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Elevated cortisol in healthy female adolescent offspring of mothers with posttraumatic stress disorder

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ABSTRACT

Offspring with maternal PTSD are at increased risk of developing PTSD themselves. Alterations in the hypothalamic-pituitary-adrenal (HPA) axis may play a role and have been noted in offspring, although evidence is mostly from adult offspring with PTSD symptoms themselves. The present study of adolescent girls ($N = 472$) and their mothers ($n = 18$ with lifetime PTSD versus $n = 454$ with no PTSD) sought to determine whether healthy, non-affected offspring of mothers with PTSD would exhibit altered HPA axis function. Saliva samples were collected from the adolescent girls at waking, 30 min after waking, and 8 pm on 3 consecutive days. Offspring whose mothers were diagnosed with PTSD demonstrated higher cortisol awakening response (CAR; Cohen's $d = 0.58$) and greater total cortisol output (Cohen's $d = 0.62$). In this preliminary study, higher cortisol levels during adolescence among offspring of mothers with PTSD may index a vulnerability in these at-risk youth.

1. Introduction

Offspring of parents with posttraumatic stress disorder (PTSD), particularly maternal PTSD, are at increased risk of developing psychopathology in general and PTSD in particular (Chemtob & Carlson, 2004; Enlow et al., 2011; Leen-Feldner et al., 2013). For example, adolescent offspring of Cambodian refugees were approximately five times more likely to have PTSD when their mother had the disorder, whereas effects from paternal PTSD were not evident (Sack, Clarke, & Seeley, 1995).

Increased risk in offspring may be associated with alterations observed in the disorder. Notably, PTSD has been associated with altered hypothalamic-pituitary-adrenal (HPA) axis activity. In both adults and adolescents with PTSD, studies reported they had *lower* basal cortisol levels (e.g., Horn, Pietrzak, Corsi-travali, & Neumeister, 2014; Keeshin, Strawn, Out, Granger, & Putnam, 2014; King, Mandansky, King, Fletcher, & Brewer, 2001; Wessa, Rohleder, Kirschbaum, & Flor, 2006), exaggerated suppression of cortisol in response to dexamethasone (for review, see de Kloet et al., 2006; de Kloet et al., 2007), and greater density and sensitivity of glucocorticoid receptor (GR; Heim & Nemeroff, 2009; Labonte, Azoulay, Yerko, Turecki, & Brunet, 2014). However, not all studies have been consistent, with some finding *higher* basal cortisol levels associated with PTSD (Carrion et al., 2002; Cicchetti & Rogosch, 2001; Lindley, Carlson, & Benoit, 2004; Pfeffer, Altemus, Heo, & Jiang, 2007; Simsek, Uysal, Kaplan, Yuksel, & Aktas, 2015; Young & Breslau, 2004;) and *lower* GR density (e.g., Gotovac, Sabioncello, Berki, & Dekaris, 2003).

Some evidence suggests altered HPA axis activity may represent a pre-existing vulnerability to the disorder (for review, see van Zuiden, Kavelaars, Geuze, Olff, & Heijnen, 2013). A number of studies have investigated whether offspring of those with PTSD have evidence of altered HPA axis activity (Bader et al., 2014; Danielson, Hankin, & Badanes, 2015; Lehrner et al., 2014; Perroud et al., 2014; Yehuda et al., 2005; Yehuda, Blair, Labinsky, & Bierer, 2007; Yehuda et al., 2014; Yehuda, Teicher et al., 2007). Similar to what is seen in PTSD, the majority of these studies found lower basal cortisol levels (Bader et al., 2014; Perroud et al., 2014; Yehuda, Teicher et al., 2007) and enhanced cortisol suppression following dexamethasone administration in the offspring (Lehrner et al., 2014; Yehuda, Blair et al., 2007). However, most offspring studies were conducted in adults and most offspring had PTSD symptoms themselves, mak-

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ing it less clear whether the alteretd HPA axis actvity existed earlier in developmental.

Two studies investigated the HPA axis activity in young, non-affected offspring with maternal PTSD (Danielson et al., 2015; Yehuda et al., 2005). The first study examined basal cortisol levels in infants of women who were pregnant during the World Trade Center attacks (Yehuda et al., 2005). Saliva samples from both mothers and their babies were collected by the mother at two times: wake-up time and bedtime. Infant offspring of mothers who developed PTSD symptoms had lower cortisol levels at both times in the first year of life compared to offspring of mothers who did not develop PTSD symptoms (Yehuda et al., 2005). Effects were only apparent for infants born to mothers exposed to the attack in the third trimester of pregnancy (Yehuda et al., 2005). The second study found attenuated cortisol reactivity to acute stress in the laboratory among non-affected adolescents of mothers with PTSD (Danielson et al., 2015).

