Disturbances in Morning Cortisol Secretion in Association with Maternal Postnatal Depression Predict Subsequent Depressive Symptomatology in Adolescents

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Background: We have previously reported higher and more variable salivary morning cortisol in 13-year-old adolescents whose mothers were depressed in the postnatal period, compared with control group adolescents whose mothers did not develop postnatal depression (PND). This observation suggested a biological mechanism by which intrafamilial risk for depressive disorder may be transmitted. In the current article, we examined whether the cortisol disturbances observed at 13 years could predict depressive symptomatology in adolescents at 16 years of age.

Methods: We measured self-reported depressive symptoms in 16-year-old adolescents who had ($n = 48$) or had not ($n = 39$) been exposed to postnatal maternal depression and examined their prediction by morning and evening cortisol indices obtained via 10 days of salivary collections at 13 years.

Results: Elevated morning cortisol secretion at 13 years, and particularly the maximum level recorded over 10 days of collection, predicted elevated depressive symptoms at 16 years over and above 13-year depressive symptom levels and other possible confounding factors. Morning cortisol secretion mediated an association between maternal PND and symptomatology in 16-year-old offspring.

Conclusions: Alterations in steroid secretion observed in association with maternal PND may provide a mechanism by which risk for depression is transmitted from mother to offspring.

Altered functioning of the hypothalamic-pituitary-adrenal (HPA) axis has been associated with the expression of several psychological disorders, including depressive disorder (Gold et al. 2002), posttraumatic stress disorder (PTSD) (Yehuda 2002), and conduct problems (Pajer et al. 2001; van Goozen et al. 1998). More recently, researchers have proposed that certain disturbances in the HPA-axis may precede the onset of psychopathology and reflect vulnerability resulting from adverse early experiences (Goodyer et al. 2000a; Yehuda et al. 2001). The role of early experience in determining adult functioning of the HPA-axis and associated stress responding is well established in the animal literature; early adversity has generally been found to increase the basal secretion of glucocorticoids in adult life or the reactivity of the HPA axis to stress (Kaufman et al. 2000). If human development is similarly affected, this may represent a mechanism by which early experiences influence subsequent risk for psychopathology.

We have previously examined salivary cortisol in a longitudinally studied sample presumed to be at risk for the development of depressive disorder due to the occurrence of maternal depression in the postpartum period (Halligan et al. 2004). Maternal postnatal depression (PND) is associated with alterations in the provision of early care, most prominently a reduced sensitivity and responsiveness to infant cues. We observed that 13-year-old adolescents whose mothers were depressed in the postnatal period showed significant disturbances in morning cortisol secretion; specifically, over 10 days of salivary collections, average 8:00 AM cortisol levels were higher, more variable, and showed higher maximum levels in adolescents whose mothers did versus did not have PND (Halligan et al. 2004). This observation of an association between morning salivary cortisol and depression risk status resonates with previous work, which has found that altered morning cortisol secretion may precede and predict the onset of depression in at-risk groups. Thus, Goodyer et al. (2000b) prospectively studied adolescents at high risk for depression, where risk was defined by a combination of psychosocial adversities, high emotionality within the adolescent, and parental psychopathology. The occurrence of one or more very high (>80th centile) morning cortisol values obtained from 4 days of repeated collections was found to significantly predict the onset of depressive disorder over the subsequent 12 months in this high-risk sample. Similarly, Harris et al. (2000) reported that higher mean morning cortisol predicted the subsequent onset of depression in a sample of adult women with psychosocial vulnerabilities to depressive disorder. The presence of similarly disturbed morning cortisol secretion in our sample of 13-year-old adolescents exposed to maternal PND is significant, as it suggests a possible mechanism whereby disturbances in the early maternal environment contribute to risk for depressive disorder in offspring via alterations in the functioning of the HPA-axis.

In the current article, we report a follow-up at 16 years-of-age of the above-described sample, comprising longitudinally studied offspring of mothers who were depressed in the postnatal period and a control group whose mothers did not have PND. Our aims were twofold. First, we examined whether morning cortisol secretion at 13 years could predict depressive symptomatology in adolescents 3 years later, over and above 13-year symptoms and other potential confounding factors. Second, we

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examined whether cortisol disturbances would mediate an association between the presence of maternal depression and depressive symptomatology in 16-year-old offspring.

