Development and Psychopathology, **13** (2001), 721–732
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Printed in the United States of America

Developmental changes in cortisol secretion in normal and at-risk youth

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Abstract
Adolescence is associated with an increase in the rate of certain psychiatric symptoms, and it is typically the developmental period when prodromal features of the major psychiatric disorders emerge. This is especially true of schizophrenia, with the majority of patients showing a marked postpubertal rise in schizotypal signs that predates the onset of clinical symptoms in early adulthood. Cross-sectional studies of youth have revealed a positive correlation between age and saliva cortisol level, suggesting a normative maturational increase in activity of the hypothalamic–pituitary–adrenal (HPA) axis. It has been hypothesized that this increase may trigger the expression of symptoms in vulnerable individuals. The present longitudinal study measured cortisol secretion and its relation with symptom development in samples of youth with schizotypal personality disorder (SPD), other personality disorders, or no Axis II disorder. The findings indicate moderate stability in cortisol levels across a 2-year period, with a longitudinal increase in cortisol levels over time. Cortisol levels at the first and second assessments were correlated with the severity of SPD symptoms at follow-up. The results are consistent with the notion that the HPA axis undergoes a postpubertal maturational process that moderates the expression of psychiatric symptoms.

It is well documented that adolescence is a critical period for the emergence of prodromal signs of certain psychiatric disorders (Orr & Hodgman, 1988; Peterson, Leffert, Graham, & Alwin, 1997; Susman, Dorn, & Chrousos, 1991). This is especially true of the major mental illnesses, such as schizophrenia. In fact, the majority of schizophrenia patients manifest signs of premorbid behavioral disturbance in adolescence (Larsen, McGlashan, Johannessan, & Vibe–Hansen, 1996; Neumann, Grimes, Walker, & Baum, 1995). It appears that, during the teenage years, at least 60% of preschizophrenic youth manifest a gradual rise in adjustment problems (Larsen, McGlashan, & Moe, 1996; Neumann et al., 1995). The heightened risk associated with the pubertal period suggests that neuromaturational processes can trigger the expression of latent vulnerability (Walker, 1994). To date, however, research findings do not have nor provide any strong leads on the biological process(es) that might underlay this developmental phenomenon.

A substantial proportion of preschizophrenic youth show a behavioral syndrome that is comparable to schizotypal personality disorder (SPD) as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; Davidson, Reichenberg, Rabinowitz, Weiser, Kaplan, & Mordehai, 1999; Neumann et al., 1995; Tyrka, Cannon, Haslam, & Mednick, 1995; Walker, Baum, & Diforio, 1998; Wolfradt & Straube, 1998). This behavioral syndrome includes interpersonal deficits and social withdrawal, as well as signs of perceptual and ideational abnormalities. It has been shown that SPD can be reliably diagnosed in preadolescents and adolescents (Grilo, McGlashan, Quinlan, Walker, Greenfeld, & William, 1998; Rawlings & MacFarlane, 1994; Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999). In one recent study of a community sample, 45% of adoles-

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https://doi.org/10.1017/S0954579401003169 Published online by Cambridge University Press

cents (mean age 13.8 years) who met DSM-IV diagnostic criteria for a Cluster A personality disorder (e.g., paranoid, schizoid, and schizotypal personality disorder) were found to meet criteria for an Axis I disorder 8–10 years later (Johnson, Cohen, Skodol, Oldham, Kasen, & Brook, 1999). However, the stability of adolescent Axis II disorders is only moderate, with about half showing a significant decline in signs of personality disorder by late adolescence.

At this point, the eventual rate of schizophrenia among adolescents who meet criteria for any specific Axis II disorder, such as SPD, is not known. However, previous research on short-term outcome with young adult SPD subjects indicates that the prognosis is poor; although some do show improvement, others manifest persistent signs of personality disorder and a subgroup develop Axis I disorders, usually in the schizophrenia spectrum (Bernstein, Cohen, Velez, Schwab–Stone, Siever, & Shinsato, 1993; McGlashan, 1986). McGorry and his colleagues identified an at-risk group of adolescents and young adults using criteria *less* stringent than those required for a DSM-IV diagnosis of SPD; within 12 months almost half met criteria for an Axis I psychotic disorder, primarily schizophrenia or a spectrum disorder (McGorry & Edwards, 1998; Yung & McGorry, 1996; Yung, Phillips, McGorry, Hallgren, McFarlane, Jackson, Francey, Harrigan, Patton, & Jackson, 1998).

