Dynamics of the human stress system in depression
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Chronicity of depressive problems and the cortisol response to psychosocial stress in adolescents: The TRAILS study

S.H. Booij, E.M.C. Bouma, P. de Jonge, J. Ormel, A.J. Oldehinkel

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Clinical and epidemiological studies, further supported by meta-analytic studies, indicate a possible association between chronicity (i.e., persistence or recurrence) of depression and hypothalamic-pituitary-adrenal (HPA) axis responsiveness to psychosocial stress. In the present study we examined whether and how chronicity of depressive problems predicts cortisol responses to a standardized social stress test in adolescents. Data were collected in a high-risk focus sample (n = 351) of the Tracking Adolescents’ Individual Lives Survey (TRAILS) cohort, a large prospective population study with bi- to triennial measurements. Depressive problems were assessed around age 11, 13.5, and 16. Cortisol levels were measured in saliva, sampled before, during, and after the Groningen Social Stress Test (GSST), to determine the cortisol response to psychosocial stress. The area under the curve with respect to the increase (AUCi) (i.e., change from baseline) of the cortisol response was used as a measure of HPA axis response. By means of linear regression analysis and repeated-measures analysis of variance, it was examined whether chronicity of depressive problems predicted the cortisol response to the GSST around the age of 16. Chronicity of depressive problems was significantly associated with cortisol stress responses. The relationship was curvilinear, with recent-onset depressive problems predicting an increased cortisol response, and more chronic depressive problems a blunted response. The results of this study suggest that depressive problems initially increase cortisol responses to stress, but that this pattern reverses when depressive problems persist over prolonged periods of time.
INTRODUCTION

One of the prime factors in the precipitation of depression is the experience of psychosocial stress (Kendler et al., 1999; Ormel et al., 2001). Psychosocial stressors are capable of activating a major player of the human stress system: the hypothalamic-pituitary-adrenal (HPA) axis (Holsboer and Ising, 2010). Abnormal HPA axis functioning has been a much studied facet of the pathophysiology of depression over the last years. Despite this, the exact role of the HPA axis response to psychosocial stressors in depressed persons is unclear. This is, at least in part, due to inconsistent findings: some studies found that individuals suffering from depression displayed increased cortisol responses to psychosocial stress, while others found blunted cortisol responses (Burke et al., 2005). A meta-analysis in adults samples revealed that, overall, depressed persons had blunted cortisol responses to psychosocial stress (i.e., change from baseline), but the results were heterogeneous. This heterogeneity was partly caused by the fact that blunted responses were seen particularly in severely depressed and in older subjects (Burke et al., 2005). To best of our knowledge, only one study examined the association between depression and HPA axis responses to stress in adolescents. In this study, depressed adolescents displayed exaggerated cortisol responses to a psychosocial stress test (Rao et al., 2008).

The finding that older depressed individuals are more likely to display blunted cortisol stress responses than younger ones could be explained by age differences, but older persons are also likely to have a persistent or recurrent depression (Burke et al., 2005). Unfortunately, studies looking into the relationship between HPA axis responses and depression have been mainly cross-sectional, and discriminated only between currently depressed and non-depressed individuals. This is in spite of evidence from several neuroimaging studies which suggests that persistent or recurrent depression coincides with changes in the brain that might affect HPA axis functioning, among which is reduced hippocampal size (Lorenzetti et al., 2009). In turn, these changes may lead to less effective inhibitory control of the hippocampus over the HPA axis, which has been thought to potentiate chronic release of cortisol and to be related to low HPA axis responses to stress (Jacobson and Sapolsky, 1991; Buchanan et al., 2009). In addition to evidence from neuroimaging studies, epidemiological studies have shown that the association between stressful life events and depression onset becomes weaker with subsequent depressive episodes (Kendler et al., 2000; Ormel et al., 2001). This so-called kindling effect (Post, 1992) indicates changes in reactivity to stress with subsequent depressive episodes.

