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Elevated repetitive behaviors are associated with lower diurnal salivary cortisol levels in autism spectrum disorder

Robin L. Gabriels[a,b,*], John A. Agnew[a,b], Zhaoxing Pan[a,b], Katherine D. Holt[a], Ann Reynolds[a], Mark L. Laudenslager[b]

[a] Children's Hospital Colorado, 13123 E. 16th Avenue, Aurora, CO 80045, USA
[b] University of Colorado Denver Anschutz Medical Campus, 13001 E. 17th Place, Aurora, CO 80045, USA

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ABSTRACT

Previously, we reported a subgroup of children with autism spectrum disorders (ASD) had consistently high rates of repetitive behaviors (RBs) with abnormal sensory sensitivity. Given evidence of lower cortisol levels in response to stress and associated sensory sensitivity in the ASD population, this pilot study evaluates whether the presence of RBs reflects an underlying pathophysiology related to cortisol regulation. Diurnal salivary cortisol from 21 children with ASD and high versus low occurrence RBs were collected at four time points over three consecutive days. Although a typical decline in salivary cortisol was observed, participants in the high RB group showed 36% lower diurnal salivary cortisol than the low RB group. Age, IQ, RB type, and sleep quality were unrelated to observed differences. These findings suggest that RBs may serve to mitigate distress or that the glucocorticoid system has been down regulated in association with prolonged distress in this sample population.

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1. Introduction

Repetitive behaviors (RBs), interests or activities; social impairments; and communication deficits are the triad of symptoms that define autism spectrum disorders (ASD) (i.e., autistic disorder, Asperger's disorder, and pervasive developmental disorders not otherwise specified) (American Psychiatric Association, 2000). The term RBs includes repetitive actions (e.g., repetitive stereotyped movements and self-injury) as well as ritualistic behaviors, hording, compulsions, insistence on sameness, and preoccupations (Bodfish, 2011). RBs are not exclusively present in the ASD population, various forms are common in early typical development (Evans et al., 1997) and present in other psychiatric populations including social anxiety disorders, obsessive compulsive disorders, and intellectual disabilities (Cath et al., 2008; Smith and Van Houten, 1996). However, RBs represent considerable challenges for individuals with ASD and their caregivers. Challenges can range from family dysfunction, exacerbated by the child's intolerance of environmental change, to requiring emergency medical care due to the child's act of self-injury. Individuals with ASD can have any combination of RBs, and the type and intensity of these behaviors may change over time or be influenced by other factors such as mood or sleep problems (Bodfish et al., 2000; Gabriels et al., 2005; Piven et al., 1996).

Studies have indicated that, for individuals with ASD, an increase or decrease in RBs may be a response to environmental sensory stimulation such as bright lighting, loud noise, or the lack of sensory stimulation (Baranek et al., 1997; Colman et al., 1976; Gal et al., 2002; Grandin, 1992; Willemsen-Swinkels et al., 1998). A previous study suggests that there may be a subpopulation of children with ASD who have both high frequencies of sensory sensitivities and RBs (Gabriels et al., 2008). Hypotheses regarding why sensitivity to sensory stimuli might lead to an increase in RBs in individuals with ASD include: (1) to induce a sensory experience/enhance arousal levels in the absence of stimulation or (2) to decrease or moderate the stress or arousal levels resulting from excessive sensory stimulation in the environment (Bodfish, 2011; Liss et al., 2006). The evaluation of RBs and sensory sensitivities is complicated, however, by the great deal of overlap that exists in the terminology and

* Corresponding author at: Children's Hospital Colorado, 13123 E. 16th Avenue, Aurora, CO 80045, USA. Tel.: +1 720 777 3404; fax: +1 720 777 7313.
E-mail addresses: Robin.gabriels@childrenscolorado.org (R.L. Gabriels), John.agnew@colorado.edu (J.A. Agnew), Zhaoxing.pan@childrenscolorado.org (Z. Pan), katherineduncanholt@gmail.com (K.D. Holt), Ann.Reynolds@childrenscolorado.org (A. Reynolds), Mark.Laudenslager@ucdenver.edu (M.L. Laudenslager).

