Journal of Affective Disorders 132 (2011) 265–269

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

# Elevated daytime cortisol levels: A biomarker of subsequent major affective disorder?

Mark A. Ellenbogen [a,*], Sheilagh Hodgins [b,c,d], Anne-Marie Linnen [a], Caroline S. Ostiguy [a]

[a] Centre for Research in Human Development, Concordia University, Montréal (Québec), Canada
[b] Institute of Psychiatry, King's College London, London, UK
[c] Department of Psychiatry, Heidelberg University, Heidelberg, Germany
[d] Département de Psychiatrie, Université de Montréal, Montréal, Canada

ARTICLE INFO

*Article history:*
Received 14 August 2010
Received in revised form 9 December 2010
Accepted 13 January 2011
Available online 16 February 2011

*Keywords:*
Cortisol
Adolescence
Hypothalamic–pituitary–adrenal axis
Affective disorder
Bipolar disorder
Risk factors
Prospective
Longitudinal

ABSTRACT

*Background:* Several studies have reported that the offspring of parents with affective disorders secrete high levels of daytime cortisol. A few studies have shown that high cortisol levels preceded the onset of affective symptoms. Only one study to date has found that an elevation in cortisol preceded the onset of an affective disorder, but this was observed only in those youth carrying the short allele of the serotonin transporter gene promoter polymorphism (Goodyer et al., 2009).
*Methods:* We followed 28 offspring of parents with bipolar disorder and 31 offspring of parents with no affective disorder from an average age of 17.5 years to an average age of 20.0 years to determine if cortisol levels at baseline predicted the subsequent development of an affective disorder. At baseline and at follow-up participants completed a diagnostic assessment, and at baseline they provided saliva samples. Daytime cortisol levels were computed as the mean of eight to 24 samples measured across two to six days.
*Results:* Among the 59 participants, cortisol levels at the mean age of 17.5 years predicted the development of an affective disorder during the subsequent 2.5 year (odds ratio: 2.1, 95% confidence interval = 1.0–4.1, $p<0.05$) after controlling for offspring mental disorders at the first assessment and having a parent with bipolar disorder.
*Limitations:* The findings should be interpreted with caution, as the sample size was small.
*Conclusion:* Elevated daytime cortisol levels in late adolescence may be a biomarker of vulnerability for affective disorders.



The offspring of parents with bipolar disorder (BD) are at increased risk to develop either major depression (MD) or BD (Birmaher et al., 2009; Lapalme et al., 1997). These offspring (Ellenbogen et al., 2006; Ellenbogen et al., 2010), like those of parents with MD (Mannie et al., 2007), exhibit abnormal hypothalamic–pituitary–adrenal (HPA) axis functioning in the natural environment, as indexed by high salivary cortisol levels at awakening and throughout the day. It is not clear, however, whether elevated glucocorticoid levels in these high-risk populations signal vulnerability for the future onset of a major affective disorder (Pariante and Lightman, 2008).

Two prospective studies of adolescents have reported that higher cortisol levels measured in the natural environment predict symptoms of depression among the offspring of parents with MD (Halligan et al., 2007) and other vulnerable youth (Goodyer et al., 2000). Only one study to date in youth has shown that elevated cortisol levels predict the subsequent development of an affective disorder (Goodyer et al., 2009). In a study of high risk adolescents, defined as having either a parent with a mental disorder or exposure to psychosocial adversity, the presence of both high levels of

* Corresponding author at: Centre for Research in Human Development, Concordia University, 7141 Sherbrooke Street West, Montréal, Québec H4B 1R6, Canada. Tel.: +1 514 848 2424x7543; fax: +1 514 848 2815.
*E-mail address:* mark.ellenbogen@concordia.ca (M.A. Ellenbogen).

0165-0327/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2011.01.007

cortisol in the morning and having one copy of the short ('s') allele of the serotonin transporter-linked promoter region polymorphism (5-HTTLPR) predicted the development of MD one year later. Cortisol levels alone, in contrast, did not predict the development of MD.

The present study followed offspring of parents with BD and of parents with no affective disorders from an average age of 17.5 years for 2.5 years (range 1 to 6 years). At the first assessment, offspring provided multiple saliva samples over several days in their natural environment (Ellenbogen et al., 2006; Ellenbogen et al., 2010). Because cortisol levels are subject to numerous confounding influences, the collection of multiple samples over different days minimizes potential sources of error, and is therefore important in establishing valid measures of daytime cortisol levels (Goodyer et al., 2001). At baseline and at follow-up, participants completed a diagnostic assessment. We hypothesized that high cortisol levels at baseline would predict the onset of affective disorders during the follow-up period, after controlling for the offsprings' past mental disorders and BD in parents. We also hypothesized that cortisol levels at baseline would not predict the onset of other mental disorders.