Methods and Materials

Participants provided written informed consent prior to taking part in this Cambridgeshire Local Ethics Committee-approved study.

Participants

Participants were part of a prospective longitudinal study of the development of children of postnatally depressed and well women (Murray 1992). The sample was originally recruited at 2 months postpartum, with further assessments when the child was 18 months, 5 years, 8 years, 13 years, and 16 years old. Initial recruitment was through screening a community sample of primiparous mothers of healthy, full-term infants for PND, by administering the Edinburgh Postnatal Depression Scale (EPDS) (Cox *et al.* 1987) at 6 weeks postpartum. Women scoring over 12 on the EPDS were interviewed; 61 women who met research diagnostic criteria (Spitzer *et al.* 1978) for depressive disorder were identified, 58 of whom were recruited for the study. Forty-two nondepressed mothers were also recruited via random selection from low scorers on the EPDS from the same postnatal population.

Fifty-two (89.7%) PND group and 40 (95.3%) comparison group adolescents were retained at 16 years. Of these, four adolescents in the PND group and one in the control group had not completed cortisol collections at 13 years due to refusal, medical ineligibility (diabetes), and scheduling problems. Thus, the final sample consisted of 48 PND group and 39 comparison families.

16-Year Measures

Adolescent Mental State.[1] Participants completed the short form Mood and Feelings Questionnaire (MFQ), a validated self-report measure of current depressive symptoms. Consistent with previously reported scale properties, scores showed a positively skewed distribution that was significantly nonnormal (Kolmogorov-Smirnov $Z = 1.77$, $p = .004$) and included several valid scores that were statistical outliers (greater than four standard deviations outside the mean). Preliminary analyses indicated violations of the assumptions for linear regression and an undue influence of extreme values resulting in the overestimation of effects. We, therefore, transformed scores into a dichotomous variable for analytic purposes; the cutoff point was set at the 75th percentile (a score of 7 or greater). Clinical interview indicated only five actual cases of current depressive disorder at 16 years; therefore, the 75th percentile cutoff point defined, for analytic purposes, a subgroup of high-scoring adolescents who reported significant depressive symptoms without necessarily meeting clinical criteria for major depression.[2]

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[1] Diagnostic interviews were also completed following the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman *et al.* 1997). However, the small number of new onsets of depressive disorder between 13 and 16 years ($n = 12$) precluded analyses based on diagnostic outcomes.

[2] All subsequently reported associations between morning cortisol indices and dichotomized symptom scores are also robust across higher and lower cutoff points. However, reported group differences in the incidence of symptomatic adolescents in relation to maternal PND are not significant using higher cutoffs (power less than .50), although the relative proportions of cases in each group are not substantially changed.

For brevity, we refer to high versus nonhigh scorers on the MFQ as "symptomatic" versus "nonsymptomatic." Prior prospective research in this age range has shown higher scores on the MFQ to be highly predictive of subsequent onset of clinical disorders over the subsequent 12 months (Goodyer *et al.* 2000a, 2000b).

Life Events. Adolescents were administered the Life Events Schedule (LES) (Goodyer *et al.* 2000b), a valid and reliable interview assessment of the occurrence of a range of undesirable life events and difficulties.

Family Environment. Adolescents completed the general functioning subscale of the Family Assessment Device (FAD) (Epstein *et al.* 1983; Miller *et al.* 1985), a self-report measure of emotional relationships and family functioning that has excellent reliability and validity. Higher scores on this measure indicate poorer family functioning.

Maternal Marital Conflict. As a measure of parental conflict, mothers of study adolescents completed 10-point rating scales on perceived and felt criticism in their marital relationship or with their ex-partner (Hooley and Teasdale 1989). Mothers also completed the Dyadic Adjustment Scale (Spanier 1979), but this proved problematic for those who were separated from their partner as items did not apply or had a different meaning. Thus, we used the marital criticism ratings to index marital conflict; criticism scores correlated $r = -.56$ with satisfaction scores on the Dyadic Adjustment Scales.

Maternal Depression. Mothers were interviewed using the Structured Clinical Interview for DSM-IV (Spitzer *et al.* 1995) at 16 years and using comparable interview measures at each prior stage of this longitudinal research study. The total number of months that mothers were depressed between the 13-year and 16-year assessments was used in the current study.

13-Year Measures

Assessments completed at 13 years were used in the current study, as follows.