In the present study, we addressed the role of chronicity, defined as persistent or recurrent depressive problems, with regard to the HPA axis response to psychosocial stress. Chronicity was defined as the presence of persistent or recurrent depressive problems, and operationalized as having depressive problems at consecutive assessment waves. We hypothesized that, compared to having no history of depressive problems (HDP), having recent-onset depressive problems would be related to an ex-
aggregated cortisol response, whereas having more chronic depressive problems would be related to a blunted cortisol response. We studied the cortisol response to a psychosocial stressor under controlled laboratory conditions in a large sample of adolescents. Adolescents are an interesting group for studying first incidence and progression of depressive problems, because the prevalence of affective disorders starts to rise dramatically during adolescence, from an estimated 1% during preadolescence to rates of up to 25% at the end of adolescence (Kessler et al., 2005). An additional advantage is that the prevalence of potentially confounding somatic disorders is relatively low at this age.

**METHOD**

*Participants*

The present sample was selected from a focus sample of TRAILS (Tracking Adolescents’ Individual Lives Survey). TRAILS is a large prospective population study of Dutch adolescents from the general population, which are followed from age 11 to at least age 21. The TRAILS study conducts measurements every two to three years. Three measurement waves (Ts) have been completed so far, while the fourth is currently being finalized. At T1, 2230 children were enrolled in the study (response rate 76.0), of whom 2149 (96.4%) participated at T2, and 1816 (81.4%) participated at T3. The mean age of the participants was 11.11 years (SD = 0.56) at T1, 13.57 years (SD = 0.53) at T2, and 16.28 years (SD = 0.71) at T3. A detailed description of this cohort is provided elsewhere (Huisman et al., 2008).

The focus sample consists of 715 adolescents who agreed to participate in a series of laboratory tasks additional to the usual assessments at T3 (response rate 96.1%). Adolescents with an increased risk of mental health problems had a greater chance of being selected for this experimental session. Increased risk was defined based upon temperament (high scores on frustration and fearfulness, low scores on effortful control), parental psychopathology (depression, anxiety, addiction, psychoses, or antisocial behavior), and environmental risk (living in a single-parent family), all measured at T1. In total, 66% of the focus sample had at least one risk factor, while the remaining 34% was randomly selected from the TRAILS cohort. Although adolescents with an increased risk of mental health problems were overrepresented, the focus sample still represented the whole range of problems seen in a normal population. This made it possible to use sampling weights in all analyses to reproduce the distribution in the total TRAILS sample. The experimental protocol was approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO). Participants were treated in accordance with the Declaration of Helsinki, and experiments were carried out with adequate understanding and written consent of the participants. More information on the selection procedure can be obtained from the corresponding author.

From the focus sample, 24 adolescents were discarded because they had missing data
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on depressive symptoms at one of the three assessment waves, and 32 because their experimental session was more than 18 months before or 12 months after the assessment of depressive problems. In addition, we excluded girls who used oral contraceptives (OC) (n = 110), because a previous study in this sample showed that OC users displayed no significant cortisol response to the social stress test (Bouma et al., 2009) and habitual smokers (i.e., at least one cigarette a day, n = 76) because smoking attenuates the cortisol response to psychosocial stress (Rohleder and Kirschbaum, 2006). Four participants were excluded because they used corticosteroid medication or antidepressants which influence responses to stress (Holsboer and Barden, 1996). Lastly, another four adolescents were excluded because of cortisol detection failures in at least two of the four cortisol saliva samples, leaving a sample of 466 adolescents (mean age 16.04, SD = 0.53, 59.0% boys).

Procedure
Experimental session
The experimental sessions involved a variety of challenging tasks and conditions which were alternated with short breaks. The Groningen Social Stress Test (GSST) was last of the sessions. In brief, the sessions took place on weekdays, in soundproof rooms with blinded windows at selected locations in the participants’ residence town, lasted about three hours, and started between 0800h and 0930h or between 1230h and 0230h (57%). Adolescents were randomly assigned to morning and afternoon sessions. Data of morning and afternoon sessions were pooled, as cortisol responses to psychosocial stress tasks, when measured as the response from baseline, have been found to be similar in the morning and afternoon in our sample (Bouma et al., 2009), as well as in other relatively large studies (Kudielka et al., 2004). Nevertheless, we cannot rule out confounding of cortisol responses by timing of the stress test (Kudielka et al., 2004), and therefore controlled for GSST start time in the analyses. Participants were asked to refrain from smoking and from using coffee, milk, chocolate, and other sugar-containing foods during the two hours before the session. More details about the experimental session can be found elsewhere (Bouma et al., 2009).