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measurement tools used to define them (see Gabriels et al., 2008, for a review).

Research regarding RBs in animals may provide insight into the role of RBs as a response to perceived stress resulting from exposure to sensory stimulation in the environment. For example, it is common for animals to engage in RBs when maintained in environments lacking stimulation (Langen et al., 2011). Stereotypies in captive animals are associated with decreased heart rate (Schouten and Wiegant, 1997), and changes in regulation of the stress response system of the hypothalamic-pituitary-adrenal (HPA) axis (Redbo, 1998), suggesting that these behaviors may serve a self-soothing function. Additionally, these types of behaviors may serve to modulate the activity of the HPA axis. For example, in schedule-induced polydipsia, a rodent consumes water in excess of its homeostatic requirement while waiting for a food reward that is being presented on a fixed-interval (Falk, 1971). If the water tube is removed (i.e., preventing this repetitive drinking behavior), rodent corticosterone levels are elevated (Brett and Levine, 1979). It is possible that RBs in individuals with ASD serve to modulate the activity of the HPA axis in a similar manner by decreasing levels of the stress hormone cortisol.

The activity of the stress response of the HPA axis in individuals with ASD is complex and existing empirical data are mixed. With regard to the regulation of this system, the activity of the HPA axis has differed in study populations with ASD depending on factors such as individual patterns of sensory sensitivity or stress levels, specific stress paradigm, or type of parameter assessed (saliva or plasma) (Brosnan et al., 2009; Corbett et al., 2006, 2008, 2009; Hamza et al., 2010; Jansen et al., 2006; Zinke et al., 2010). In typically developing individuals, cortisol levels fluctuate with a diurnal rhythm; these levels begin to increase before awakening, show a rapid rise from awakening over the next 30–45 min, and then fall throughout the day, reaching a low point during the normal sleep cycle, to rise again in preparation for awakening (Clow et al., 2010).

The diurnal rhythms of cortisol levels in children with ASD are not always consistent with those of typically developing individuals, as evidenced by one study, which reported children with ASD having lower morning cortisol levels and higher evening cortisol levels, as compared with typically developing controls (Corbett et al., 2008). Although the cortisol diurnal cycle has been shown to vary between the typically developing and ASD populations, for individuals with ASD, the pattern has been found to be self-consistent for salivary cortisol samples collected on two sequential days (Corbett et al., 2006). This diurnal cycle of cortisol level can be affected by environmental events such as stress that can cause in increase in cortisol levels in the body. Studies examining cortisol levels in individuals with ASD exposed to a stressor (i.e., entering the confined space of a mock MRI scanner) found significantly greater variability in salivary cortisol response when compared to a healthy control group (Corbett et al., 2008). In summary, these studies have found greater variability in both diurnal cortisol rhythm and for the cortisol response to stress in the ASD population compared with the typically developing population.

A portion of the variation in salivary cortisol diurnal patterns in children with ASD may be accounted for by stress levels. Specifically, children with ASD identified as having higher stress levels versus those with lower stress levels (per caregiver report) had lower morning and higher evening cortisol levels (Corbett et al., 2009). Several groups have concluded that these high stress levels could contribute to a flattening of diurnal slope, which is frequently associated with populations at increased risk for pathology (Bernard et al., 2010; Corbett et al., 2009; Gunnar and Quevedo, 2008). These results suggest that better behavioral characterization (e.g., occurrence levels of RBs) of individuals with ASD will improve understanding of the variance in the salivary cortisol diurnal patterns observed in children with ASD.

The purpose of this pilot study was to examine diurnal salivary cortisol patterns in a sub-population of children with ASD having high versus low occurrence levels of RBs. In order to maximize the chance to observe an effect within this pilot study and to justify extending this line of research, the authors opted to recruit participants with either high or low levels of RBs rather than to treat RBs as a continuous variable. Our aim was to investigate the extent to which high versus low levels of RBs may account for the variability in diurnal salivary cortisol previously noted in children with ASD. We tested the hypotheses that the diurnal decline in salivary cortisol would differ between those children with ASD who had high occurrences of RBs from those with low occurrences of RBs. Further, given animal behavior research findings suggesting that RBs may serve a coping function, we hypothesized that participants with high occurrences of RBs would have lower cortisol levels as well as a steeper decline over the course of the day.