Although SPD is linked with a substantial increase in risk for psychotic disorders, many youth with SPD, perhaps more than 50%, will not develop serious psychopathology. At this juncture, the challenge to researchers is to identify factors that are linked with the emergence of more serious psychopathology. Of particular interest are indicators of central nervous system (CNS) function that (a) undergo neuromaturational change and (b) reflect the activity of neural systems that might be linked with symptom expression.

Diathesis–stress models of schizophrenia and other psychiatric disorders have posited an interaction between constitutional vulnerabilities and exposure to stressful events. But, ultimately, exposure to stress will only have negative behavioral consequences if the CNS processes it as such. Findings from several independent lines of investigation have converged to suggest that the hypothalamic–pituitary–adrenal (HPA) axis plays a central role in mediating the effects of stress on behavioral maladjustment and psychiatric illnesses (Stansbury & Gunnar, 1994; Walker & Diforio, 1997). The HPA axis involves three chemical messengers: corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (Friedman, Charney, & Deutch, 1995). In response to stress, cells in the periventricular nucleus of the hypothalamus release CRH. The pituitary contains receptors for CRH, and when these are stimulated the pituitary releases ACTH. ACTH then stimulates the adrenal cortex to release glucocorticoids, including cortisol in primates and corticosterone in rats. Glucocorticoids have effects throughout the body, and they are critical to the physiological changes that constitute the adaptation to stress. It is plausible that the HPA axis is the key neural system mediating the effects of stress on the manifestation of psychiatric symptoms.

Findings from our research on the development of at-risk youth indicate that schizotypal adolescents manifest elevated salivary cortisol when compared to age-matched normals, as well as those with other personality disorders (Weinstein et al., 1999). The diagnostic group difference was most pronounced for the first saliva sample, suggesting that SPD is associated with an elevated cortisol response to the novelty or stress of the assessment. Further, we observed a positive correlation between age and cortisol level, suggesting that adolescent development is linked with a rise in HPA activity. *Cross-sectional* studies of normal children also reveal a gradual rise in salivary cortisol (Kiess, Meidert, Dressendorfer, Scheiver, Kessler, & Konig, 1995; Lupien, King, Meaney, & McEwen, 2001) and urinary cortisol (Kenny, Gancayo, Heald, & Hung, 1966; Kenny, Preeyasombat, & Migeon, 1966) during middle childhood, then a marked increase in adolescence. Further, Kiess et al. (1995) and Kenny, Gancayo, et al. (1966) found that sexual maturation was predictive of heightened HPA activity, indi-

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cating that the increase in cortisol secretion is linked with biological maturation. This suggests the possibility that there is a normative increase in HPA activity during the postpubescent period, and that this increase may serve to trigger symptom expression in vulnerable individuals. Thus, maturational changes in the HPA axis may be one of the factors contributing to the rise in prodromal features during the postpubertal period.

To date, there have been no published reports on *longitudinal* changes in salivary cortisol during adolescence. In order to clarify the nature of developmental changes in HPA function, and their potential role in triggering latent vulnerabilities, prospective research on normal and at-risk youth is needed. In this article, we report the results of a follow-up assessment of the adolescent participants in our study of youth at-risk for psychosis. Four central questions are addressed: (a) Is there temporal stability in levels of cortisol secretion as youth pass through adolescence? (b) Do longitudinal data indicate a rise in cortisol secretion during the adolescent years? (c) Does the developmental trend in cortisol secretion vary as a function of the child's psychiatric status? (d) More specifically, do youth with SPD or other personality disorders show a more pronounced developmental increase?

