



## Children suffering from separation anxiety disorder (SAD) show increased HPA axis activity compared to healthy controls

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### ABSTRACT

**Research questions:** Separation anxiety disorder (SAD) is one of the most common mental disorders in childhood, and one of the earliest emerging. Little is known about the association between SAD and the hypothalamic-pituitary-adrenocortical (HPA) axis activity. Therefore, the present study aimed at investigating this association in children suffering from separation anxiety compared to healthy controls.

**Methods:** A total of 31 children with diagnosed SAD (mean age: 8.45; 17 females, 14 males) and 25 healthy controls (HC; mean age: 9.74; 12 females, 13 males) took part in the study. All participants underwent psycho-physiological testing for HPA axis challenge. Testing consisted of a separation and a social exposure paradigm. Saliva samples to assess HPA axis-related cortisol secretion were gathered in parallel.

**Results:** Compared to healthy controls, children with SAD showed greatly increased HPA axis activity, as reflected by an increased cortisol secretion throughout the entire period of investigation. The rise of cortisol was already observed in anticipation of, but not following the separation paradigm. No gender-related differences of cortisol secretion were observed.

**Conclusions:** Separation anxiety disorder (SAD) in children is reflected in greatly increased HPA axis activity. Compared to healthy controls, children with SAD showed increased cortisol values from the beginning of, and throughout, the entire investigation. This pattern of results suggests that both the anticipation of a separation and a persistent hyperactivity of the HPA axis system leads to an increased cortisol secretion.

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### 1. Introduction

The peak onset for many psychiatric disorders is adolescence, a time of remarkable physical and behavioural changes (Paus et al., 2008), but evidence for the onset of psychiatric disorders earlier in childhood is provided, for example, by ADHD and anxiety disorders (Sadock and Alcott Sadock, 2009). Among the varieties of anxiety disorders, separation anxiety disorder (SAD) demand particular attention for three reasons. First, children suffering from separation anxiety disorder cause major and readily observable difficulties in everyday social life between the affected child and her or his parents. That is, children with SAD are reluctant to be separated from major attachment figures because of fears that something horrible might happen to the attachment figure (American Psychiatric Association (APA), 2009: Diagnostic and statistical manual of mental disorders DSM-IV; see also Allen et al., in press).

Second, separation anxiety disorder is one of the most common mental disorders in childhood, and one of the earliest emerging (Cartwright-Hatton et al., 2006; Kessler et al., 2005). Third, there is remarkable evidence that separation anxiety disorder precedes a variety of psychiatric disorders in adolescence and adulthood. For example, as results from a community study unfold, participants meeting DSM-IV criteria for separation anxiety disorder have been shown to be at increased risk for developing panic disorder with agoraphobia, specific phobia, social phobia (Brückl et al., 2007; Otto et al., 2001), generalized anxiety disorder, obsessive-compulsive disorder, bipolar disorder, pain disorder, and alcohol dependence (Brückl et al., 2007). Additionally, in children and young adults suffering from separation anxiety disorder increased rates have been found for depressive disorders (Lewinsohn et al., 2008; Aschenbrand et al., 2003; Hayward et al., 2000), as well as for generalized (Lipsitz et al., 1994) and specific phobias, obsessive-compulsive disorders, posttraumatic stress disorders (Bittner et al., 2007), and acute stress disorders (Aschenbrand et al., 2003). Moreover, Balon et al. (1989) demonstrated a stronger correlation

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between separation anxiety disorder in childhood and agoraphobia in females than in males. In sum, separation anxiety disorder (termed SAD from now on) in children is readily observable, causes high strain both for the affected child and her or his caregivers, and dramatically increases the risk of subsequent psychiatric disorders.

To describe neurobiological mechanisms underlying psychiatric disorders, in recent years the hypothalamic-pituitary-adrenocortical (HPA) system has attracted considerable attention (Jezova and Hlavacova, 2008). For example, compelling evidence indicates that the HPA axis is compromised in major depressive disorders (Holsboer et al., 1995; Hatzinger et al., 2004; for review: Zimmermann and Stansbury, 2004; Holsboer and Ising, 2010), in bipolar disorders (Rybakowski and Twardowska, 1999), as well as in anxiety disorders such as posttraumatic stress disorder (Heim et al., 2001). Moreover, individual differences in the activity of the HPA axis have recently been shown to be associated with differences in the risk for depression. Elevations in morning cortisol levels predicted the development of depressive disorders in those exposed to psychosocial risk factors for depression (Goodyer et al., 2000; Harris et al., 2000; Aubry et al., 2010).