The Groningen Social Stress Test (GSST)
The GSST is a standardized protocol, inspired by the Trier Social Stress Test, for the induction of moderate performance-related social stress (Kirschbaum et al., 1993). The GSST has been found to elicit significant cortisol changes in heart rate and in the HPA system (Bouma et al., 2009, 2011). It entails the elements necessary to induce a significant cortisol response, namely uncontrollability and social-evaluative aspects (Dickerson and Kemeny, 2004). In short, the participants were, on the spot, instructed to prepare and deliver a six-minute speech about themselves and their lives, and to perform a difficult mental arithmetic task in front of a camera, while being videotaped. The videotape was said to be judged by peers on content of speech and use of voice and posture. Participants were debriefed directly after the task.
Chapter 2

Cortisol sampling during the GSST

HPA axis responses towards the GSST were assessed by four salivary samples of cortisol, referred to as C1, C2, C3, and C4. Free cortisol levels in saliva reflect HPA axis activity about 20 minutes earlier, as there is a time window between the production of cortisol by the adrenal glands upon stress and the presence of cortisol in saliva (Aardal-Eriksson et al., 2005). Sample C1 was collected before the GSST, reflecting pre-test HPA axis activity during rest. At that time, participants were filling out rating scales while sitting quietly. C2 was collected immediately after the GSST, reflecting HPA axis activity at the beginning of the GSST, when participants had to deliver a speech. C3 was collected 20 minutes after the end of the GSST, reflecting HPA axis activity at the end of the GSST. Finally, C4 was collected 40 minutes after the end of the GSST, reflecting post-stress HPA axis activity.

Measures

Cortisol

Salivary cortisol samples were collected using Salivettes®, which are small cotton swabs in plastic tubes (Sarstedt, Numbrecht, Germany). After the experimental session, the samples were placed in a refrigerator at 4 °C, and within three to four days brought to the laboratory of the University Medical Center in Groningen, and stored at -20 °C until analysis. All samples were analyzed with the same reagent, and all experimental samples from a participant were assayed in the same batch. Missing experimental samples (C1, n = 9; C2, n = 4; C3, n = 8; C4, n = 7) were due to detection failures in the lab (54%) or insufficient saliva in the tubes (46%). Missing values were imputed on the basis of a combination of the group mean and standard deviation for the missing cortisol sample and the mean of the participant’s cortisol samples that were present. Because we were particularly interested in the HPA axis response to stress, we used the area under the curve with respect to the increase (AUCi) as an outcome measure. The AUCi represents the area under the curve above baseline levels (cortisol sample C1). It was computed according to the method described elsewhere (Pruessner et al., 2003).

History of depressive problems

At T1, T2, and T3, depressive symptoms were assessed by the Affective Problems Scale (APS) of the Youth Self-Report (YSR) (Achenbach et al., 2003), the self-report version of the Child Behavior Checklist (CBCL) (Achenbach, 1991). The APS consists of 13 items (Cronbach’s α T1 = 0.72, T2 = 0.76, T3 = 0.76) covering depressed mood, anhedonia, loss of energy, feelings of worthlessness and guilt, suicidal ideation, sleep problems, and eating problems, which can be rated as 0 = not true, 1 = somewhat or sometimes true, or 2 = very or often true in the past six months. The scale has been found to correspond closely to the symptom criteria for DSM-IV Major Depressive Disorder (van Lang et al., 2005). The presence of depressive problems was defined as having a mean score of at least 0.46 per item (total score of 6 on the APS). With this cut-off, roughly 20% of the adolescents had depressive problems at every assessment wave. The average mean item score of adolescents with depressive
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Problems was 0.62 at T1, 0.65 at T2, and 0.66 at T3. Because we were particularly interested in chronicity of current depressive problems, we excluded adolescents who had experienced depressive problems in the past but not anymore at the time of the social stress test, and those with depressive problems at T1 and T3, but not at T2 (n=155). The remaining adolescents were categorized into four history of depressive problems (HDP) groups: no HDP = no depressive problems at T1, T2, and T3; short HDP = depressive problems at T3; intermediate HDP = depressive problems at T2 and T3; long HDP = depressive problems at T1, T2, and T3. This resulted in a sample of 351 adolescents (59% boys), distributed over the HDP groups as shown in Table 1.

