



# In search of the HPA axis activity in unipolar depression patients with childhood trauma: Combined cortisol awakening response and dexamethasone suppression test



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## ABSTRACT

The aim of the present study was to examine the impact of childhood trauma on HPA axis activity both in depression patients and healthy controls in order to determine the role of HPA axis abnormalities in depression and to find the differences in HPA axis functioning that may lead certain individuals more susceptible to the depressogenic effects of childhood trauma. Eighty subjects aged 18–45 years were recruited into four study groups ( $n = 18$ , depression patients with childhood trauma exposures, CTE/MDD;  $n = 17$ , depression patients without childhood adversity, non-CTE/MDD;  $n = 23$ , healthy persons with childhood trauma, CTE/non-MDD; and  $n = 22$ , healthy persons without childhood adversity, non-CTE/non-MDD). Each participant collected salivary samples in the morning at four time points: immediately upon awakening, 30, 45, and 60 min after awakening for the assessment of CAR and underwent a 1 mg-dexamethasone suppression test (DST). Regardless of depression, subjects with CTE exhibited an enhanced CAR and the CAR areas under the curve to ground (AUCg) were associated with their childhood trauma questionnaire (CTQ) physical neglect scores and CTQ total scores. In addition, the CTE/MDD group also showed a highest post-DST cortisol concentration and a decreased glucocorticoid feedback inhibition among four groups of subjects. The present findings suggested that childhood trauma was associated with hyperactivity of HPA axis as measured with CAR, potentially reflecting the vulnerability for developing depression after early life stress exposures. Moreover, dysfunction of the GR-mediated negative feedback control might contribute to the development of depression after CTE.

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## 1. Introduction

Major depressive disorder (MDD) has been frequently linked with dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis, one of the major stress systems of the body (Vreeburg et al., 2009). Observations for hyperactivity of the HPA axis as indicated by hypersecretion of cortisol (Knorr et al., 2010), elevated corticotrophin-releasing hormone (CRH) and adrenocorticotropin

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hormone (ACTH) levels (McKay and Zakzanis, 2010), and failure to suppress cortisol concentrations after administration of dexamethasone (dexamethasone suppression test, DST) (Carroll et al., 1981) among patients with MDD have been reported in a growing body of studies. In addition, alteration of circadian HPA rhythms is involved in poor regulation of HPA axis activity in MDD patients as well (Sjogren et al., 2006). However, results still have been controversial and only parts of depression patients show an overactivity of HPA axis based on previous research (Nestler et al., 2002). Activity of the HPA axis in depression patients may vary with heterogeneity of clinical characteristics, e.g., severity of illness (Appelhof et al., 2006) and presence of childhood trauma (Harkness et al., 2011).

Increasing evidence demonstrates that childhood adversity may

contribute to physical and mental diseases in adulthood as an independent factor, specifically, it is a documented predictor of developing MDD (Danese et al., 2007; Heim et al., 2008b). Two earlier studies have reported that individuals with childhood trauma are found to have a 4-fold increase in the risk of depression as compared to those without and nearly 35% of depression patients, which is far more than normal controls (about 15%), experience histories of childhood abuse, including sexual, physical or emotional abuse (Felitti et al., 1998; Young et al., 1997).

In recent years, studies have attempted to identify mechanisms that trigger childhood trauma to depression. Preclinical studies suggest that childhood trauma can alter the development of HPA axis, resulting in persistent sensitization of the stress responses as well as disrupted dynamics of the HPA axis which closely overlap with neuroendocrine findings in depression (Kalinichev et al., 2002). In concordance with this, our previous study has revealed that childhood trauma was associated with increased cortisol awakening response (CAR) in a group of young healthy adults (Lu et al., 2013a). More interestingly, childhood trauma has also been demonstrated to increase HPA activity in adults independent of depression diagnosis as measured with the dexamethasone/corticotrophin-releasing factor test or trier social stress test (TSST) (Heim et al., 2008a; Heim and Nemeroff, 2002). These finding may suggest that dysregulation of the HPA axis is more likely to represent the vulnerability to the development of depression after early life stress exposures rather than neurobiological consequence of the disease (Heim et al., 2008b). This will also be helpful to explain why current studies documenting the presence of HPA axis hyperactivity in depression patients without consideration for histories of childhood trauma have revealed intricate findings (Pariante and Lightman, 2008). However, to date, all these remain to be hypothesis and limited studies have examined the HPA activity in both depression patients and normal subjects that carefully stratify groups by childhood trauma.

