



Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults

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ABSTRACT

Epidemiological studies have reported associations between measures of size and weight at birth and disease risk in later life. Alteration in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis in response to prenatal stress has been proposed as one underlying mechanism. The present study investigated in humans the association of prenatal psychosocial stress exposure with subsequent HPA axis regulation in adult life, with a focus on measures of response to challenge and feedback sensitivity. Healthy young adults whose mothers experienced severe stress during their pregnancy in form of major negative life events (e.g. death of someone close; prenatal stress (PS) group, $n=31$) and an age-matched comparison group (CG, $n=30$) underwent the Trier Social Stress Test (TSST) and a 1 μg ACTH_{1–24} stimulation test. In addition, a diurnal cortisol profile was assessed. ACTH concentrations following a standardized behavioural challenge paradigm (TSST) were marginally significantly higher in PS subjects than in CG subjects ($p=.06$). Pre-TSST adrenocortical (cortisol) levels were lower ($p=.007$), whereas the increase in cortisol in response to the TSST was higher ($p=.03$) in PS subjects compared to CG subjects. Cortisol concentrations following a pharmacological stimulation test simulating pituitary activity (ACTH_{1–24} test) were significantly lower in PS than in CG subjects ($p=.006$). No differences emerged between the two groups in basal diurnal cortisol levels. This study provides first evidence in humans of an association between prenatal psychosocial stress exposure and subsequent alterations in the regulation of the HPA axis.

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Introduction

A large number of epidemiological studies across the world have reported associations between an individual's birth phenotype such as low birth weight and small body size and subsequent risk of disease in adult life, including type 2 diabetes, dyslipidemia, raised blood pressure and depression (Barker, 1998; Barker et al., 1989; Newsome et al., 2003; Phillips, 1998; Thompson et al., 2001). These associations are independent of adult weight or BMI and other established disease risk factors, and the effects extend continuously across the normal range of birth phenotype; they are not just a function of adverse birth outcomes such as low birth weight or small-for-gestational age at birth (Barker, 2002; Gluckman and Hanson, 2004a). It is, however, unlikely that birth phenotype *per se* plays a causal role in increasing disease risk. Instead birth phenotype is more likely a crude reflection of developmental processes in intrauterine life that also may influence the structure and function of physiological systems that underlie

health and disease risk in later life (Gluckman and Hanson, 2004b; Morley et al., 2002).

Several studies on the effects of adverse early environment have focused on the role of prenatal nutrition. We and others have proposed that psychosocial stress exposure during pregnancy may represent yet another adverse environment that may impact both birth phenotype and the physiology of the developing organism. In humans, maternal stress during pregnancy has been shown to predict low birth weight (Paarlberg et al., 1999, 1995; Wadhwa et al., 2001) as well as preterm delivery (Hedegaard et al., 1993; Paarlberg et al., 1995; Wadhwa et al., 2001). Other studies have linked low birth weight with alterations in hypothalamus–pituitary–adrenal (HPA) axis regulation (Jones et al., 2006; Kajantie et al., 2003; Levitt et al., 2000; Phillips, 1998; Phillips et al., 2000; Reynolds et al., 2001; Ward et al., 2004; Wüst et al., 2005), particularly HPA responses to challenge as opposed to basal function (Fall et al., 2002; Kajantie et al., 2004). Several animal studies have reported associations between prenatal stress exposure and alterations in HPA axis function (for recent reviews see Kapoor et al., 2006; Weinstock, 2005). Some studies have linked maternal anxiety or depression during pregnancy with HPA axis reactivity in infants and children (Field et al., 2004; O'Connor et al., 2005). But, to the best of our

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knowledge, there are no studies in humans that have investigated the direct link between maternal psychosocial stress during pregnancy and HPA axis reactivity in their adult offspring.

Because impaired functioning of the HPA axis has been associated with several physical and psychiatric disorders, such as the metabolic syndrome, fibromyalgia, depression, or post traumatic stress disorder (PTSD) (Bjorntorp and Rosmond, 2000; Holsboer, 2000; Parker et al., 2001; Yehuda, 1997), it is important to identify the antecedents, or determinants, of the marked inter-individual and intra-individual variation in HPA axis response to challenge that is observed in these conditions. Exposure to maternal psychosocial stress *in utero* may be one further important factors underlying changes in HPA axis function that may mediate the effects of early adversity on individual susceptibility to stress-related disorders.

