If such is the case, what are the consequences of increased arousal and stress in this population?

Conclusion

If a pattern of acute physiological arousal intensifies during the adolescent transition already shown to be more volatile, it is likely to contribute to increased risk and vulnerability. It is long established that moderate levels of arousal and stress are adaptive and even necessary for survival[64,65]. However, repeated, exaggerated and prolonged physiological responsivity to stressors can be deleterious and result in pronounced dysregulation of the LHPA axis[66,67]. Although there is no evidence that dysregulation of the LHPA axis is causally related to autism, enhanced reactivity of the system may be a developmental risk factor, specifically during the adolescent transition. As such, careful consideration of stress and anxiety in individuals with ASD is critical, especially during developmental periods marked by novel, unpredictable and social evaluation[9,10]. Knowledge of factors that can exacerbate or facilitate ease of transition will be far reaching in preparing adolescents with ASD for this hopeful, albeit precarious developmental milestone. Studies are underway to examine such factors with the goal of informing treatment for youth with ASD to make it less of a period of 'storm and stress' and more a time of strength and resiliency.

Abbreviations list

ASD, autism spectrum disorder; CAR, cortisol awakening response; HPA, hypothalamic–pituitary–adrenocortical; LHPA, limbic–hypothalamic–pituitary–adrenocortical

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