## 1. Methods

### 1.1. Participants

Participants were 59 offspring, from a total of 139, who completed diagnostic assessments at baseline and follow-up as part of a prospective study comparing the development of the offspring of parents with BD and parents with no affective disorders in Québec, Canada (see Table 1 for demographic and clinical characteristics). The subject sample consisted of offspring who participated in at least one of three previous studies of salivary cortisol (Ellenbogen et al., 2004; Ellenbogen et al., 2006; Ellenbogen et al., 2010), all of which used the same two-day home sampling methodology and assay kit. Specifically, 28 offspring had participated in one study (two days of sampling), 23 offspring had participated in two studies (four days of sampling), and eight offspring had participated in all three studies (six days of sampling).

Parental diagnoses (or the absence of) were confirmed by an experienced clinician using the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1992) and from an examination of psychiatric records. Informed written consent was obtained from parents of offspring less than 18 years old or from offspring 18 and older. All procedures were approved by the Université de Montréal and Concordia University's Research Ethics Committees.

### 1.2. Baseline saliva sampling

Participants collected saliva at awakening, 30 and 60 min post-awakening, 1500 h, 2000 h, and at bedtime on sampling days while following their routine schedule. The first two samples, meant to assess the cortisol response following awakening, are not reported here. For more details on saliva sampling methodology, see Ellenbogen et al. (2006). For offspring who participated in more than one study, we opted to aggregate data, rather than exclude samples, to provide more stable estimates of cortisol and maximize statistical power. Therefore, cortisol levels at each time point were computed as the mean across two (n = 28), four (n = 23), or six (n = 8) days. Sampling procedures were identical in all studies, except that a small number of participants (n = 14, but applies to only some of their samples) sampled at 1900 h instead of 2000 h during the 2-day sampling period (Ellenbogen et al., 2004). Aggregated cortisol levels at 60 min post-awakening, 1500 h, 2000 h, and at bedtime were then averaged, to provide an overall measure of daytime cortisol based on the mean of 8 to 24 samples. Cortisol levels were standardized using a z-transformation to provide logistic regression odds ratios that were comparable to other studies.

### 1.3. Assessment of salivary cortisol levels

Saliva was absorbed into a small cotton roll and expressed through a plastic tube into a sterile vial ("Salivette" device). Saliva was assayed for cortisol by a sensitive radioimmunoassay using a commercial kit from Diagnostic Systems Laboratory Inc. (DSL-2000; Sanofi Diagnostics, Montréal, CAN). The inter- and intra-assay coefficients of variation for all assays were 3.6% to 6.4% and 4.6% respectively.

**Table 1**
Demographic information, diagnoses, and cortisol levels among the offspring of parents with bipolar disorder and parents with no mental disorder.

| | Offspring of parent with bipolar disorder | Offspring of parents with no affective disorder |
|---|---|---|
| N | 28 | 31 |
| Gender | 15 M/13 F | 13 M/18 F |
| *Baseline assessment* | | |
| Mean age ± SD (range), years [a] | 17.8 ± 2.4 (15 to 25) | 17.4 ± 2.1 (13 to 21) |
| Any mental disorder, n (%) | 6 (21) | 8 (26) |
| Mean daytime cortisol levels, μg/dl | 0.17 ± 0.064 | 0.14 ± 0.059† |
| Mean z-transformed daytime cortisol levels | 0.26 ± 1.0 | −0.24 ± 0.94† |
| *Follow-up assessment* | | |
| Mean age ± SD (range), years | 20.4 ± 2.2 (16 to 26) | 20.1 ± 2.6 (14 to 24) |
| Mean time interval, baseline to follow-up ± SD (range), years | 2.6 ± 1.5 (1 to 6) | 2.6 ± 1.6 (1 to 6) |
| Lifetime affective disorder, n (%) | 9 (32) | 4 (13)†† |
| Bipolar disorder | 1 | 0 |
| Major depressive disorder | 8 | 4 |
| Lifetime non-affective mental disorders, n (%) | 15 (54) | 9 (29)† |

Note. [a] refers to the age of participants during the most recent sampling period, for those who took part in multiple studies; † $p<0.06$; †† $p<0.08$.