### Table 1. Frequencies of groups according to history of depressive problems

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>n (%)</th>
<th>n girls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HDP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>270 (76.9)</td>
<td>101 (37.4)</td>
</tr>
<tr>
<td>Short HDP</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td>31 (8.8)</td>
<td>19 (61.3)</td>
</tr>
<tr>
<td>Intermediate HDP</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>13 (3.7)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Long HDP</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>37 (10.5)</td>
<td>17 (46.0)</td>
</tr>
</tbody>
</table>

Note: HDP = history of depressive problems, x = presence of depressive problems, - = absence of depressive problems, T = assessment wave, n = number of participants. 115 participants did not fall in any of these HDP categories.

**Statistical analyses**

Adolescents with an increased risk of mental health problems were overrepresented in the study sample. Therefore, sampling weights were used to reproduce the distribution in the total TRAILS sample in all analyses. Sampling weights denote the inverse probability that a subject is included in a sample. The relationship between HDP and the HPA axis response was tested by linear regression analysis, with the AUCi as the dependent variable, using SPSS 18. Considering the nature of our hypothesis, we tested both linear and curvilinear effects by including a quadratic term (HDP2) in the model. In case the quadratic term explained significant additional variance, it was pertained in the final model. GSST start time was included as a covariate (Kudielka et al., 2004). Because cortisol responses to psychosocial stress tasks have consistently shown to be higher in men than in women, gender was included as a covariate as well (Kirschbaum et al., 1992; Bouma et al., 2009). Menstrual phase has been shown to affect the cortisol response to psychosocial stress in adults. We did not control for menstrual phase, however, because a previous study indicated that menstrual cycle phase did not influence cortisol responses significantly in the TRAILS sample (Bouma et al., 2009). In addition to main effects, we tested interactions of HDP and HDP2 with gender. In case of significant interaction effects, analyses were conducted separately in boys and girls to explore the nature of the differences. To exclude the possibility that a state effect of depressive symptom severity accounted for the associations under study, the analysis was repeated including depressive symptoms at T3 as a covariate. In addition, we studied the relationship between HDP and the HPA axis response by means of repeated-measures General Linear Modeling (GLM) to see whether a different type of analysis, less specific to our hypothesis, would yield similar results.
Using the same predictor variables and covariates, we assessed their influence on the cortisol response pattern (samples C1, C2, C3, and C4). When appropriate, Greenhouse-Geisser corrections were applied to the degrees of freedom used to calculate the p-value. In every analysis a p-value < .05 was considered statistically significant.

RESULTS

Descriptive statistics
Characteristics of the study sample can be found in Table 2. Mean cortisol concentrations of the participants were lowest before the start of the GSST (sample C1), whereas they were highest at the start of the GSST (sample C2). Table 3 shows bivariate correlations of the variables under study. HDP was negatively and weakly correlated to the concentrations of cortisol samples during the GSST.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16.03 (0.53)</td>
</tr>
<tr>
<td>GSST start time (hh:mm)</td>
<td>14:00 (02:16)</td>
</tr>
<tr>
<td>C1 (nmol/l)</td>
<td>3.29 (1.79)</td>
</tr>
<tr>
<td>C2 (nmol/l)</td>
<td>4.59 (2.63)</td>
</tr>
<tr>
<td>C3 (nmol/l)</td>
<td>4.50 (2.74)</td>
</tr>
<tr>
<td>C4 (nmol/l)</td>
<td>3.75 (2.02)</td>
</tr>
<tr>
<td>AUCi (nmol/l)</td>
<td>58.06 (119.04)</td>
</tr>
<tr>
<td>DS T1 (0-2)</td>
<td>0.29 (0.24)</td>
</tr>
<tr>
<td>DS T2 (0-2)</td>
<td>0.25 (0.24)</td>
</tr>
<tr>
<td>DS T3 (0-2)</td>
<td>0.25 (0.24)</td>
</tr>
</tbody>
</table>