Mental State. Participants completed the MFQ, a measure of their depressive symptoms, as described above.

Cortisol. Adolescents collected saliva samples at 8:00 AM and 8:00 PM for 10 consecutive school days, following instructions supplied for home completion. We measured cortisol using enzyme-linked immunosorbent assay (ELISA) on 20 μL samples of saliva without extraction (antibody Cambio, Cambridge, United Kingdom). Intra-assay variation was 4.1% and interassay variation was 7.6%. For each individual, we derived mean cortisol, maximum cortisol, and variability over the 10-day sampling period for morning and evening saliva collections. We used the coefficient of variation [(variance/mean)/n] to index variability to control for the fact that variance increased with mean levels. Arcsine transformation of the resulting scores created an unbounded variable suitable for statistical tests. Height, weight, and pubertal development—Tanner stage being assessed via self-report based on standard line drawings (Netherton *et al.* 2004; Tanner 1962)—were obtained at the time of salivary cortisol assessments at 13 years-of-age as important potential covariates.

Approach to Analyses

Our analytic approach primarily employed binary logistic regression to examine the prediction of 16-year adolescent symptomatic status. A preliminary set of analyses examined the prediction of 16-year depression (symptomatic versus nonsymptomatic) status by 13-year cortisol indices alone. We subsequently examined a number of factors that represented possible

Table 1. Sample Characteristics Reported by the Presence or Absence of Maternal Postnatal Depression

	Control $n = 39$	PND $n = 48$	
	M (SD)	M (SD)	Statistics
16-Year Characteristics			
Proportion of Boys (%)	52.1%	48.7%	$\chi^2 (1) = .10$
Social Class I, II, and III Non manual (%)	66.7%	60.4%	$\chi^2 (1) = .36$
Age at Assessment (Months)	192.7 (1.8)	193.0 (1.9)	$t(85) = -.76$
12-Month Life Events (LES; Median, Range)[a]	1.0 (0–3)	.5 (0–3)	$Z (n = 87) = -.57$
Family Discord (FAD General Functioning)	20.6 (5.2)	22.9 (6.3)	$t(85) = -1.82$[b]
Maternal Marital Discord (0–10)[a]	3.62 (2.26)	4.68 (2.20)	$t(85) = -2.17$[c]
Months Maternal Depression from 13–16 Years[a]	1.29 (4.56)	3.75 (6.12)	$Z (n = 87) = -3.04$[d]
13-Year Characteristics			
13-year Body Mass Index	20.3 (3.6)	21.3 (3.7)	$t(85) = -1.32$
13-year Tanner Stage (Median, Range)[a]	3 (1–5)	3 (2–5)	$Z (n = 87) = -.57$

Descriptive statistics are means and standard deviations, unless otherwise specified.
PND, postnatal depression; FAD, Family Assessment Device; LES, Life Events Schedule.
[a]Mann-Whitney *U* test used for non-parametric data.
[b]$p < .10$.
[c]$p < .05$.
[d]$p < .01$.

confounds of, or moderating influences on, observed cortisol-symptom associations. Analyses were organized on the basis of theoretical considerations. Thus, we first considered several potential confounding factors in the association between 13-year cortisol and 16-year depressive symptoms, namely 13-year pubertal development, body mass index (BMI), depressive symptom levels, and adolescent gender. We next examined possible environmental moderators of cortisol-symptom associations that occurred between 13- and 16-year assessments: the occurrence of negative life events, maternal marital partner conflict, and disturbances in the family environment. Third, we investigated whether 13-year morning cortisol disturbances mediated an association between maternal PND and 16-year adolescent symptomatology and whether there was an impact of intervening maternal depression on this association. Finally, we simultaneously examined previously identified significant factors in the prediction of 16-year symptoms in a single regression model. In addition to being theoretically driven, this approach to analyses allowed us to examine multiple relevant sets of variables while being mindful of the constraints of our modest sample size.

Results

The final sample comprised 44 female and 43 male adolescents, with a mean age of 16 years 1 month (range 15 years 8 months to 17 years). Sample characteristics are reported by maternal group in Table 1. The PND and no PND groups were similar in terms of age in months, gender distribution, and socioeconomic status. In addition, at the time of the 13-year cortisol collections, the groups were comparable in terms of BMI and degree of pubertal development (Tanner stage), as previously reported (Halligan *et al.* 2004).