Methods

Subjects

In 1995, we initiated a study of adolescents with SPD and other personality disorders. A sample of 11- to 18-year-old subjects was recruited from the local community between September 1995 and April 1996. Recruitment of participants was primarily through announcements directed at clinicians and at parents who had concerns about their child's adjustment. Following procedures used in previous studies, the announcement described signs of schizotypal personality disorder in lay terms. (The announcement stated that the child was eligible if her or she was "experiencing problems in at least two of the following areas: social relationships, unusual ideas or behavior, unusual emotional reactions or fears.") A screening interview was administered to parents over the phone, and appropriate subjects were scheduled for assessment. The goal was to obtain a sample of subjects with SPD, as well as samples with other personality disorders and no disorder. The diagnostic measures were the Structured Clinical Interview for DSM III-R Personality Disorders (SCID-II) questionnaire (Spitzer, Williams, Gibbon, & First, 1990a), the SCID-II interview (Spitzer, Williams, Gibbon, & First, 1990b), and the SCID Psychotic Screen (all administered by an advanced graduate student or PhD-level psychologist). The Beck Depression Inventory (BDI) and the Child Behavior Checklist (CBCL—Parent version) were also administered. The CBCL is a standardized behavior problem checklist, which contains 113 items and yields scores on multiple behavior dimensions (Crijnen, Achenbach, & Verhulst, 1997).

The resultant samples were comprised of 20 subjects (12 males) who met DSM-IV diagnostic criteria for SPD, 20 (13 males) who met criteria for one or more other Axis II disorder (other disorder [OD] group), and 26 (17 males) who did not meet criteria for any Axis II disorder (normal control [NC] group). The diagnoses of the OD group were as follows: paranoid, $n = 3$; schizoid, $n = 3$; borderline, $n = 1$; antisocial or conduct disorder, $n = 6$; dependent, $n = 1$; passive–aggressive, $n = 5$; obsessive–compulsive, $n = 4$; not otherwise specified, $n = 2$. As expected, there was a high rate of comorbidity, so the sum of these numbers exceeds the number of OD subjects. Similarly, consistent with evidence of comorbidity in personality disorders in adolescents (Johnson et al., 1999), some of the subjects in the SPD group also met criteria for other Axis II disorders. However, none of the participants met criteria for an Axis I disorder.

Mean ages for the SPD, OD, and NC groups were 14.2 ($SD = 1.2$), 14.7 ($SD = 2.2$), and 13.9 ($SD = 1.6$ years), respectively. Of the 20 SPD subjects, 10 had previous outpatient contact (pediatrician, psychiatrist, or psychologist) because of parental concerns about the child's adjustment. The Vocabulary and Information subtests of the Wechler IQ test (Wechsler, 1991) were administered at the

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initial assessment. The NC group scored slightly higher than the SPD group ($t = 1.70$, $p = .05$), but there were no other significant group differences. Mean scaled scores were 9.97 ($SD = 3.15$), 11.65 ($SD = 3.56$), and 12.08 ($SD = 3.33$) for the SPD, OD, and NC groups, respectively.

Procedures

Saliva sampling. All assessments were scheduled to begin at the same time of day, and subjects were instructed to abstain from caffeinated beverages and all medication the day of the assessment. Saliva samples were obtained in specimen tubes at predetermined points throughout the assessment (one each hour). At least four samples were obtained from each subject. Cortisol (µg/dl) was assayed as described below.

It should be noted that plasma, urinary, and salivary cortisol measures are highly interrelated (Shipley, Alessi, Wade, Haegle, & Helmbold, 1992), suggesting that all are indexing activity of the HPA axis. However, salivary cortisol appears to be a more sensitive measure of stress reactivity than either urinary (Bassett, Marshall, & Spillane, 1987) or plasma cortisol (Rahe, Karson, Howard, Rubin, & Poland, 1990). Also, saliva cortisol shows a higher correlation with ratings of psychiatric symptoms (Rahe et al., 1990). This may indicate that the more invasive nature of obtaining plasma and urine samples results in increased measurement error.

Cortisol assay. Saliva samples were stored at −20°C in a 13-ft^3 S/P brand cryofreezer. In preparation for assay, the samples were rapidly thawed and centrifuged for 10 min to remove coagulated protein and other insoluble material. Cortisol was assayed in duplicate 200-µl aliquots of the clear supernatant using materials and procedures provided by Incstar Corporation (Stillwater, MN). The assay was performed in tubes coated with an antiserum which shows significant cross-reactivity only with prednisone (83%), 11-deoxycortisol (6.4%), cortisone (3.6%), and corticosterone (2.3%). Standards in the range of 1–30 ng/ml consisted of the serum standards provided with the kit materials diluted with 200 µl of phosphate-buffered saline. Protein concentrations were equalized in standards and samples by adding cortisol-free serum to the samples. For the most recent assays conducted by the lab, the mean coefficients of variation between duplicates and between assays were less than 5%. Compared with the serum standards, the mean recovery of cortisol from saliva has been indistinguishable from 100%. Using this method, the range (central 95%) of salivary cortisol concentrations in normal adults has been determined as 1.8–10.1 ng/ml.

