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# Identification and characterization of HPA-axis reactivity endophenotypes in a cohort of female PTSD patients



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#### **KEYWORDS**

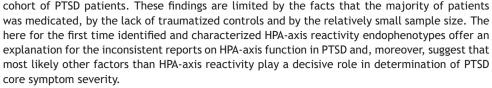
Posttraumatic stress disorder; PTSD; PTSD subtypes; Trier Social Stress Test; Stress reactivity; Gene expression; FKBP5 Summary Analysis of the function of the hypothalamic—pituitary—adrenal (HPA)-axis in patients suffering from posttraumatic stress disorder (PTSD) has hitherto produced inconsistent findings, inter alia in the Trier Social Stress Test (TSST). To address these inconsistencies, we compared a sample of 23 female PTSD patients with either early life trauma (ELT) or adult trauma (AT) or combined ELT and AT to 18 age-matched non-traumatized female healthy controls in the TSST which was preceded by intensive baseline assessments. During the TSST, we determined a variety of clinical, psychological, endocrine and cardiovascular parameters as well as expression levels of four HPA-axis related genes. Using a previously reported definition of HPA-axis responsive versus non-responsive phenotypes, we identified for the first time two clinically and biologically distinct HPA-axis reactivity subgroups of PTSD. One subgroup ("non-responders") showed a blunted HPA-axis response and distinct clinical and biological characteristics such as a higher prevalence of trauma-related dissociative symptoms and of combined AT and ELT as well as alterations in the expression kinetics of the genes encoding for the mineralocorticoid receptor (MR) and for FK506 binding protein 51 (FKBP51). Interestingly, this non-responder subgroup largely drove the relatively diminished HPA axis response of the total

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#### 1. Introduction

Posttraumatic stress disorder (PTSD) develops in about 7 to 12% of individuals after exposure to a traumatic incident like combat or abuse (Kessler et al., 1995). Current treatment options for the devastating PTSD core symptoms, namely nervous hyperarousal, avoidance anxiety, aversive re-experiencing of trauma-related memories and emotional numbing (American Psychiatric Association, 1994), are limited: less than one third of PTSD patients treated with the first-line pharmacotherapy for PTSD, i.e. with selective serotonin reuptake inhibitors, achieve full remission (Berger et al., 2009). Although exposure-based psychotherapy has proved to be effective in PTSD symptom reduction (Hensel-Dittmann et al., 2011), a significant proportion of patients does not benefit from it (Yehuda et al., 2009). Together with this unsatisfactory treatment situation, the lack of clinically applicable biomarkers for PTSD (Pitman et al., 2012; Schmidt et al., 2013b) creates the need for further elucidation of its psychological and biological underpinnings.

Despite the fragmentary state of knowledge on PTSD, some findings regarding PTSD pathobiology are generally accepted, for instance the association of PTSD with hippocampal volume loss (Herrmann et al., 2012; Levy-Gigi et al., 2013; Schmahl et al., 2009), with dysfunction of the prefrontal cortex (PFC) (Fani et al., 2012; Schmidt et al., 2013a) and of the hypothalamic-pituitary-adrenal (HPA)-axis (Pitman et al., 2012) as well as with the HPAaxis regulating gene FKBP5 (Klengel et al., 2013; Schmidt et al., 2014b) which has recently been shown to counteract the stress-induced decline in expression of another putative PTSD candidate molecule, i.e. of the presynapsic vesicle protein synapsin (Herrmann et al., 2012), in the PFC of mice (Schmidt et al., 2014a). The HPA-axis has been shown to play a central role not only in PTSD, but also in a variety of other psychiatric diseases like panic disorder (Erhardt et al., 2006), schizophrenia (Guest et al., 2011) and, particularly, major depressive disorder (MDD), which was repeatedly reported to be associated with HPAaxis overactivity (Anacker et al., 2011). Analysis of HPA-axis function in PTSD has so far produced conflicting results that showed up also in the two most recent meta-analyses on this topic: on the one hand, Klaassens and colleagues inferred that neither adult trauma (AT) nor PTSD were associated with differences in HPA-axis functioning. However, their subgroup analyses suggested AT to potentially increase cortisol (CORT) suppression in trauma-exposed healthy controls (TE-HC) versus non-exposed healthy controls (NE-HC) in the dexamethasone suppression test (DST) (Klaassens et al.,

2012). On the other hand, another recent meta-analysis concluded that post-DST CORT levels were attenuated in both PTSD patients and TE-HC in comparison to NE-HC (Morris et al., 2012). Again, another review highlights the necessity of further research on the relationship between HPA-axis reactivity and early life trauma (ELT) (Frodl and O'Keane, 2013). Several TSST studies suggest that TE per se may induce flattening of the HPA-axis response (Elzinga et al., 2008; Lovallo et al., 2012; Trickett et al., 2014). Remarkably, an elevated HPA-axis response of PTSD patients was found in several studies employing other psychological challenge paradigms: PTSD patients exhibited an exaggerated HPA-axis response upon confrontation with trauma reminders (Elzinga et al., 2003; Gola et al., 2012) and with a non-laboratory stressor (Stoppelbein et al., 2012) as well as in anticipation of a stressful cognitive challenge (Bremner et al., 2003).

Studies on the HPA-axis reactivity of PTSD patients in the TSST are scarce and also revealed conflicting results: two of the in total four studies reported no differences between PTSD patients and HC (Roelofs et al., 2009; Simeon et al., 2007), one found a blunted HPA-axis response in adolescent females to be associated with TE but not with current PTSD (MacMillan et al., 2009) and the fourth study detected an association of unresolved trauma with a flattened HPA-axis response (Pierrehumbert et al., 2009). Here, we aimed to address these inconsistencies in a convenience sample of adult female PTSD patients comprising individuals who were exposed to either AT, ELT, or to combined AT and ELT. The study at hand did not aim to answer a directional hypothesis. Instead, our goal was to comprehensively assess the psychological, endocrine, and cardiovascular stress reactivity of these patients in comparison to an age-matched cohort of female healthy controls (HC) in the TSST. In addition, we selected four genes, namely the two major regulators of the HPA-axis, the glucocorticoid receptor (NR3C1), and the mineralocorticoid receptor (NR3C2) as well as their already mentioned inhibitor FKBP51 (FKBP5) together with its functional antagonist FKBP52 (FKBP4) (Wochnik et al., 2005) for gene expression analysis. In addition to biological factors, we assessed a variety of clinical and psychological parameters both at baseline and during the TSST.

#### 2. Materials and methods

#### 2.1. Participants

With approval from the Ethic Committee of the Ludwig Maximilians University in Munich, 23 female adult Caucasian patients with PTSD and 18 age-matched ( $\pm 2$  years) female

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