13-year Cortisol and Depressive Symptoms at 16 Years

We first examined whether 13-year morning cortisol predicted depressive symptomatology at 16 years. A preliminary set of logistic regressions indicated that 13-year morning cortisol mean [Exp(β) = 1.60, 95% confidence interval (CI) = 1.05–2.43; Wald = 4.86, *df* = 1, *p* = .028], maximum [Exp(β) = 1.53, 95% CI = 1.16–2.01; Wald = 9.25, *df* = 1, *p* = .002], and variability [Exp(β) = 5.39, 95% CI = 1.06–27.5; Wald = 4.11, *df* = 1, *p* = .043] each significantly predicted 16-year depression status (MFQ

dichotomous variable) when examined independently; adolescents who were symptomatic at 16 years had morning cortisol secretion at 13 years that showed a higher mean level, higher maximum value, and higher variability over 10 days of collection than that of nonsymptomatic adolescents (Table 2). In contrast, when repeated logistic regressions were used to examine whether evening cortisol indices (mean, maximum, variability) predicted 16-year symptomatic status, none of these variables proved to be significant (all *p*'s > .35; means reported by status in Table 2).

We further examined whether the above relationship between 13-year morning cortisol and 16-year depression status still held when controlling for potential confounding factors, namely, adolescent gender and BMI, Tanner stage, and depressive symptom levels at 13 years. Binary logistic regression was carried out with 16-year depression status (symptomatic versus nonsymptomatic) as the dependent variable. Predictors were entered into the regression equation in two steps: 13-year MFQ scores, BMI and Tanner Stage, and gender were controlled for in the first step, and 8:00 AM morning cortisol indices were then entered in the second step. Due to the significant intercorrelations between the three morning cortisol measures (mean,

Table 2. 13-Year Morning and Evening Cortisol Secretion in Relation to the Presence or Absence of Depressive Symptomatology at 16 Years

	16-Year Depression	
	Nonsymptomatic $n = 61$	Symptomatic $n = 25$
	M (SD)	M (SD)
13-Year 8:00 AM Cortisol		
Mean	2.78 (1.13)	3.40 (1.17)
Maximum	4.69 (1.71)	6.31 (2.35)
Variability[a]	1.34 (1.10)	2.64 (2.12)
13-Year 8:00 PM Cortisol		
Mean	.33 (.29)	.40 (.25)
Maximum	.96 (1.48)	.96 (.75)
Variability[a]	.19 (.63)	.11 (.20)

[a]Variance reported for clarity; analyses conducted using transformed coefficient of variation.

maximum, and variability), a forward conditional enter procedure was used for the second step. The results indicated that the initial model was highly significant ($\chi^2 = 21.0$, $df = 4$, $p < .0001$). However, maximum 13-year 8:00 AM cortisol also entered the model in the second step and significantly improved the prediction of 16-year depression ($\chi^2 = 4.56$, $df = 1$, $p = .033$). In the final model, maximum 13-year 8:00 AM cortisol [Exp(β) = 1.37, 95% CI = 1.01–1.85; Wald = 4.18, $df = 1$, $p = .041$] and 13-year MFQ scores [Exp(β) = 1.19, 95% CI = 1.04–1.36; Wald = 6.49, $df = 1$, $p = .01$] were independently significant predictors of 16-year depressive symptomatology, but gender, BMI, and Tanner Stage were not (all p's > .13).

Effects of Intervening Environmental Stress

We investigated whether likely environmental contributors to adolescent depressive symptoms influenced their association with 13-year morning cortisol disturbances, namely, maternal marital discord, disturbed family functioning, and intervening negative life events. Each of these variables represents both a possible confound and a potential moderator of the association between 13-year cortisol and 16-year symptoms, the latter effect being a likely activation of biological vulnerability in the presence of environmental stress.[3] Thus, logistic regression was used, in each case, to examine the prediction of 16-year symptomatology by 8:00 AM maximum cortisol together with the respective environmental contributor and the interaction between these two. The results indicated that neither intervening life events nor reported marital conflict (mutual criticism score) were significant predictors of adolescent symptomatology at 16 years, either alone or in interaction with 8:00 AM maximum cortisol (all p's > .163). Disturbed family functioning (FAD, general functioning subscale) was positively associated with symptomatic status at 16 years [Exp(β) = 1.19, 95% CI = 1.08–1.32; Wald = 11.04, $df = 1$, $p = .001$]. However, 13-year 8:00 AM maximum cortisol was also retained as a significant predictor [Exp(β) = 1.57, 95% CI = 1.17–2.10; Wald = 9.17, $df = 1$, $p = .002$], and the addition of the interaction term in a second step did not significantly improve the fit of the model ($\chi^2 = .02$, $df = 1$, ns).

