



## The role of childhood abuse in HPA-axis reactivity in Social Anxiety Disorder: A pilot study

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### ABSTRACT

**Background:** Studies on depression have found that childhood abuse (CA) is associated with a persistent sensitization of the hypothalamic–pituitary–adrenal (HPA)-axis to stress in adulthood. So far, it is unknown whether this HPA-axis sensitization is specific to depression, or whether this is a more general outcome associated with CA in patients with mood and anxiety disorders. The aim of this study was to investigate whether CA is associated with enhanced cortisol reactivity to psychosocial stress in Social Anxiety Disorder (SAD).

**Methods:** Salivary cortisol levels before, during, and after exposure to psychosocial stress (i.e., Trier Social Stress Task, TSST) in SAD patients *with* a history of childhood abuse (SAD + CA,  $n = 9$ ) were compared to cortisol levels in SAD patients *without* a history of childhood abuse (SAD – CA,  $n = 9$ ), patients with PTSD related to childhood abuse ( $n = 16$ ), and healthy controls *without* a history of childhood abuse ( $n = 16$ ).

**Results:** Analyses showed that the SAD + CA group had a strongly increased cortisol reactivity (mean peak:  $17.5 \pm 1.9$  nmol/l) compared to SAD – CA (mean peak:  $9.0 \pm 1.1$  nmol/l), PTSD (mean peak:  $9.0 \pm 1.1$  nmol/l) and healthy controls (mean peak:  $9.6 \pm 1.4$  nmol/l), whereas baseline cortisol levels did not differ. The enhanced increase in the SAD + CA group was not explained by stronger anxiety in response to the TSST.

**Conclusions:** Consistent with the findings in depression, these results show for the first time that childhood abuse is also associated with strongly increased cortisol reactivity in SAD. When replicated in a larger sample, these findings may have important implications for the treatment of SAD.

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### 1. Introduction

Social Anxiety Disorder (SAD) is the most common anxiety disorder, which is characterized by persistent fear and avoidance of social situations (Stein and Stein, 2008; Mannuzza et al., 1995). The causes and pathogenesis of SAD are not well elucidated. Besides inheritable traits, several studies reported that childhood abuse (CA), and particular emotional abuse, is an important risk factor for the development of SAD (Gibb et al., 2007; Heim and Nemeroff, 2001).

Research in animals found that chronic exposure to early adverse events, such as maternal deprivation, may have a lasting impact on the neurobiology of the stress response, particularly on

the stress-regulating hypothalamic–pituitary–adrenal (HPA) axis (see Heim and Nemeroff, 2001; Kaufman et al., 2000; Sanchez, 2006, for reviews). Epigenetic regulation of hippocampal glucocorticoid receptor expression may mediate the effects of early life experiences on adult behavior (Weaver et al., 2004, 2007; McGowan et al., 2009). Despite the importance for our understanding of how childhood abuse might lead to psychopathology, only a few studies investigated the impact of early adverse experiences on HPA reactivity (Heim et al., 2000; Bremner et al., 2003; Elzinga et al., 2003). Consistent with the animal studies, these studies found that CA is associated with increased HPA-axis sensitivity to stress in women with MDD (Heim et al., 2000), and to a smaller extent in Post-traumatic Stress Disorder (PTSD) (Bremner et al., 2003; Elzinga et al., 2003). In healthy subjects, in contrast, CA has been related to *hypo*-responsiveness of the HPA-axis to psychosocial stress (Elzinga et al., 2008; Carpenter et al., 2007). An important question that needs to be elucidated is whether HPA-axis sensitization is specific for MDD (and PTSD), or whether it is a

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more general outcome of CA in patients with mood or anxiety disorders, including patients with SAD.

So far, a number of studies investigated cortisol reactivity to psychosocial stress in SAD, with mixed results (Condren et al., 2002; Furlan et al., 2001; Levin et al., 1993; Martel et al., 1999). Recently, we reported increased cortisol responses to the Trier Social Stress Test (TSST) in SAD compared to PTSD and healthy controls (Roelofs et al., 2009). This was in line with one other study reporting increased cortisol responses to psychological stress in SAD (Condren et al., 2002), but other investigations failed to find group differences (Furlan et al., 2001; Levin et al., 1993; Martel et al., 1999). Besides several methodological differences, CA might play an important role in these (inconsistent) findings, as none of these studies included information about the presence of CA.

The aim of the present retrospective study is to investigate HPA reactivity to a psychosocial stressor (TSST) in patients with SAD who report a history of (emotional, physical, or sexual) CA vs patients with SAD who do not report experiences of abuse during childhood. To investigate the specificity of the relation between abuse and HPA reactivity in SAD, we also included patients with PTSD related to CA and healthy participants without a history of CA.

## 2. Methods

### 2.1. Participants

Demographic variables and other characteristics of the groups are presented in Table 1. Participants described here were part of a larger study (see Roelofs et al., 2009). Patients with generalized SAD and PTSD were diagnosed with the Structured Clinical Interview for DSM-IV Axis-I Disorders, SCID-*i/p* (First et al., 1996). Healthy control (HC) participants were recruited via advertisements in local newspapers.

Exclusion criteria were: age <18 or >65 years, left handedness, psychotic disorder, use of neuroleptics, substance use/addiction, chronic disease, use of corticosteroids max 6 months before participation, and pregnancy or breast feeding.