Although the persistent neuroendocrine changes induced by childhood adversity have been supposed to elucidate the vulnerability to depression in survivors of childhood trauma, not every individual exposed to childhood trauma will develop depression and in particular, some individuals remain resistant to depression even when experienced to additional stressors in their later life (Heim et al., 2009). In such a case, it is critical to identify the biological bases which provoke different individuals with childhood trauma to two extremely opposite directions. Recently, accumulating evidence suggests that genetic factors, such as epigenetic modification or gene polymorphism, may mediate the association between childhood trauma, as an adverse environment, and depression (Monroe and Reid, 2008). Interestingly, most investigated genes in prior studies are involved in the HPA system, such as *corticotrophin receptor 1* (*CRHR1*), *glucocorticoid receptor* (*GR*) and the gene encoding the GR-associated heat-shock protein FKBP5, meanwhile, dysregulation of these genes has been reported to be correlated with GR resistance and deficient glucocorticoid feedback regulation (Heim and Binder, 2012). Importantly, childhood adversity in rodents has been confirmed to induce decreased expression of GR in central nervous system by epigenetic programming, leading to functional impairment of the GR and subsequently impaired feedback control (Meaney and Szyf, 2005). Since then, it is conceivable that there must be individual differences in the HPA system among victims of childhood trauma that serve as markers of escaping from depression after childhood adversity (van Rossum et al., 2006). Of note, impaired or not impaired GR-mediated feedback control of HPA axis may contribute to one of those differences.

The aim of the present study was to examine HPA axis activity with respect to histories of childhood trauma in both depression

patients and normal controls, trying to investigate i) the impact of childhood trauma on HPA axis activity; ii) the role of HPA axis abnormalities in depression, and iii) the differences in HPA axis functioning that may lead certain individuals more susceptible to the depressogenic effects of childhood trauma. To assess HPA axis activity, the CAR and DST were administered to evaluate morning cortisol release to awaken and HPA feedback sensitivity via salivary and plasma cortisol respectively. The CAR, characterized by a sharp increase in cortisol level between 20 and 30 min after awakening in the morning, is a reliable biological marker of reflecting the dynamic activity of HPA axis and offers benefits over isolated measures that evaluate basal cortisol concentration at a permanent time, e.g., at 8 a.m. or 9 a.m. (Bhagwagar et al., 2005; Mangold et al., 2011). The DST is a best-known measure of the negative feedback effects of dexamethasone via GR activation (Watson et al., 2006). The DST is a sensitive tool to detect HPA activity and decreased levels of suppression or early escape from suppression are treated as indications of dysregulation within the HPA axis's negative feedback mechanism (Guerry and Hastings, 2011).

## 2. Methods

### 2.1. Participants

The study group comprised 80 subjects (male/female, 34/46), ages 18–45 years, including 18 patients with childhood trauma exposures (CTE/MDD), 17 patients without childhood adversity (non-CTE/MDD), 23 healthy persons with a history of childhood trauma (CTE/non-MDD) and 22 healthy persons without a history of childhood adversity (non-CTE/non-MDD). For assignment to the CTE groups, individuals must have had experienced chronic moderate-severe trauma exposures (abuse or/and neglect) before the age of 16 as assessed by the Childhood Trauma Questionnaire (CTQ). MDD patients were recruited from the psychiatric clinic of the First Affiliated Hospital of Zhejiang University and the Second Xiangya Hospital of Central South University. The inclusion criteria for patients were as follows: 1) met the Diagnostic and Statistical Manual of Mental Disorders, IV Edition (DSM- IV) criteria for current unipolar MDD episode; 2) free of treatment for at least 2 weeks; 3) at least junior middle school level of education; 4) the Han nationality. Age- and gender-matched healthy samples were recruited from a survey that we had carried out to investigate the occurrence of childhood trauma in local communities and universities. A total of 555 individuals by convenience sampling were involved in the survey, a proportion of 18.6% (103) subjects had self-reported CTE. Then, 45 volunteers were recruited via telephone calls, and were screened in this study. All the subjects responded with no direct reference to childhood trauma as a key variable. General exclusion criteria were current medical illness, lifetime psychiatric axis-I or axis-II disorders (except MDD in patients), alcohol or substance abuse, with a family history of bipolar disorder, woman with pregnancy or in lactation or menstrual period, and receiving hormone for treatment. Written informed consent was obtained and this study was approved by the ethic committee of the First Affiliated Hospital of Zhejiang University and the Second Xiangya Hospital of Central South University.

### 2.2. Procedure

Subjects were asked to come to the lab and stay there for three consecutive days, while during daytime they were free to follow their normal activity. On the first day night (Day 1), they are arranged to provide the general information and complete the evaluation. The Structured Clinical Interview for DSM-IV (SCID) was used for the diagnostic assessment of MDD and further psychiatric

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