1997 follow-up. Follow-up assessments were conducted between February and August of 1997, 1.5–2 years after the first assessment. The assessment included the following measures: (a) the SCID-II questionnaire (Spitzer et al., 1990a), (b) the SCID-II interview (Spitzer et al., 1990b) and the SCID Psychotic Screen, and (c) the CBCL—Parent version). As in the initial assessment, saliva cortisol was measured four times, at hourly intervals.

Of the total sample of 66 subjects, 44 were able to return to our laboratory for the follow-up assessment. The breakdown of followed subjects by initial diagnostic group was 12 SPD, 11 OD, and 21 from the NC group. Information on current status for an additional 19 subjects was obtained in telephone interviews with a parent or the child or both. Of these 19 participants, 5 did not undergo follow-up evaluation in the clinic because they were either hospitalized ($n = 3$) or in a detention facility ($n = 2$) at the time. The other 14 youth resisted scheduling a follow-up visit, despite the encouragement of their parents. Three participants could not be reached by telephone or mail. Comparisons were conducted to determine whether those who did not undergo the second clinical assessment differed from those who returned for the follow-up. Although those who did not return to the clinic tended to show more severe symptoms and behavior problems at the first assessment, the group differences were not statistically significant. Thus, it appears that the sample who underwent both assessments may have been biased in the direction of less severe symptoms.

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As expected (Livesley, 1999), DSM-IV diagnoses changed for a subset of the subjects from the first to the second assessment. Across groups, 32% of the sample changed diagnostic status. From the SPD group, five no longer met criteria for SPD but instead met criteria for another Cluster A personality disorder ($n = 2$) or no personality disorder ($n = 3$). Among the OD subjects, one was diagnosed with SPD and one received no diagnosis. Finally, four of the NC subjects met criteria for a personality disorder on follow-up.

Results

Analyses were conducted to determine whether those who did not participate in the follow-up differed from subjects who did. For each subject, ratings of the SPD symptoms from the SCID were summed.

Comparisons of the followed and nonfollowed subjects revealed no significant differences in the initial scores for SPD symptom ratings or cortisol. When scores from the CBCL were compared, those who did not participate in the follow-up showed higher ratings for social withdrawal, $t\ (68) = 1.69 =$, $p = .05$ (one-tailed), and externalized symptoms, $t\ (68) = 1.73 =$, $p = .05$ (one-tailed), at the initial assessment.

Group differences in cortisol based on follow-up diagnoses

At the initial assessment the SPD group showed elevated mean cortisol levels (Weinstein et al., 1999). Using the diagnostic group classification based on the follow-up interview, group comparisons of mean cortisol levels at the follow-up assessment were conducted. The values for the four samples are presented in Figure 1. The SPD group showed elevated mean cortisol compared to the NC group, $t\ (31) = 1.66$, $p < .05$, but not the OD group, $t\ (19) = 1.55$, $p > .05$. (However, it should be noted that the absence of a significant difference between the SPD and OD group is a consequence of the lower statistical power due to the smaller size of the OD group.) There was no significant difference between the OD and NC groups.

Temporal stability of cortisol

Correlational analyses were conducted to examine temporal stability in levels of cortisol secretion. For each subject, the average cortisol level across the four saliva samples was computed. The correlations between the initial and the follow-up assessment cortisol means were computed. There was a significant correlation between mean cortisol levels for the entire sample ($r = .50$, $p < .05$). When the correlations were computed separately for the diagnostic groups, based on the diagnostic classification of subjects at the first assessment, there was a significant relation for the NC group ($r = .60$, $p = .002$) and the OD group ($r = .56$, $p = .03$), but the coefficient did not reach significance for the SPD group ($r = .33$, $p = .15$). These findings indicate that there is at least moderate stability across time in levels of cortisol secretion in the laboratory setting. Although the coefficient for the SPD group was not statistically significant, comparisons revealed no significant group differences in the magnitude of the correlation coefficients.