Note: C1 = mean cortisol concentration before the Groningen Social Stress Test (GSST), C2 = mean cortisol concentration during the GSST, C3 = mean cortisol concentration at the end of the GSST, C4 = mean cortisol concentration 20 minutes after the end of the GSST, AUCi = area under the curve with respect to the increase, DS T1 = mean depressive symptoms score at T1 (mean age 11.1 years), DS T2 = mean depressive symptoms score at T2 (mean age 13.6 years), DS T3 = mean depressive symptoms score at T3 (mean age 16.0 years). Sampling weights were used to represent the distribution in the general population.

Effects of history of depressive problems on the cortisol response to psychosocial stress
Effects of HDP on the AUCi are presented in Table 4. HDP was positively, and HDP2 inversely related to the AUCi. As shown in Figure 1, the AUCi data follow (part of) an inverted U-shaped pattern, with disproportionally high cortisol responses in adolescents with a short HDP and disproportionally low responses in those with a long HDP. Two-way interactions of HDP and HDP2 with gender were non-significant (β=
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Depressive symptoms at T3 were not significantly related to the AUCi ($\beta=0.05$, $p=.86$), and the relationship between HDP2 and the AUCi remained significant after adjustment for depressive symptoms ($\beta=-0.57$, $p=.02$). Figure 2 displays the cortisol response to the GSST, as indicated by the mean cortisol concentration of every sample, for each of the HDP groups. Cortisol concentrations of the four groups did not differ at sampling point C1 ($p=.30$), but diverged at the other three sampling points (C2: $p<.01$, C3: $p<.01$, C4: $p<.01$). Repeated-measures GLM confirmed results of the linear regression analysis. Effects of HDP and HDP2 on the cortisol response were significant (respectively, $F=3.99$, $p=.02$ and $F=5.58$, $p<.01$), and concerned the quadratic contrast of the cortisol response in particular. Details can be obtained from the corresponding author upon request.

Table 3. Bivariate correlations

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>DS T1</th>
<th>DS T2</th>
<th>DS T3</th>
<th>HDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>.49*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>.36*</td>
<td>.85*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>.40*</td>
<td>.71*</td>
<td>.83*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS T1</td>
<td>.03</td>
<td>-.07</td>
<td>-.07</td>
<td>-.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS T2</td>
<td>-.07</td>
<td>-.10*</td>
<td>-.11*</td>
<td>-.09</td>
<td>.56*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS T3</td>
<td>.03</td>
<td>-.03</td>
<td>-.03</td>
<td>-.05</td>
<td>.39*</td>
<td>.54*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDP (0-3)</td>
<td>-.05</td>
<td>-.12*</td>
<td>-.13*</td>
<td>-.12*</td>
<td>.68*</td>
<td>.82*</td>
<td>.80*</td>
<td></td>
</tr>
</tbody>
</table>

Note: C1 = cortisol concentration before the Groningen Social Stress Test (GSST), C2 = cortisol concentration during the GSST, C3 = cortisol concentration at the end of the GSST, C4 = cortisol concentration 20 minutes after the end of the GSST, AUCi = area under the curve with respect to the increase, DS T1 = depressive symptoms score at T1 (mean age 11.1 years), DS T2 = depressive symptoms score at T2 (mean age 13.6 years), DS T3 = depressive symptoms score at T3 (mean age 16.0 years), HDP = history of depressive problems, where ‘0’ indicates no HDP, ‘1’ indicates a short HDP, ‘2’ indicates an intermediate HDP, and ‘3’ indicates a long HDP. Sampling weights were used to represent the distribution in the general population.

