SHORT COMMUNICATION

Children with high-functioning autism show a normal cortisol awakening response (CAR)

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Summary Individuals with high-functioning autism spectrum disorders (HFA) show difficulties in the ability to react to change. A recent study suggested that variations in the functioning of the hypothalamus—pituitary—adrenal (HPA) axis, especially in one of its markers — the cortisol awakening response (CAR) — may be related to those difficulties in adolescents with Asperger’s syndrome. The current study investigated the CAR in a younger sample with diagnoses from the whole autism spectrum: A group of children with HFA (N = 15) was compared to a group of typically developing children (N = 25). Findings suggest that the frequency of a CAR as well as the increase in cortisol levels from awakening to 30 min later were similar between groups, indicating that variations in the CAR in HFA may not be present early in life but only develop later in adolescence or may only occur in some diagnoses from the autism spectrum.

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The ability to react to unfamiliar situations or unexpected changes in daily routines is essential to human life. Individuals with autism spectrum disorders (ASD: childhood autism, atypical autism, and Asperger’s syndrome) show profound difficulties in handling these sudden changes, which is also referred to as a ‘desire for sameness’ or ‘adherence to routines and rituals’ (Kanner, 1943; WHO, 2006). ASDs are characterized by difficulties in social interaction and communication (WHO, 2006). Even individuals with ASD with average intellectual abilities (high-functioning autism, HFA) show impairments in everyday life including difficulties in organizing and coordinating their daily activities (Ozonoff et al., 2002).

These difficulties in adapting to change in individuals with ASD may be related to variations in the functioning of the hypothalamus—pituitary—adrenal (HPA) axis (see Lam et al., 2006, for a review), an important neuroendocrine system with the end product cortisol, which is essentially involved in adapting the individual to bodily and environmental challenges. Findings on HPA-axis activity in ASD are not entirely consistent: whereas some studies find increased variability in cortisol daily profiles (Richdale and Prior, 1992; Corbett et al., 2008), others report no differences in basic cortisol levels and/or cortisol response in reaction to stressors (Tordjman et al., 1995; Jansen et al., 2003). A reliable marker of HPA-axis activity is the so-called cortisol awakening response (CAR), a profound increase of cortisol levels within the first 30 min after awakening that is superimposed on the circadian variation of cortisol secretion (Wüst et al., 2000). The CAR has been suggested to be involved in the preparation of the individual...
for the demands and challenges of the upcoming day (Fries et al., 2009).

A recent study indicated a blunted CAR in adolescents with Asperger’s syndrome (11–16 years) who lived in a special residential school compared to typically developing controls (Brosnan et al., 2009). Only 5% of the adolescents with Asperger (vs. 28%) were considered as showing a significant CAR, when applying the commonly used responder criterion of a cortisol increase by at least 2.49 nmol/l (Wüst et al., 2009). Sixty percent of the adolescents with Asperger (vs. 72%) showed any rise of cortisol. Given the suggested involvement of the CAR in the preparation of the individual for the upcoming day, a blunted CAR in individuals with ASD may be related to some of their difficulties in adapting to change.

The observations by Brosnan et al. (2009) are, however, limited to male adolescents with Asperger’s who live in an institution. To extend these findings, the current study aimed at characterizing the CAR in individuals (a) who are younger, (b) have diagnoses from the whole autism spectrum, and (c) live in their home environment rather than an institution. As a further extension, we ensured compliant assessment by using electronic monitoring devices.

1. Methods

1.1. Participants

Participants of the current study were 15 high-functioning children with ASD (13 boys) and 25 typically developing children (21 boys), ranging in age from 6 to 12 years (see Table 1 for sample characteristics). Children with HFA were recruited and diagnosed at a local autism clinic. All children met the ICD-10 criteria for either childhood autism (N = 9), Asperger’s syndrome (N = 1), or atypical autism (N = 5), assessed using the German version of structured diagnostic instruments: the Autism Diagnostic Observation Schedule (ADOS, Rühl et al., 2004) and the Autism Diagnostic Interview-Revised (ADI-R, Rühl et al., 1995). All children with HFA had sufficient verbal abilities and were high-functioning with a full scale IQ of at least 78 (M = 98.6, S.D. = 15.1) on the German version of the WISC-III (Tewes et al., 2000). Typically developing children were recruited through advertising in local newspapers and schools. Exclusion criteria for all children were associated genetic, infectious, or metabolic disorders. Any other comorbid condition and/or intake of medication were assessed via parental report and (for children with HFA) diagnoses from the autism clinic. All participants and parents received extensive oral and written information about the study. Only if parents gave written informed consent children were included into the study. The study was conducted in accordance with the ethical guidelines proposed in the Declaration of Helsinki.