Developmental changes

As described in a previous report, there was a significant positive correlation between age and mean cortisol as measured at the first assessment ($r = .48$, $p < .01$; Weinstein et al., 1999). Analyses of data from the entire follow-up sample also revealed a correlation between age and mean cortisol level measured at the second assessment ($r = .50$, $p < .01$). Follow-up assessment cortisol values, by age, are presented in Figure 2. The same findings held within the diagnostic groups, for the SPD group ($r = .51$, $p = .05$), the other disorders group ($r = .63$, $p = .02$), and normals ($r = .46$, $p = .02$). Thus, the cross-sectional relation observed in the first assessment was replicated in the second assessment.

The developmental change is shown in Figure 3, where the Time 1 and Time 2 data (followed sample only) are presented. Cortisol level is presented as a function of assessment time and saliva sample (1–4). As illustrated, there was a significant increase in mean corti-

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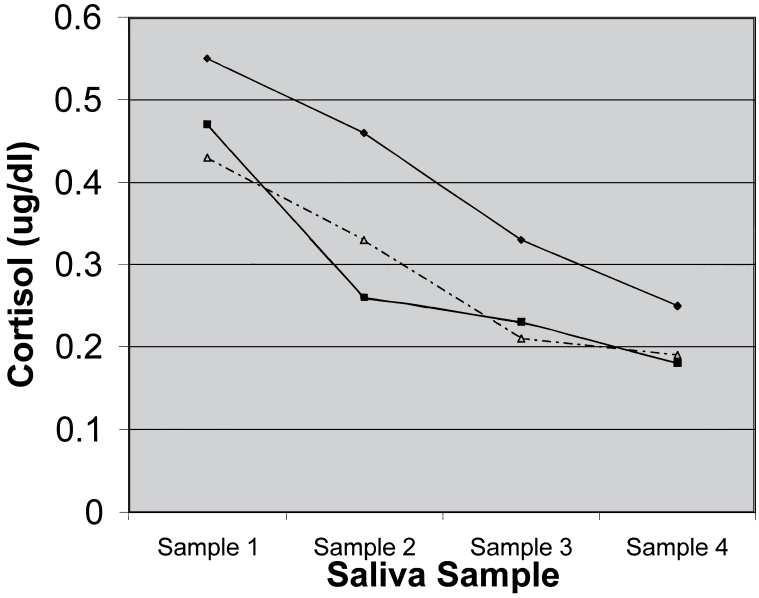


Figure 1. The cortisol levels by diagnostic group and sample at the follow-up assessment: (◆) SPD, (■) OD, and (△) NC.

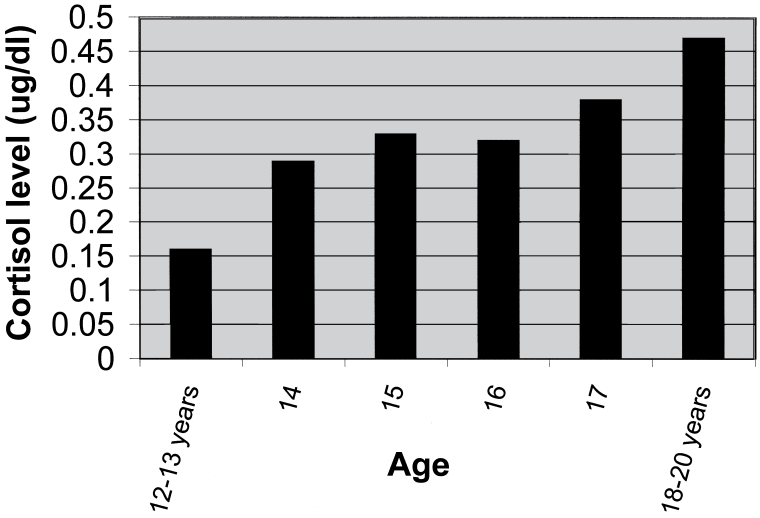


Figure 2. The cortisol values at follow-up by age.

sol level between the initial and follow-up assessments ($t = 1.81$, $p < .05$). This was primarily due to a significant rise in the first ($t = 3.19$, $p = .01$) and second saliva samples ($t = 1.98$, $p < .05$), suggesting the sample is showing an increase in the biological response to novelty during adolescence.