* $p <0.05$. 

0.55, $p=.13$ and $\beta=-0.54$, $p=.13$, respectively).
Figure 1. Cortisol response to the GSST, according to history of depressive problems.
Error bars are standard errors of the mean. HDP indicates history of depressive problems; C1, sample collected before the GSST, reflecting pre-test HPA axis activity during rest; C2, sample collected immediately after the GSST, reflecting HPA axis activity at the beginning of the GSST; C3, sample collected 20 minutes after the end of the GSST, reflecting HPA axis activity at the end of the GSST; and C4, sample collected 40 minutes after the end of the GSST, reflecting post-stress activity of the HPA axis.

Table 4. Linear regression model, AUCi of the cortisol response to psychosocial stress

<table>
<thead>
<tr>
<th>Variable</th>
<th>R2 adjusted</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of depressive problems</td>
<td>2.2%</td>
<td>0.47</td>
<td>.04</td>
</tr>
<tr>
<td>History of depressive problems squared</td>
<td></td>
<td>-0.58</td>
<td>.01</td>
</tr>
<tr>
<td>Gender (girls=0, boys=1)</td>
<td>0.07</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>GSST start time</td>
<td>0.06</td>
<td>.27</td>
<td></td>
</tr>
</tbody>
</table>

Note: AUCi = area under the curve with respect to the increase. Sampling weights were used to represent the distribution in the general population. Significance of the model p = .02.
DISCUSSION

In the present study, we examined the relationship between chronicity of depressive problems and the HPA axis response to psychosocial stress in adolescents. As hypothesized, we found that recent-onset depressive problems were related to an increased cortisol response, whereas chronic depressive problems were related to a blunted cortisol response.

To the best of our knowledge, no previous studies have examined whether chronicity of depression can explain part of the variance found in cortisol responses to stress. One study examined the cortisol response to psychosocial stress in healthy and depressed adolescents (Rao et al., 2008). In this study (n = 55), being depressed was related to a more pronounced cortisol response. Although some adolescents had been depressed for quite a long time, mostly adolescents with a first depressive episode were included (U. Rao, personal communication). The cortisol response to the social
stress task of our recent-onset group was more pronounced as well. A study in depressed adults examined the relationship between previous depressive episodes and HPA axis dysregulation by means of the combined dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test (Rybakowski and Twardowska, 1999). Compared to patients with a first depressive episode, patients with a recurrent depressive episode displayed an increased cortisol response to DEX/CRH, indicating an increased negative feedback to the HPA axis. The study did not discriminate between the number of previous episodes, nor mentioned the length of the history of depression. Moreover, pharmacological challenges might not be directly comparable to psychosocial stress challenges. Nonetheless, these results suggest that HPA axis function can change due to a longer history of depression.

Although no prior studies examined the relationship between HPA axis responses to stress and chronicity of depression, many have investigated the association between stressful life events and the onset of first and recurrent depression (Kendler et al., 2000; Ormel et al., 2001; Morris et al., 2010). This association decreases with increasing number of prior depressive episodes, a phenomenon often referred to as kindling (Post, 1992). Among several mechanisms which have been postulated to underlie the kindling effect, the stress sensitization model has received most evidential support (Monroe and Harkness, 2005; Morris et al., 2010; Stroud et al., 2011). This model assumes that stressors become increasingly capable of triggering depressive symptoms. Hence, the likelihood of developing a depressive episode increases with subsequent episodes, as a person becomes more sensitized to stress. Because minor stressors gain potential, the association between depression and major stressful life events becomes weaker with subsequent episodes (Morris et al., 2010). Our findings would complement the stress sensitization hypothesis if one assumes that low cortisol responses to psychosocial stress indicate ineffective coping, which seems plausible. Cortisol is released to adapt to stress-induced demands, e.g., by increasing energy availability. Theoretically, low cortisol responses to psychosocial stress could result in depressive symptoms such as low energy supply and fatigue (Segal et al., 2005), which in turn may promote other depressive symptoms. Empirical support comes from multiple studies which have found an association between low cortisol responses to psychosocial stress and high post-stress perceived arousal and unpleasantness (Reuter, 2002; Schlotz et al., 2008; Oldehinkel et al., 2010). Longitudinal studies addressing changes in the HPA axis response with progression and remission of depressive symptoms are necessary to provide further clarification.