Effects of Maternal Depression

We have previously reported that adolescents in the current sample whose mothers were depressed in the postnatal period showed higher mean, higher maximum, and more variable morning cortisol at 13 years than control group adolescents, controlling for multiple potential confounding factors (Halligan *et al.* 2004). We, therefore, examined whether 13-year cortisol disturbances would mediate an association between maternal PND and 16-year depressive symptomatology. Mediation was tested according to the recommendations of Baron and Kenny (1986). Thus, we have already demonstrated that 13-year 8:00 AM cortisol indices are significantly associated with both the presence of maternal PND (Halligan *et al.* 2004) and with depressive symptomatology at 16 years. It remained to confirm that maternal PND is a significant predictor of 16-year offspring symptomatology and that this significant association is accounted for by disturbances in morning cortisol secretion at 13 years.

With respect to the association between maternal PND and 16-year offspring depressive symptomatology, logistic regression confirmed that maternal PND was a significant predictor of

adolescent symptomatic versus nonsymptomatic status at 16-years [Exp(β) = 2.74, 95% CI = 1.04–7.49; Wald = 3.87, $df = 1$, $p = .049$]; 37.5% of PND group versus 17.9% of control group adolescents were symptomatic according to MFQ scores. To examine whether this association was mediated by observed cortisol disturbances, we next repeated this logistic regression analysis including 13-year maximum morning cortisol in a second step. When maximum 8:00 AM cortisol was added to the regression model in the second step [Exp(β) = 1.47, 95% CI = 1.11–1.95; Wald = 7.23, $df = 1$, $p = .007$], the maternal PND effect was reduced to nonsignificant [Exp(β) = 1.85, 95% CI = .64–5.41; Wald = 1.27, $df = 1$, $p = .26$], consistent with mediation. In a final analysis, we confirmed that the indirect pathway from maternal PND to 16-year symptomatology in offspring via disturbed morning cortisol secretion was itself significant (Sobel test statistic = 2.11, $p = .03$).

Mothers who were depressed in the postnatal period were also more likely than mothers who were not postnatally depressed to have subsequent episodes of depression.[4] Significantly, mothers in the PND group spent more months depressed than control group mothers in the interval between our 13- and 16-year assessments (Table 1); 37.5% ($n = 18$) of PND group mothers versus 12.8% ($n = 5$) of those in the control group reported one or more episodes of depression during this time. We, therefore, examined whether the presence of intervening maternal depression would either account for, or moderate, the association between 13-year cortisol secretion and 16-year depressive symptomatology by acting as an environmental stressor that is particularly present in the PND group. This was not the case. Logistic regression indicated that the total number of months of maternal depression occurring between 13 and 16 years was not a significant predictor of 16-year adolescent symptomatology [Exp(β) = 1.07, 95% CI = .98–1.16; Wald = 2.32, $df = 1$, ns] when examined together with 13-year 8:00 AM maximum cortisol [Exp(β) = 1.56, 95% CI = 1.18–2.07; Wald = 9.77, $df = 1$, $p = .002$], and the addition of the interaction between these two variables did not significantly improve the fit of the regression model ($\chi^2 = .16$, $df = 1$, ns).

Overall Regression Model

The above analyses suggested that cortisol disturbances may be one factor that mediates between the presence of maternal depression and the development of depressive symptoms in offspring. However, we also wished to ensure that 13-year morning cortisol was a significant predictor of 16-year symptoms independent of maternal PND, once other possible confounding factors were controlled. We, therefore, conducted a final regression analysis, simultaneously examining maternal PND status, 8:00 AM maximum cortisol, and other significant factors (i.e., 13-year MFQ scores and 16-year FAD scores) in the prediction of 16-year symptomatology. The results indicated that the model was highly significant ($\chi^2 = 33.3$, $df = 4$, $p < .0005$); 13-year maximum 8:00 AM cortisol [Exp(β) = 1.41, 95% CI = 1.04–1.92; Wald = 4.75, $df = 1$, $p = .029$], 13-year MFQ scores [Exp(β) = 1.20, 95% CI = 1.04–1.38; Wald = 6.12, $df = 1$, $p = .013$], and 16-year general functioning FAD scores [Exp(β) = 1.17, 95% CI = 1.05–1.30; Wald = 7.80, $df = 1$, $p = .005$] were all independently significantly associated with 16-year depressive symptom-