Because of the small sample sizes in the two personality disordered groups, there is limited statistical power for detecting diagnostic subgroup differences in this developmental effect. When the same analyses were conducted within-group, the Time 2–Time 1 difference in mean cortisol for the normal group was marginally significant, t (20) = 1.55, $p = .06$). The increase over time did reach sta-

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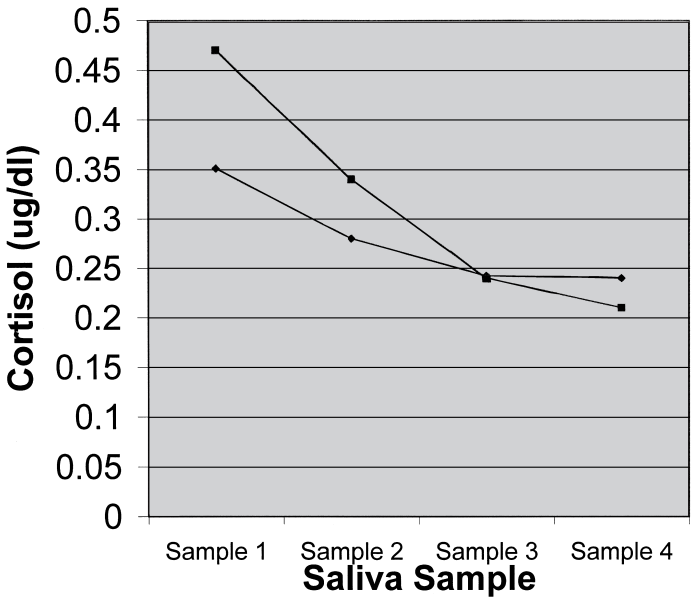


Figure 3. The cortisol values at the (◆) initial and (■) follow-up assessments.

tistical significance for the first saliva sample, t (20) = 2.89, $p < .01$. The difference between the Time 1 and Time 2 mean cortisol levels was not statistically significant for the SPD and OD groups. However, the pattern of change from the initial to the second assessment paralleled that shown in Figure 3 for all of the diagnostic groups.

The relation between cortisol and SPD symptoms

As previously reported, the SPD group showed elevated cortisol levels at the initial assessment (Weinstein et al., 1999). At the follow-up assessment, diagnostic group status changed for some subjects. However, because these status changes can occur as a result of a change in the rating of only one symptom, they do not necessarily reflect meaningful changes in clinical status. We therefore computed a continuous measure of SPD symptoms. For each of the symptom criteria on the SCID II, the interviewer rates symptom severity (1, *absent;* 2, *subthreshold;* 3, *threshold*). These ratings were summed for the items that comprise the criteria for SPD. Correlational analysis revealed that there was significant temporal stability for the composite SPD symptom ratings ($r = .62$, $p < .001$).

Bivariate correlational analysis yielded a significant positive relation between mean cortisol at the initial assessment and total SPD symptoms at follow-up ($r = .36$, $p < .01$). The relationship between mean cortisol at follow-up and total SPD symptoms was significant and similar in magnitude ($r = .36$, $p < .01$). When the mean cortisol values at the two time points were averaged, the magnitude of the correlation with SPD symptoms increased ($r = .41$, $p < .01$). Regression analysis was conducted to determine whether the addition of mean cortisol at the second assessment improved the prediction of follow-up SPD scores. There was no significant increment in R^2.

Discussion

The findings of this longitudinal study suggest three general conclusions. First, there is moderate temporal consistency in levels of salivary cortisol during the adolescent period. Second, both cross-sectional and longitudinal analyses reveal an increase in cortisol secretion as subjects progress through late childhood, although this may vary as a function of

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psychiatric status. Third, heightened cortisol release is linked with more severe SPD symptoms. This is consistent with findings from studies of patients with psychosis, which reveal a positive correlation between cortisol levels and symptom severity (Walder, Walker, & Lewine, In press).

The significant correlations between mean cortisol measured in the initial and follow-up assessments provide evidence for the reliability of the assay, as well as the stability of individual differences in HPA activity. There is evidence that both genetic factors and experience, including prenatal and postnatal events, influence HPA function (Walker, Bonsall, & Walder, 2000; Walker & Diforio, 1997). Thus, the cross-temporal stability of cortisol levels may reflect stable biological differences among subjects or persistent situational factors.