1.2. Cortisol assessment and analysis

Salivary sampling for cortisol was conducted at home on two average weekdays using the Salivette sampling device (Starstedt, Nümbrecht, Germany). Parents were instructed to wake their children, take the first sample immediately after awakening and the second sample 30 min later. The sampling swabs were stored in a tube with an electric monitoring cap (MEMS, Aardex Ltd., Switzerland) that registered the exact time the tube was opened and swabs were removed. These monitoring devices have been shown to increase compliance with the assessment protocol (Kudielka et al., 2003). Additional information concerning the sampling (duration of sleep, day of the week, experienced stress in the morning on a scale from 0 to 10) were assessed using a questionnaire.

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Table 1  Sample characteristics of children with high-functioning autism (HFA) and typically developing children.

<table>
<thead>
<tr>
<th>Measure</th>
<th>HFA group</th>
<th>Control group</th>
<th>Test statistics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15 (S.D.)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (boys/girls)</td>
<td>13/2</td>
<td>21/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 9.1 (1.5)</td>
<td>9.0 (2.0)</td>
<td></td>
<td>t(38) = −0.11</td>
<td>.91</td>
</tr>
<tr>
<td>BMI 17.9 (3.0)</td>
<td>16.3 (1.7)</td>
<td></td>
<td>t(13.1) = −1.63</td>
<td>.13</td>
</tr>
<tr>
<td>Comorbid conditions b</td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication c</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep duration (in h)</td>
<td>9.4 (0.5)</td>
<td>9.7 (0.8)</td>
<td>t(37.8) = 1.34</td>
<td>.19</td>
</tr>
<tr>
<td>Stress in the morning (on a scale from 1 to 10)</td>
<td>2.8 (1.5)</td>
<td>3.1 (2.1)</td>
<td>t(38) = 0.59</td>
<td>.56</td>
</tr>
<tr>
<td>Vocabualry</td>
<td>10.9 (3.1)</td>
<td>13.1 (1.6)</td>
<td>t(20.0) = 2.47</td>
<td>.02</td>
</tr>
<tr>
<td>Block design</td>
<td>10.7 (2.8)</td>
<td>13.3 (3.0)</td>
<td>t(30) = 2.45</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Levene’s test for equality of variances was significant, indicating unequal variances, therefore the adjusted t statistic not assuming homogeneity of variance was computed. Comorbid diagnoses in the HFA group were specific developmental disorder of motor function, allergy, migraine, sleep disorder; in the control group one child had fructose malabsorption and two had an allergy. Six children with HFA were taking methylphenidate, fluoxetine, or opipramol. Comparison of cognitive functioning includes only those participants with complete data, which were 15 children with HFA and 17 children without HFA.
The samples were stored in a freezer and then analysed using a commercially available chemiluminiscence-immuno-assay (IBL-International, Hamburg, Germany).

1.3. Data analysis

Before statistical analysis, the data was scanned for missing values (three) and sampling days that were not assessed complianly. Following Kudielka et al. (2003), compliant collection was defined as taking the first sample within the first 10 min after awakening and the second sample 30 min ± 7 after waking. All further analyses were conducted with only these measures. Due to missing values and/or noncompliant assessment one child with ASD had to be removed from the analysis (not included in the sample description). Furthermore, only 1 complete sampling day was available for 11 children (4 children with HFA, 7 control children).

Among these compliantly assessed cortisol measures there were no apparent outliers with values more than three standard deviations above the mean for each study group. Cortisol levels were averaged across sampling days, if available, to obtain a more representative measure. Analyses of variance (ANOVA) for repeated measures were run to compare the mean cortisol levels. For comparing demographic variables χ²-test and t-tests were used.

2. Results

As shown in Table 1, the groups were similar in age, gender distribution, BMI, and sleep-related measures that could possibly influence cortisol levels. As would be expected considering their disorder, more children with HFA had comorbidities and were taking medication than typically developing controls. Because of the unequal proportion of comorbid conditions and medication intake, analyses of the main dependent variables were repeated including only the nonmedicated children or only children without comorbid diagnosis. Because the general pattern of results did not change, results including the whole sample will be reported. There was a significant difference in baseline cognitive functioning between groups, as measured by the vocabulary and the block design subtest of the German adaptation of the WISC-III (Tewes et al., 2000). However, performance on those tests did not correlate with the main dependent measure, the averaged cortisol levels upon awakening and 30 min later, r < .3, all p > .10.

Twelve of the 15 children with HFA (80%) showed a rise of cortisol, as did 22 out of 25 typically developing children (88%). When considering a cortisol increase of at least 2.49 nmol/l as a criterion for a CAR (Wüst et al., 2000), 11 of the 15 children with HFA showed a CAR (73%), as well as 21 out of the 25 typically developing children (84%). Neither the rate of children showing any rise of cortisol, nor the rate of children showing a considerable CAR differed significantly between groups, exact Fisher p = .65.