The aim of the present study was to test the hypothesis that HPA axis regulation, particularly in response to challenge, is altered in adult individuals whose mothers experienced high levels of psychosocial stress during their pregnancies. Thus, in the present study, HPA axis function was assessed in healthy young adults whose mothers experienced high levels of psychosocial stress during pregnancy in form of major negative life events (PS group), and in a group of comparison subjects (CG group). To assess psychological as well as pituitary (ACTH) and adrenal (cortisol) responses to a behavioural challenge paradigm that activates the HPA axis through central pathways, the two groups underwent the Trier Social Stress Test (TSST). Furthermore, a pharmacological stimulation test that simulates pituitary activation (1 µg ACTH_{1–24} test) was conducted. Last, daytime cortisol profiles were collected to assess baseline adrenocortical function.

Materials and methods

Subjects

The study sample included a total of 61 subjects. Thirty-one young adults (mean age 25, SEM: ±.80 years, 26 women and 5 men) whose mothers experienced a high level of psychological stress during pregnancy (negative life events during pregnancy, see below) constituted the prenatal stress group (PS). A sample of 30 subjects (mean age 24±.60 years, 22 women, 7 men) constituted the comparison group (CG). All subjects were university students, and all subjects were of Western European descent.

Subjects were recruited through an announcement in local newspapers and by presenting the study to students at the University of Trier. Before entering the study, the absence of acute or chronic health problems was ascertained by self-report and confirmed by a medical examination. All subjects were non-smokers and reported to be medication free, except for oral contraceptives (OC; all female control subjects and 22 subjects in the PS group were OC users). A copy of the maternal prenatal medical record (which is handed to the mother by the obstetrician during her first prenatal visit) was obtained from each participant. From this record, information about maternal parity, maternal age at birth, length of gestation and subjects' weight, height and head circumference at birth were extracted. Participants received a modest monetary incentive on completion of the experiment. Written informed consent was obtained from all subjects. To avoid a potential self-selection bias, subjects were not informed about the hypothesized directions of the findings. The investigation described in this manuscript was conducted in accordance with the guidelines described in the declaration of Helsinki and the study protocol was approved by the ethics committee of the German Psychological Society, DGPs.

Conceptualization and assessment of prenatal psychosocial stress exposure

We adopted a conservative strategy for the conceptualization of prenatal stress in the present study. We defined a high level of

prenatal psychosocial stress exposure as the presence of major negative life events that occurred to the mother while she was pregnant (see Table 1 for list and frequency of events). Psychosocial stress is a multi-component construct that includes the occurrence of negative life events, appraisal of the stress (e.g., degree of predictability and control), and psychological symptoms such as anxiety and negative affect. Because retrospective assessment of stress appraisals and symptoms is known to be unreliable, we focused on only the presence or absence of negative life events during the index pregnancy. Moreover, we selected those events that are considered as highly stressful across individuals (see Table 1).

In all subjects we conducted semi-structured interviews based on a questionnaire about exposure to major negative life events during the prenatal period that subjects were instructed to review with their mothers prior to the interview. The subjects that were recruited to constitute the comparison group were asked to review the same questionnaire with their mothers to ascertain that their mothers had not experienced any negative life events during pregnancy. In most of the cases (70%) we were able to verify this information by communicating directly with the mothers by phone, e-mail or letters. All subjects received the same information before entering the study regarding the assessments of HPA axis function, the subjects were not informed about the hypothesized direction of the effects, and the experimenters were blind to which group a subject belonged to.

Questionnaires

Since it is possible that prenatal stress exposure is associated with adverse postnatal experiences such as poor maternal care and presence of other stressors during childhood we assessed several measures to control for these potential confounding factors.

In order to obtain an important aspect of the family environment during the postnatal period we administered the maternal care scale of the Parental Bonding Inventory (PBI; German version by Lutz et al. (1995), originally developed by Parker et al. (1979). The PBI measures the self reported perception of being parented to the age of 16 years. Studies assessing re-test reliability of the PBI suggest that the parental evaluation is a rather stable measure, which is not affected by confounding variables like dysthymia, neuroticism, depressive episode or gender (Lizardi and Klein, 2005; Parker, 1990; Plantes et al., 1988; Wilhelm et al., 2005). Good validity of the PBI can be concluded e.g. from high agreement between sibling ratings (Parker, 1990). Furthermore, subjects' and subjects' mothers' socio-economic status (SES) was assessed by educational level.

A translated version of the Childhood Traumatic Events Survey (Pennebaker and Susman, 1988) was administered. The instrument

Table 1
List of life events during pregnancy included in the study

Event		N (31)	%
Relationship conflicts	Divorce	11	35
	Break up		
	Paternity denial		
	Marital infidelity		
Death of someone close	Partner	7	24
	Parent		
	Other child		
Severe illness of someone close	Cancer	6	19
	Heart attack		
	Stroke		
Severe financial problems	Loss of house by flooding	3	10
	Sudden unemployment of husband		
	Foreclosure		
Car accident		2	6
Unmarried, father not accepted by family		1	3
Becoming political refugee		1	3

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