Developmental changes in the HPA axis

The present findings yield further support for the notion that adolescence is associated with a normative increase in cortisol secretion. We observe cross-sectional relations between age and cortisol, as well as a longitudinal increase in cortisol over a 2-year period.

Although we are not aware of any previous reports on longitudinal changes in saliva cortisol, at least one recent longitudinal investigation of serum cortisol in 28 adolescents found no developmental change (Knutsson, Dahlgren, Marcus, Rosberg, Bronnegard, Stierna, & Albertsson–Wiklund, 1997). This discrepancy might be due to differences in assay procedures or to differences in subjects' responses to blood versus saliva sampling, or it may reflect differential subject attrition based on sampling procedure (Davies, Collins, Gregory, & Clarke, 1996; Keks, Copolov, Mackie, Stuart, Singh, McGorry, & Coffey, 1991). It has been shown that salivary cortisol is a more sensitive measure of adrenal gland hyperfunction than is plasma cortisol (Bolufer, Gandia, Rodriguez, & Antonio, 1966). Further, the invasiveness of blood draws may induce a stress response in some subjects and thus obscure normative maturational changes. Consistent with this assumption, it has been shown that a substantial proportion of children and adults refuse participation in studies involving blood sampling, and that those who refuse are more likely to have adjustment problems. Susman, Dorn, Inoff–Germain, Nottelman, and Chrousos (1997) sampled blood in their longitudinal study of adolescents but obtained complete data on only 36 of an initial 108 subjects. They found that the adolescents who failed to complete the longitudinal protocol tended to express greater reluctance about blood sampling and to have more behavioral problems. (This report is one of the few well-controlled studies using blood sampling that provides information on the characteristics of the noncompleters.)

We are not aware of any published data on the rate of noncompliance with saliva sampling, but it has been our experience that rates of refusal are very low. Further, recent unpublished data from our research group indicate that almost half of young adult subjects who agree to saliva sampling would refuse participation in research that required blood collection. Although more systematic research on this issue is needed, the above considerations tentatively suggest that saliva sampling has distinct advantages over blood sampling, especially in longitudinal studies.

It is not clear what causes an increase in HPA activity during adolescence. There are a myriad of hormonal and brain changes occurring at this time, and further research is needed to elucidate the mechanisms. In speculating on the causal mechanisms, Kenney, Gancayo, et al. (1966) suggest that thyroid hormone, rather than gonadal hormones, may be the precipitant, given that indicators of thyroid function increase during adolescence.

It is important to note, however, that we observed a significant increase in cortisol secretion only when the entire sample was combined, and *not* within the SPD or OD groups. It is likely that this simply reflects the decreased statistical power for detecting change in the smaller subsamples. Alternatively, there may be group differences in the developmental course of HPA activity. Group comparisons showed that the SPD sample manifested elevated cortisol levels at the initial assessment (Weinstein et al., 1999), and this was replicated in the follow-up. Thus, the

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SPD youngsters may have experienced a developmental increase in cortisol secretion prior to the initial assessment.

Clearly, there is a need for further research to elucidate the developmental course of HPA activity. If the peri- and postpubertal periods are associated with an enhancement of cortisol secretion, this may explain the increased risk for certain psychiatric symptoms and syndromes during adolescence. This is consistent with findings from studies of rodents which indicate that there is a postpubertal onset of increased biological responsiveness to stress (Meaney, Sapolsky, & McEwen, 1985), particularly in animals with neonatal hippocampal damage (Lipska, Jaskiw, & Weinberger, 1993).

Cortisol secretion and SPD symptoms

Cortisol levels measured at both the first and second assessments were positively related with ratings of SPD symptoms at follow-up. This held for the entire sample, as well as the SPD group alone. These findings are consistent with a growing body of literature that indicates that heightened HPA activity is associated with schizophrenia and other psychotic disorders (Walker & Diforio, 1997).