So far, there is considerable experimental evidence from animal (Champagne and Meaney, 2001; Weaver et al., 2001; Liu et al., 2000; Kalinichev et al., 2002; Fahlke et al., 2000; Coplan et al., 2001) and human studies (Ashman et al., 2002; Essex et al., 2002; Halligan et al., 2007; Hessel et al., 1998) that early experience can alter later HPA activity. That is, early adversity increases either the basal secretion of glucocorticoids in adult life or the reactivity of the HPA axis to stress. Results from cross-sectional studies have shown task-related increases in salivary cortisol to be linked with a pattern of negative control-related beliefs (that is, the low concept of being able to cope with stressful situations; Granger et al., 1996) as well as with internalizing symptoms, which are typically referred to disturbances in mood and anxiety (Zahn-Waxler et al., 2000). In a similar vein, high basal levels of cortisol (particularly in the early morning) and heightened stress responses (that is, increased behavioral reactions to unfamiliar events) have been noted in young children described as behaviorally inhibited and shy (Kagan et al., 1998; Schmidt et al., 1997; Nachmias et al., 1996; Watamura et al., 2003). In contrast, children with externalizing problems, i.e. aggressive or other antisocial behavior, exhibited rather low levels of cortisol or less HPA axis reactivity (Flinn and England, 1995; Moss et al., 1995). Specifically, assessing a non-clinical sample of 102 kindergarten children, Hatzinger et al. (2007) was able to show that increased HPA system activity was significantly associated with hyperactivity/impulsivity and emotional problems in boys, and with positive emotions in girls. Importantly, girls' cortisol secretion in the morning and during a non-pharmacological stress challenge was significantly higher compared to boys' cortisol secretion. For three reasons, these findings are of note. First, both positive and negative emotions may lead to an increased HPA axis activity. Second, there were neurobiological changes related to gender. Third, this pattern of results was apparent in a non-clinical sample of preschoolers at the age of five years.

With regard to the relation between different forms of anxiety and neuroendocrine functioning, results are mixed and inconsistent: Granger et al. (1994) found in 102 children and adolescents aged 7–17 years that social anxiety was associated with a higher increase in salivary cortisol concentrations after a parent–child conflict discussion task. In a similar vein, Feder et al. (2004) reported an increased HPA axis activity in children and young adolescents aged 6- to 12-year suffering from anxiety disorders. Importantly, high anxiety levels were associated with changes in basal HPA axis activity. In contrast, Gerra et al. (2000) observed no significant differences between 22 male adolescents with an anxiety disorder and 20 male healthy controls in salivary cortisol

secretion after a non-pharmacological challenge. In contrast, Coplan et al. (2002) reported increased cortisol concentrations before carbon dioxide (CO<sub>2</sub>) inhalation in children and adolescents with an anxiety disorder compared to healthy controls. Last, Kallen et al. (2008) reported positive associations between the HPA axis activity and anxiety disorders in children and adolescents, with level of cortisol secretion varying as a function of level of anxiety.

In sum, there is no clear pattern to the results concerning the HPA axis activity and anxiety disorders in children. Moreover, gender-related issues have not been addressed thus far. In particular, to our knowledge, no methodological paradigm embodying high ecological and external validity has yet been used to assess SAD under laboratory conditions.

The aims of the present study were therefore to (1) compare HPA axis activity of children suffering from SAD with that of healthy age- and gender-matched controls, to (2) investigate HPA axis activity under a study paradigm reflecting the most threatening situation for a child suffering from SAD, that is, separation from the most important person, and (3) to explore gender-related differences in HPA axis activity.

We hold that, in professional psychological and psychiatric contexts, there is a high probability that children's issues and concerns surrounding separation anxiety will be encountered. However, given the high prevalence of SAD in childhood and adolescence (approximately 4%; Shear et al., 2006; Sadock and Alcott Sadock, 2009; Allen et al., in press), and given the increased risk for developing a broad variety of psychiatric disorders in later adolescence and adulthood, surprisingly, findings related to neuroendocrine functioning of SAD in childhood are scarce and mixed. Most importantly, females are at increased risk for developing affective disorders (Hyde et al., 2008) including anxiety disorders (Zahn-Waxler et al., 2008; Shear et al., 2006).

Four hypotheses were formulated. First, following Granger et al. (1994), Kallen et al. (2008), and Feder et al. (2004), cortisol secretion is elevated in children suffering from anxiety disorders; therefore, we anticipated that children suffering from SAD would show increased HPA axis activity as reflected by higher cortisol secretion. Second, following Kirschbaum and Hellhammer (1989), Dickerson and Kemeny (2004), and Kudielka et al. (2004), the HPA axis activity is highly stimulated by social challenge and exposure, which, as a rule, involves subjectively perceived high ego-involvement; conditions of this kind can include speaking, singing, or performing mental arithmetic in front of an audience or, in the case of children suffering from SAD, being separated from a major attachment figure. Accordingly, as a second hypothesis, we expected a marked rise of cortisol secretion in children suffering from SAD compared to controls in a study paradigm involving separation of the child from his or her mother. In contrast, as a third hypothesis, we anticipated no increase in cortisol secretion among healthy controls in the separation condition paradigm, but under a condition of social exposure. Fourth, Hatzinger et al. (2007), Hyde et al. (2008), and Zahn-Waxler et al. (2008) all found that females showed an increased cortisol secretion at the age of five; moreover, female adolescents and adults report an increased risk of developing psychiatric affective disorders. Therefore, we expected an increased cortisol secretion in female compared to male participants.

## 2. Methods

### 2.1. Sample

A total of 31 children with a primary DSM-IV diagnosis of SAD (mean age in years:  $M = 8.45$ ,  $SD = 2.50$ ; 17 females, 14 males) and 25 healthy controls (mean age in years:  $M = 9.36$ ,  $SD = 2.75$ ; 12 females, 13 males) took part in the study. The two groups did not

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