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[3]Note that neither marital discord nor the occurrence of life events explained the association that we observed between maternal PND and adolescent morning cortisol secretion at 13 years (Halligan *et al.* 2004).

[4]This was also the case at 13 years, and total study months of maternal depression were taken into account in our previous analyses of associations between maternal PND and offspring cortisol secretion (Halligan *et al.* 2004).

atology, but maternal PND status was not [Exp(β) = 1.36, 95% CI = .39–4.66; Wald = 0.23, *df* = 1, ns].

Discussion

We have previously reported that 13-year-old adolescents whose mothers had PND showed higher and more variable morning cortisol secretion than adolescents whose mothers were not depressed postnatally (Halligan *et al.* 2004). In the current article, we extended these findings by demonstrating that these disturbances in 13-year morning cortisol status 1) predicted depressive symptom status at 16 years and 2) mediated an association between maternal PND and 16-year depressive symptoms in adolescents. A significant positive association between higher morning cortisol at 13 years and depressive symptoms at 16 years was apparent when 13-year depressive symptoms, disturbances in the intervening environment, and other potential confounding factors were taken into account.

The association between disturbances in morning cortisol secretion and subsequent depressive symptomatology in adolescents is consistent with prior reports. Goodyer *et al.* (2000b) studied a sample of high-risk adolescents and found that the occurrence of one or more very high morning cortisol values over several days of salivary collection predicted the onset of depressive disorders in the subsequent 12 months. Similar findings have also been reported for a prospective study of a high-risk sample of women over a 1-year follow-up (Harris *et al.* 2000). The current study, which focused on the emergence of depressive symptoms rather than overt depressive disorder, extends these observations; although we found both mean morning cortisol and cortisol variability over 10 days of salivary collection to predict depressive symptomatology 3 years later, the maximum recorded cortisol value was the most significant predictor of 16-year symptomatology. Indeed, maximum 8:00 AM cortisol predicted 16-year depressive symptoms over and above 13-year symptomatology, consistent with prior reports that endocrine functioning may index risk for depression independent of concurrent mood.

The occurrence of extreme morning cortisol values has physiological significance. Glucocorticoid receptors are usually only partially occupied, with maximum occupation occurring during the morning peak in cortisol secretion (Reul and de Kloet 1985). Consequently, the occurrence of very high morning cortisol concentrations may result in the activation of a distinct population of receptors. This possibility is supported by research indicating that stress-induced cortisol elevations in the morning, but not the afternoon, result in impairments in memory function (Het *et al.* 2005; Maheu *et al.* 2005). The current observations are also broadly consistent with a body of research which suggests that aspects of morning cortisol secretion may be linked to stable personality or environmental characteristics; in particular, high morning cortisol has been linked to traits including neuroticism and negative affectivity (Polk *et al.* 2005; Portella *et al.* 2005; Pruessner *et al.* 2003) and to the presence of perceived chronic environmental stress (Ockenfels *et al.* 1995; Pruessner *et al.* 2003; Schulz *et al.* 1998; Steptoe *et al.* 2005), factors which also predispose to depression. However, findings have been mixed, with other researchers linking increases in evening cortisol secretion or a flattening of the diurnal rhythm with the presence of major depressive disorder (Dahl *et al.* 1991; Gold *et al.* 1988a, 1988b). Perturbations associated with the concurrent expression of disorder may need to be distinguished from those that serve a predictive function.