In the present study the focus is on schizotypal signs, and we did not examine the relation of cortisol with other symptom dimensions or syndromes. Yet there is reason to believe that the HPA axis is a generalized moderating system that is linked with the expression of several disorders. For example, studies of depression, eating disorders, and panic have revealed elevated cortisol release (Colomina, Canals, Carbajo, & Domingo, 1997; Stones, Groome, Perry, Hucklebridge, & Evans, 1999; Susman et al., 1997; Zobel, Yassouridis, Frieboes, & Holsboer, 1999). The one notable exception is conduct disorder; several reports suggest that conduct disordered and aggressive youth manifest lower levels of cortisol than normal controls (McBurnett, Lahey, Rathouz, & Loeber, 2000; Moss, Vanyukov, Yao, & Kirillova, 1999; Schulz, Halperin, Newcorn, & Sharma, 1997; Vanyukov, Moss, Plail, & Blackson, 1993).

The association of cortisol secretion with the expression of a variety of psychopathologies suggests that the HPA axis is a nonspecific moderating system. Although the neural mechanisms mediating the relations between cortisol and symptom expression are unknown, it is likely that they involve the effects of glucocorticoids on various neurotransmitter systems. A discussion of the empirical literature in this area is beyond the scope of this paper; however, it should be noted that plausible neural mechanisms have been hypothesized for both depression (Post, Weiss, & Leverich, 1994) and schizophrenia (Benes, 1994; Walker & Diforio, 1997).

In the case of schizophrenia, overactivity of the dopamine (DA) system has been implicated in the neuropathophysiology (Davis, Kahn, Ko, & Davidson, 1991; Den Boer, 1995). As described by Walker and Diforio (1997), cortisol augments DA activity (Mittleman, Blaha, & Phillips, 1992; Rothschild, Langlais, Schatzberg, Miller, Salomon, Lerbinger, Cole, & Bird, 1985; Schatzberg, Rothschild, Langlais, Bird, & Cole, 1985; Wolkowitz, 1994), so that DA is enhanced by stress exposure (Antelman & Chiodo, 1990; Grossman, 1993; McMurray, Newbould, & Bouloux, 1991; Sorg & Kalivas, 1995). Several lines of animal research suggest that activation of the HPA axis can also alter DA receptors in some strains, indicating a role for individual differences in the neural consequences of stress exposure (Biron, Dauphin, & Di Paolo, 1992; Cabib & Puglisi–Allegra, 1991). These and other findings suggest that activation of the HPA axis might contribute to the expression of psychotic symptoms when there is a preexisting vulnerability to abnormalities in the DA system (Walker & Diforio, 1997).

The incorporation of the HPA system into diathesis–stress models of developmental psychopathology yields a framework for explaining several key findings. First, it suggests a biological mechanism for explaining the relation between stress and psychopathology. Second, the demonstrated effects of persistent HPA overactivation on hippocampal morphology and on subsequent stress sensitivity provide an explanation for the apparent worsening of the prognosis for depression and schizophrenia when episodes recur or go un-

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treated (Post et al., 1994; Wyatt, 1995). Third, the apparent sensitivity of the HPA axis to prenatal events helps to explain the association between prenatal complications and risk for mental illness (Cantor–Graae, McNeil, Sjostrom, Nordstrom, & Rosenlund, 1995; Cantor–Graae, McNeil, Torrey, Quinn, Bowler, Sjostrom, & Rawlings, 1994; Eyler–Zorilla & Cannon, 1995; Guth, Jones, & Murray, 1993). Finally, neuromaturational changes in HPA function may be implicated in the gradually escalating behavior problems observed in adolescents who subsequently show serious psychopathology (Neumann et al., 1995).

Conclusion

There is a growing body of research on animals which indicates that the adolescent period is associated with an increase in biological sensitivity to stress (Spear, 2000, in press). This has been attributed to maturational changes in the frontal and limbic regions of the brain, as well as changes in neurotransmitter systems. Recent research suggests that there may be similar developmental brain changes in humans, and it has been proposed that this may increase risk for certain psychological disorders during the pubescent period (Spear, 2000).

The present findings are consistent with these assumptions; they suggest that the HPA axis undergoes maturational change during the pubertal period and that elevated cortisol is linked with greater signs of SPD. Clearly, further research on the link between adjustment and hormonal changes during adolescence is needed. If risk for mental disorders is indeed influenced by maturational changes in the HPA axis, new models for preventive intervention are likely to emerge.

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