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Long-term stability of the cortisol awakening response over adolescence

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Summary The cortisol awakening response (CAR) has been widely assessed as a measure of hypothalamic-pituitary-adrenal (HPA) axis activity. Short-term stability is high; however, little is known about the long-term stability of the CAR. Because there are indications that development in adolescence influences HPA axis activity, this study investigated the stability of the CAR over adolescence.

Participants were 229 boys and 181 girls from an adolescent general population sample who were assessed in three consecutive years, at mean ages of 15.0 (SD = 0.4), 16.0 (SD = 0.4) and 17.0 (SD = 0.4) years. Cortisol was analyzed in saliva sampled at awakening, and 30 and 60 min later. Stability was investigated both as rank-order and as mean-level stability. Effects of physical development during adolescence on stability were investigated as well.

Rank-order stability was moderate to low, with tracking coefficients (interpretable as stability coefficients over time) of .15 ($p < .001$) for cortisol at awakening and .24 ($p < .001$) for cortisol 30 and 60 min after awakening. Mean-levels of cortisol at awakening did not change, while the response to awakening increased over the years (linear slopes for cortisol 30 and 60 min after awakening all $p < .01$). The increase may reflect the physical development of the adolescents.

This is the first study, in a large population based sample, indicating that the rank-order of the CAR is stable over the course of several years. Interestingly, mean-levels of the cortisol response to awakening increased over the years, suggesting a maturation of HPA axis reactivity in relation to physical development over adolescence. Physical development should therefore be taken into account when investigating the CAR as a measure of HPA axis activity in adolescence.

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1. Introduction

The cortisol awakening response (CAR) has been widely assessed as a measure of hypothalamic-pituitary-adrenal (HPA) axis activity. The CAR is superimposed on the circadian rhythm of cortisol secretion, and in addition to basal activity as reflected by day-time cortisol, it also reflects the reactivity or flexibility of the HPA axis (Fries et al., 2009). It is often used as a biological marker for disorders related to HPA axis (dys)functioning, such as anxiety and depression which are associated with increased CARs (Pruessner et al., 2003a; Greaves-Lord et al., 2007), and disruptive behavior disorders, which are associated with fearlessness and decreased CARs (Popma et al., 2007; Alink et al., 2008). Short-term stability of the CAR (i.e. over several days) has been shown to be remarkably high in adult samples (Wust et al., 2000; Edwards et al., 2001). Because the CAR is increasingly being used in longitudinal studies predicting behavioral and emotional outcomes (e.g. Adam et al., 2010; Ruttle et al., 2011), it is of relevance to learn more about the long-term stability of this measure of HPA axis activity. At present, it is not clear whether the CAR is a stable biological marker. It is also unknown whether the CAR changes with age or normal development. This fundamental knowledge is essential for interpretation of associations with disorders related to HPA axis (dys)functioning. Particularly in adolescence, physical development is an issue, as it is likely to influence HPA axis activity (Kiess et al., 1995; Walker et al., 2001; Rosmalen et al., 2005). For these reasons, in this study the long-term stability of the CAR over adolescence was investigated, taking into account physical development. Stability is investigated both as rank-order and as mean-level stability. While rank-order stability reflects the stability of an individual's position within the group, mean-level stability reflects the stability or change in mean-levels for the whole group.

To date, long-term rank-order stability of the CAR has not been described. As for day-time cortisol levels, there are indications that HPA axis activity is stable over time, with correlations up to .60 over 1.5—2 years (Walker et al., 2001). This stability level was, however, calculated over only 21 adolescents. Therefore it remains unclear whether the CAR constitutes a stable biological characteristic. Further study of the rank-order stability of the CAR is warranted.

As for mean-level stability, there are indications that the typical cortisol awakening response is not yet mature in childhood and adolescence (Clow et al., 2004). When studied in adult samples (Clow et al., 2004), cortisol levels follow a specific response curve with a sharp increase after awakening, followed by a gradual decrease. Several studies in child and adolescent samples, however, have found smaller (Pruessner et al., 1997, commented on by Clow et al., 2004; Rosmalen et al., 2005) or no (Freitag et al., 2009) cortisol response to awakening. It has therefore been suggested that the typical CAR as seen in adults may be different for children. An age effect on the response curve of cortisol after awakening has not been found cross-sectionally in child or adult populations (Pruessner et al., 1997; Wust et al., 2000; Edwards et al., 2001), although an age affect has been reported in children on the level of the total CAR (Michels et al., 2012). However, in the developmental phase in which maturation of the CAR is most likely to occur (i.e. adolescence), an age effect has remained uninvestigated. Further, the cross-sectional designs compared different groups of individuals, making them unable to distinguish true differences with age, from differences between individuals of different ages. The only longitudinal study describing long-term stability of mean-level HPA axis activity in adolescents focused on day-time cortisol levels (Walker et al., 2001). They reported an increase over 1.5—2 years in cortisol levels measured four times during the day. However, because to date changes in the CAR over time have not been investigated in the same individuals, conducting such a study is a necessity, as this is the only way to elucidate the issue of stability or change in the CAR over adolescence.

Physical development, e.g. pubertal development and changes in body mass index, is likely to influence the maturation and stability of the CAR during adolescence. Cross-sectional studies have shown cortisol levels to be higher in later compared to earlier stages of puberty (Kiess et al., 1995), while the CAR was found to differ by pubertal stage and gender (Matchock et al., 2007). Girls generally are about two years ahead of boys in pubertal development, and they have often been reported to show a higher CAR (Pruessner et al., 1997; Rosmalen et al., 2005). Furthermore, increasing body mass index (BMI) accompanying puberty is also likely to affect cortisol levels (Kiess et al., 1995; Rosmalen et al., 2005). Gender and physical development during adolescence should therefore be taken into account when investigating the stability of HPA axis activity.

Therefore, the aim of this study was to investigate the stability of the CAR as a measure of HPA axis activity over adolescence, in three annual assessments at ages 15, 16 and 17. Across these ages, (physical) maturation from adolescence to young adulthood may be captured (Root, 1973). Effects of gender and physical development during adolescence on stability of the CAR were investigated.

2. Methods

2.1. Participants

Participants in the final analyses were 410 adolescents (229 boys and 181 girls). They were part of the RADAR study (Research on Adolescent Development And Relationships), a Dutch population based cohort study on adolescent relationships with family members and friends and the development of personality and psychopathology. The RADAR study has been approved by the responsible Medical Ethics Committee, and all participants and their parents gave informed written consent. Participants were recruited from 230 elementary schools in urban and rural areas in the Netherlands. Of the 1569 randomly selected students, 364 (23%) did not meet inclusion criteria (both parents and sibling age $\geq$ 10 present, and sufficient understanding of the Dutch language) and 99 (6%) were not reachable. Of all eligible students, 636 (70%) agreed to participate in the study. However, 114 (7%) failed to provide written informed consent of all study members (adolescent, both parents, sibling and best friend) and could therefore not be included in the final study sample. The total RADAR cohort thus consists of 522 adolescents (294 boys and 228 girls), participating in annual assessment waves from age 13 on. Cortisol measurements were assessed from age 15 (wave 3) on.