The SAD group with a history of childhood abuse (SAD + CA) consisted of SAD patients who reported emotional, physical or sexual abuse involving the primary caretaker, which took place before the age of 16 (as assessed with the TEC). Similarly, for the PTSD group, participants were only included when posttraumatic stress symptoms were related to adverse events experienced before the age of 16 (excluding  $n = 3$  patients from our original sample with PTSD associated with trauma that occurred after age 16). From the HCs, participants who reported emotional, physical or sexual abuse that had taken place before the age of 16 (excluding  $n = 6$  healthy controls from the original sample) were excluded. These inclusion and exclusion criteria resulted in the following groups: SAD + CA,  $n = 9$ ; SAD – CA,  $n = 9$ ; PTSD,  $n = 16$ ; HC,  $n = 16$ .

All participants were instructed to minimize physical exercise during the hour preceding the experiment and not to take large meals, coffee, drinks with low pH or cigarettes, because these variables can affect cortisol levels. The study was approved by the local ethics committee and all participants provided written informed consent.

### 2.2. Materials

#### 2.2.1. The Trier Social Stress Test

The psychological challenge test consisted of a free speech (5 min) and a mental arithmetic task (5 min), performed in front of an audience of three individuals, which was preceded by an anticipation phase (5 min) in which participants prepared the speech. During the speech, participants took on the role of a job-applicant (job-definition is predefined, based on what is challenging and relevant for the participant). In case participants reported being unable to proceed with the free speech they received a modified version of the TSST with up to three measures helping participants to fulfill the task, without dropping out. The measures were in fixed order, and the next step was applied only if necessary: (1) giving verbal encouragements during the free speech; (2) structured interview in stead of free speech, involving direct questions about job application; (3) preterm cancellation of free speech, and immediate continuation with the mental arithmetic task.

**Table 1**  
Demographic variables and group characteristics.

Variable	SAD + CA ( $n = 9$ )	SAD – CA ( $n = 9$ )	PTSD ( $n = 16$ )	HC ( $n = 16$ )	F-value	p-value
Gender (M/F)	4M/5F	4M/5F	4M/12F	5M/11F	0.98( $\chi^2$ )	0.61
Age	32.9 (9.5)	27.8 (6.3)	35.1 (11.3)	39.3 (17.6)	1.61	0.20
Axis-I comorbidity <sup>a</sup>	6	5	14	0	19.38( $\chi^2$ )	0.000
GAD	1	1	3	0		
Panic disorder	0	0	4	0		
Obsessive comp. dis.	0	1	1	0		
MDD	4	3	5	0		
Dysthymic disorder	1	0	1	0		
Medication <sup>b</sup>	3N/6Y	4N/5Y	3N/13Y	11N/5Y	8.38( $\chi^2$ )	0.04
AD	3	3	2	0		
Sedatives <sup>c</sup>	2	2	3	0		
Other <sup>d</sup>	1	0	3	2		
Oral contraceptives	2	2	7	4		
Social anxiety (SPAI)	166.8 (20.6)ad	152.0 (29.2)b	137.5 (32.3)cd	92.3 (34.3)abc	14.11	0.000
Depression (BDI)	22.4 (10.5)a	12.6 (15.1)b	17.1 (13.4)c	3.1 (2.1)abc	7.45	0.000
Childhood abuse (TEC)	4.3 (1.9)a	1.8 (1.3)b <sup>e</sup>	8.6 (6.2)abc	2.3 (2.1)c <sup>e</sup>	9.22	0.000
Emotional	3.9 ( $n = 8$ )	0.9 ( $n = 3$ )	4.9 ( $n = 12$ )	0.1 ( $n = 1$ )	8.74	0.000
Physical	0.8 ( $n = 3$ )	0.0 ( $n = 0$ )	2.2 ( $n = 8$ )	0.1 ( $n = 1$ )	6.12	0.001
Sexual	0.7 ( $n = 2$ )	0.0 ( $n = 0$ )	4.6 ( $n = 12$ )	0.1 ( $n = 1$ )	9.89	0.000
Age						
Emotional	7.6 years (1–15)	n.a.	6.5 years (1–14)	n.a.		
Physical	5.5 years (1–12)	n.a.	5.1 years (1–12)	n.a.		
Sexual	7.0 years (4–10)	n.a.	7.1 years (1–11)	n.a.		
Duration						
Emotional	10 years (2–18)	n.a.	13.4 years (1–29)	n.a.		
Physical	8.5 years (6–12)	n.a.	11.0 years (2–24)	n.a.		
Sexual	3.0 years (3)	n.a.	6.6 years (1–16)	n.a.		
Impact						
Emotional	3.9 (3–5)	n.a.	3.8 (2–5)	n.a.		
Physical	2.5 (2–3)	n.a.	3.8 (2–5)	n.a.		
Sexual	2.5 (2–3)	n.a.	4.3 (2–5)	n.a.		

*n*: number of participants.

Data from questionnaires are presented in mean score and SD.

Cells with similar letters differ significantly from each other ( $p < 0.05$ ).

<sup>a</sup> Assessed using the SCID.

<sup>b</sup> Total numbers do not correspond with the sum of the four subtypes because of overlap (patients may use more than one type of medication).

<sup>c</sup> Participants refrained from taking the medication min. 24 h before the experiment.

<sup>d</sup> Including medication for respiratory tracts and blood pressure control.

<sup>e</sup> In the case of SAD – CA and HC, this only refers to events after 16 years.

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