2. Methods

2.1. Participants

Twenty-one pre-pubescent males between 3 and 9 years of age diagnosed with autistic or Asperger's disorder (described in Section 2.2 below) and a standard IQ score at or above 40 participated in this study, approved by the Institutional Review Board of the University of Colorado Denver. The IQ score criterion was set to include participants who had the cognitive capacity to cooperate with the saliva collection process. Because of the known effects of puberty on HPA axis regulation (Gunnar et al., 2009; Netherton et al., 2004), puberty status was gathered by caregiver report using screening questions based on the Tanner criteria (Tanner, 1962). Participants were recruited from a pool of participants from a previous study (Gabriels et al., 2008) as well as by study announcements distributed at the Children's Hospital Colorado and in community settings. The presence of RBs was determined using the caregiver-report repetitive behavior scale-revised (RBS-R) (Bodfish et al., 2000). Based on the RBS-R scores, participants who displayed either high or low occurrences of RBs were recruited for the study. The two RB groups were defined by selecting the upper quartile (RBS-R mean total score ≥ 50) and lower quartile (RBS-R mean total score ≤ 25) as determined by data from a previous study ($n = 52$) (Gabriels et al., 2008). Of the 21 participants, 11 fell within the high RB group (RBS-R mean total score: 58 ± 9.9) and 10 fell within the low RB group (RBS-R mean total score: 15.4 ± 7.8).

2.2. Measures

2.2.1. Screening and demographic measures

Tanner criteria. The Tanner criteria (Tanner, 1962) are well-established criteria for defining puberty status based on physically observable pubertal maturation features (presence of genital and pubic hair development in boys and breast and pubic hair development in girls). There are five Tanner stages of sexual development, however, for the purposes of this study, a broad distinction will be made; Tanner stage 1 (pre-pubescent) and all other Tanner stages 2–5 (pubescent), which indicate varying degrees of pubertal development. Caregivers of participants rated puberty status of the participant based on the criteria described by Tanner and summarized above.

Repetitive behavior scales-revised (RBS-R). The RBS-R (Bodfish et al., 1999, 2000) is a 15-min empirically derived clinical rating scale for measuring the frequency/severity of RBs and provides a quantitative, continuous measure of the full spectrum of RBs. The six subscales (stereotyped behavior, self-injurious behavior, compulsive behavior, routine behavior, sameness behavior and restricted behavior) of the RBS-R permit differential identification and scoring of discrete varieties of RBs. The psychometric properties of the RBS-R from studies with adults with intellectual disabilities (Bodfish et al., 1995) and children and adolescents with an autism spectrum (Bodfish et al., 2000) have been found to be in the acceptable range for a clinical rating scale (inter-rater reliability $r = 0.88$, test-retest stability of $r = 0.71$, validity based on agreement with direct observation measurement $r = 0.84$) (Bodfish et al., 2000).

The child and caregiver information form – research version (CCIF-RV) adapted from Gabriels and Hill (2007) was completed by caregivers. The CCIF-RV provides family demographic and socioeconomic status information along with child medical and treatment history.

The social communication questionnaire (SCQ) (Rutter et al., 2003a) was completed by caregivers as part of the overall diagnosis of autistic or Asperger's disorder. The SCQ is a 40-item survey for all ages and is based on the autism diagnostic interview-revised (ADI-R) (Lord et al., 1994; Rutter et al., 2003b). The SCQ provides developmental history information in addition to the child diagnostic observation measure (ADOS). Both types of information are necessary to verify a DSM-IV TR (American Psychiatric Association, 2000) diagnosis of autistic or Asperger's disorders. The SCQ is able to help discriminate autism from non-autism based on meeting or exceeding the empirically derived screening cut-off score of 15 on this measure.