Previous studies have not evaluated whether similar effects for adolescent offspring of maternal PTSD exist for cortisol awakening response (CAR; Pruessner et al., 1997). CAR is particularly important since it is distinct from other indices of circadian cortisol secretion (Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007; for review, see Stalder et al., 2016) and is less influenced by stressful events throughout the day (for review, see Chida & Steptoe, 2009). Moreover, CAR also differs from cortisol reactivity to an acute stress task, the index assessed in the previous study of adolescent offspring of mothers with PTSD (Danielson et al., 2015). A recent review has suggested cortisol measured through CAR is a better index of basal HPA axis activity compared to such laboratory-based paradigms (Stalder et al., 2016).

Given this background, the present study sought to compare basal cortisol activity, including CAR, in healthy (non-PTSD) female adolescent offspring with and without maternal PTSD. Offspring studies reviewed above are consistent with a hypothesis of lower basal HPA axis activity in the adolescent offspring of those with maternal PTSD. Exploratory analyses considered whether effects would differ across distinct indices of basal cortisol activity.

2. Methods

2.1. Participants

A total of 550 adolescent girls between the ages of 13.5 and 15.5 (M_{age} = 14.39, SD = 0.63) and one of their parents originally enrolled in an ongoing longitudinal study of adolescents, the Adolescent Development of Emotions and Personality Traits (ADEPT) project. In total, 78 participants were excluded because (1.) diagnostic history was not collected from the biological mother (n = 40), (2.) the biological mother's diagnostic history for PTSD was ambiguous (i.e., subsyndromal PTSD; n = 16), and (3.) the daughter's cortisol sample was deemed an outlier (n = 22; see below for details on outlier analysis). Of the remaining 472 participants in the present analysis, 18 mothers were diagnosed with lifetime PTSD; of those, eight of them were also diagnosed with current PTSD. The ethnic and racial composition of the adolescents was 81.6% non-Hispanic Caucasian, and 86% of the adolescents' mothers had a bachelor's degree or greater. Participants were recruited from the community through school events, online classifieds, word-of-mouth referral, and a commercial mailing list of homes in the area. Families were financially compensated for their participation. Inclusion criteria into the ADEPT project were ability to read and understand questionnaires and participation of at least one biological parent. To ensure a healthy sample, exclusion criteria were medication use (i.e., anti-inflammatory drugs) or disease that may impact HPA axis activities, lifetime history of major depressive disorder (MDD), dysthymia, or intellectual disabilities. Lifetime history of MDD or dysthymia was determined using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS; Kaufman et al., 1997). This clinical interview was administered by trained diagnostic interviewers who were under close supervision of clinical psychologists (R.K., G.P., and D.K.). None of the adolescents in the final sample met criteria for a diagnosis of PTSD themselves based on KSADS. The study was approved by the Stony Brook University Institutional Review Board.

2.2. Clinical assessment

Trauma exposure and the history of psychopathology in mothers was assessed via the Structured Clinical Interview for DSM-IV Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1997). All SCID interviews were recorded. PTSD diagnosis was operationalized as meeting the *DSM-IV* diagnostic criteria for PTSD. Inter-rater reliability of PTSD diagnosis from 25 SCID recordings was excellent (kappa = 0.87).

Adolescent depression and anxiety symptoms were assessed with the Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012). The IDAS-II is a 99-item self-report measure that yields scores on 19 symptom scales (Watson et al., 2012). The General Depression, Traumatic Intrusions, and Traumatic Avoidance subscales were the focus of the present study, as the latter two scales were designed to measure PTSD core symptoms dimensionally in diverse populations and were validated for adults and adolescents (Watson et al., 2007; 2012). The General Depression scale was designed to capture broad, non-specific psychological distress-related symptoms shared by depression and anxiety disorders (Watson et al., 2007). Participants were asked to rate their experience with each symptom in the last month on a 5-point Likert scale from 1 (*not at all*) to 5 (*extremely*). Scales had excellent internal consistency (α's > 0.79).

2.3. Biological assessment

2.3.1. Saliva collection and cortisol assay

Saliva samples were collected with Salivette sampling devices (Salimetrics, Inc., the United States of America) from all adolescents. Samples were collected on three days at home. To capture peak cortisol values in the early morning in response to waking and total cortisol output, saliva samples were collected upon waking, 30 min after waking, and at 8 pm. Participants were asked to keep a diary of their waking time, the time of each cortisol sample collection, and any illness symptoms on a given sample collection day. Collection times were verified using a MEMSCap^{TM} device that recorded when each saliva swab was taken from a storage container. Adolescents were instructed to store samples in the freezer before they delivered them to the lab. After their return to the lab, saliva samples were placed in a −80 °C freezer. Experimenters followed standard laboratory safety procedures for handling saliva samples. Salivary cortisol levels were determined by a time-resolved immuno-assay with fluorescence detection (DELFIA). An average coefficient of variation (CV) of duplicate assays of each sample was calculated. Any CV values greater than 12% for cortisol values greater than 5 nmol/L were reanalyzed, as were any values ≥100 nmol/L. The average of the two assay values was used for analysis.

2.3.2. Adolescent body mass index (BMI) and pubertal stage

Adolescent BMI was calculated based on self-reported height and weight. Pubertal stage was assessed with two measures. The Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) is a self-report measure that includes five indices of pubertal growth: growth in height, body hair, skin changes, and breast development on a 4-point Likert-type scale ranging from 1