So far, it has not been clarified by what biological mechanism a longer duration or prior episodes of depression can influence HPA axis responses to subsequent stressors, but several studies provide clues for possible explanations. Individuals with persistent or recurrent depression are characterized by high levels of neuroticism and poor coping skills (Ormel et al., 2004). They are more likely to experience daily hassles, and report more stressful life events (van Eck et al., 1996). Stressful life events and chronic stressors trigger the excretion of excessive amounts of glucocorti-
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coids. Evidence suggests that the experience of chronic or repeated stress can lead to a hypo-reactive HPA axis (Miller et al., 2007), for instance, by an increased sensitivity to the negative feedback signal of glucocorticoids at the level of the pituitary (Fries et al., 2005). In addition, excessive amounts of glucocorticoids can cause hippocampal damage (Sapolsky, 2000), resulting in less inhibitory control over hypothalamic CRH production, leading to chronically high levels of glucocorticoids and impaired reactivity to stress (Jacobson and Sapolsky, 1991). Interestingly, reduced hippocampal size has been found in depressed patients, compared to non-depressed individuals, notably in those with multiple episodes and long-lasting depression (Lorenzetti et al., 2009). Reduced hippocampal size has also been found to be predicted by early life adversities, and to be a partial mediator of the association between early life adversities and depression later in life (Rao et al., 2010). This suggests that small hippocampal size can be both a consequence of stress (i.e., glucocorticoids) and a risk factor for stress-related disorders. Similarly, HPA axis functioning may be altered by stress via several mechanisms, among which hippocampal damage, and these alterations may increase risk for future stress-related disorders.

Our findings should be interpreted in the light of several limitations. First, the YSR Affective Problems Scale was not specifically developed to assess depressive problems according to DSM-IV criteria. Nevertheless, it was found to have high diagnostic accuracy, with a score between 5 and 9 best predicting clinical depression (Aebi et al., 2009), so we are fairly confident that it is an adequate measure. The use of this dimensional depression scale may also explain the absence of a clear increase in depressive symptoms with age in our sample; studies reporting such an age effect have mainly used clinical diagnoses (Kessler et al., 2005), while evidence for increases at symptom level is less clear (e.g., Canals et al., 2002; Meadows et al., 2006). A second limitation is that we had information about depressive problems in the six months prior to the three measurement waves but not about the residual time between the measurements, which may have decreased the reliability of our measure and hence deflated the effect sizes. Third, although the experimental session was preferably planned close to the date at which the depressive problems were assessed, this was not always possible because of logistical reasons. A fourth limitation is the exclusion of smokers and oral contraceptive users, which restricts the generalizability of our findings to non-smokers and non-oral contraceptive users. We chose to do so nonetheless, because smoking and oral contraceptives use are known to interfere with cortisol stress responses and might contaminate the associations under study. Fifth, although the overall sample size was quite large for this type of study, the history of depressive problems groups had limited sample sizes. A final limitation is that, due to the nature of our design, we cannot rule out the possibility that age at onset of depressive problems influenced the cortisol response.

The results of this study indicate that recent-onset depressive problems predict increased HPA axis responses, whereas depressive problems that started a longer time ago predict decreased HPA axis responses to psychosocial stress. The current consen-
sus is that depression is a stress-related disorder and that HPA axis functioning plays a part in the etiology of depression (Holsboer and Ising, 2010). Adhering to this view, this study shows that depression is not a static phenomenon, but may take different forms during its course. Consequently, depression interventions may also be differentially effective in individuals with a recent compared to a longstanding depression. Future research should examine why the HPA axis becomes underresponsive to psychosocial stress with increasing chronicity of depression, and whether this change in responsiveness is key to an increased risk to develop future episodes of depression.

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