We were also able to demonstrate a significant pathway from maternal postnatal depression to 16-year depressive symptoms in adolescents via 13-year morning cortisol disturbance. This observation is consistent with a body of animal research that suggests that the quality of the early environment, particularly as defined by maternal characteristics, may contribute to the intergenerational transmission of stress reactivity via sustained alterations in the functioning of the HPA-axis. In rats, epigenetic programming of the glucocorticoid receptor via maternal licking and grooming behaviors in the first week of life has been demonstrated (Weaver *et al.* 2004). Specifically, Weaver *et al.* (2004) observed that rats exposed to low levels of licking and grooming showed increased methylation of the promoter region of the glucorticoid receptor (GR) gene in the hippocampus, with a consequent reduction in GR expression. As one of the functions of the glucocorticoid receptor is providing negative feedback that switches off the HPA axis response to stress, this reduction in GR contributes to enhanced stress responding in low-licking and low-grooming pups. Whether similar mechanisms operate in human development has yet to be established. However, evidence for an association between early life experiences and subsequent HPA-axis functioning is accumulating, with both prenatal and postnatal maternal disturbance reportedly being significant. To our knowledge, the current study is the first to directly link altered cortisol secretion occurring in the context of early environmental disturbance to the subsequent expression of psychopathology, as indexed by high depressive symptoms at 16 years.

Although our research particularly examines cortisol disturbances associated with the presence of maternal postnatal depression, any conclusions as to the origin of the reported association would be premature. Thus, while the above-described animal research would suggest that maternal PND-related disturbances in early care may have impacted on offspring HPA-axis development, there are multiple likely contributors to the effects that we observed. Variation in morning cortisol secretion shows a degree of heritability and, therefore, genetic transmission is indicated (Bartels *et al.* 2003; Kupper *et al.* 2005). The presence of maternal stress or depression in the antenatal period is another possible contributor to both disturbances in cortisol secretion and disorder in the postnatal depression group (O'Connor *et al.* 2002, 2005). Furthermore, mothers who were depressed in the postnatal period also experienced substantially more depression subsequently than mothers who did not develop postnatal depression in the current study. In our previous analyses, such intervening depression did not appear to account for disturbed morning cortisol secretion observed in association with maternal PND (Halligan *et al.* 2004), and concurrent maternal depression also did not account for the association between 13-year cortisol secretion and 16-year symptomatology reported in the current study. However, PND and recurrent depression are heavily confounded in our sample, making them difficult to disentangle. Furthermore, the presence of recurrent maternal depression may have had an unmeasured and chronic environmental influence that explains both cortisol disturbances and 13-year and adolescent depressive symptoms at 16 years in our sample.

The current findings are preliminary. The small sample size meant limited power, which was particularly problematic in our investigation of interactions between aspects of the intervening environment and cortisol disturbances in the prediction of 16-year symptoms. Similarly, the lack of power precluded a more comprehensive examination of other likely moderators of the reported effects, such as gender, other biological vulnerabilities,

or cognitive vulnerability to depression. Although the repeated salivary collections carried out in the current study ensured that reliable indices of cortisol secretion were obtained, the use of only two collections per day is also a limitation. Prior studies have suggested that the peak of cortisol secretion that occurs approximately 30 minutes after awakening may be the most reliable index of adrenocortical activity (Pruessner *et al.* 1997). Morning cortisol was collected without reference to awakening time in the current study and reported levels might not reflect the apex of waking secretion, which has been the focus of recent research. The omission of wake time data also raises the issue of whether depression-related sleep disturbances influenced 13-year cortisol secretion. However, we controlled for 13-year depressive symptoms in examining both maternal PND-related disturbances in cortisol secretion (Halligan *et al.* 2004) and current associations with 16-year symptoms, which should preclude any spurious associations arising as a result of such an effect. The absence of other data of potential relevance to cortisol secretion (e.g., on quality of sleep, food consumption) is a further limitation of the current study.

The origins of the cortisol disturbances discussed in the current study remain to be determined. As discussed above, although our study focused on disturbances in the early postnatal environment, genetic factors and prenatal maternal disorder are also likely to have contributed to the effects that we observed. Furthermore, major depression is etiologically heterogeneous, with different mechanisms likely to operate in different populations. Thus, a tentative analysis of the current data indicated a trend for higher morning cortisol to be specifically associated with depression in adolescents exposed to PND compared with depressed adolescents not so exposed (results not reported). The sample was too small to formally test for an interaction of this kind. However, future work in this area should consider the possibility of such interactions, which could reflect either a genetic vulnerability requiring an environmental trigger or an environmentally mediated biological disturbance that interacts with a genetic vulnerability. Further investigation of the neuroendocrine regulation underlying the observed individual differences in morning cortisol secretion is warranted.

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