Next, a repeated measures ANOVA was run to compare the amount of increase in cortisol levels between groups. Analysis revealed a significant rise in cortisol levels from awakening to 30 min later, effect of time: F(1,38) = 45.90, p < .0001, partial η² = .55 (see Fig. 1). The cortisol level increased on average by 52.5% (M = 6.60 nmol/l, S.D. = 5.69) from 12.57 to 19.17 nmol/l. There was neither a significant effect of group, F(1,38) < 1.36, p > .25, partial η² = .03, nor a significant interaction of group × time, F(1,38) < 1.53, p > .22, partial η² = .04, indicating neither average cortisol levels nor cortisol rise differed between the two groups. Also, when looking at groups separately, both groups showed a significant cortisol rise from the first sampling to the second: dependent t-tests, both p < .002, children with HFA d' = 1.0, children without HFA d' = 1.5.

3. Discussion

The current study investigated whether the CAR, a marker of HPA-axis activity, was altered in children with HFA living at home. Children with HFA showed a CAR as frequently as typically developing children. Furthermore, the increase in cortisol levels from awakening to 30 min later was significant and comparable in size in both groups. The rate of children who showed a CAR (about 80%) and the mean increase of cortisol levels (about 50%) is comparable to research in adults (Wüst et al., 2000) and children (Rosmalen et al., 2005). However, current findings are in contrast to findings of an absent CAR in adolescents with Asperger’s syndrome by Brosnan et al. (2009).

What could explain these divergent findings? The current sample differed in many ways from the sample of Brosnan et al. (2009): first of all, the current sample included other diagnoses of the autism spectrum than just Asperger’s syndrome. It could be that the CAR is only altered in Asperger’s syndrome and not in other diagnoses. Interesting to note, in the current sample the only child with Asperger’s syndrome showed a considerable rise of cortisol between first and second sample with a relatively low baseline level. Second, the children in the current study were living at home rather than in an institution: it is conceivable that children with HFA living in a residential school differ from those living at home, for example in the severity of their condition or their daily routines. Assuming the CAR is involved in preparatory processes, it can be speculated that individuals living in an
institution may be confronted with different amounts of preparation for the demands of the day than those living at home, possibly leading to differences in the CAR. Furthermore, living at home may serve as a kind of buffer (e.g., more social support) leading to less alterations in HPA-axis functioning. Moreover, the current sample was considerably younger. It is tempting to speculate that the alterations observed by Brosnan et al. (2009) may not be present in younger children and only develop later. This notion is supported by a study showing normal morning cortisol levels in young children with HFA (Corbett et al., 2008). As children with HFA grow older, the HPA axis may adapt to high levels of stress that they are exposed to (maybe especially when they live in an institution). This process may then lead to a blunted CAR in later life as has been hypothesized to be the case in individuals with posttraumatic stress disorder or burnout (see Clow et al., 2004 for a review). Other than sample characteristics, the divergent findings could also be related to differences in methodology between the two studies, e.g. the use of electronic monitoring devices.

There are some limitations to the current study. The sample included different diagnoses from the whole autism spectrum and was rather small. However the current sample size is comparable to Brosnan et al.’s (2009) sample, so current findings do not seem to be an issue of statistical power. The exclusion of the noncompliant measures further decreased the sample size, sometimes only measures for one sampling day were available. Nevertheless, excluding noncompliant measures has been shown to increase the quality of the data. Furthermore, inherent to this group of children, some of them were taking medication, which may have influenced cortisol assessment. However, a recent study showed no influence of methylphenidates or antidepressants on cortisol secretion in children (Hibel et al., 2007). Also, when repeating the current analyses with only the nonmedicated children, the general pattern of results did not change. An additional point that could have influenced the findings and should be considered in future studies is the pubertal stage the children were in.

Despite these limitations, the current findings indicating the occurrence of a CAR in children with HFA support preliminary evidence of relatively normal basic HPA-axis functioning in ASD (Tordjman et al., 1995; Lam et al., 2006). This is in contrast to evidence suggesting alterations in specific HPA-axis regulation like the variability of cortisol daily profiles across several days (see e.g., Corbett et al., 2008) or cortisol suppression (Hoshino et al., 1987). Of course current preliminary findings need to be replicated and extended in order to hold. One question that awaits further investigation preferably with a longitudinal study design is whether the CAR, as a marker of HPA-axis activity, may become altered as individuals with ASD grow older and/or whether the CAR is influenced by aspects of the environment they live in. To fully encompass the functioning of the HPA axis in ASD, assessing the daily cortisol profile and the reaction to different stressors in addition to the CAR in different diagnostic groups will be necessary.

**Conflict of interest**

No conflict of interest is declared.

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**References**


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