

Schizophrenia: A Neural Diathesis-Stress Model

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There is a substantive literature on the behavioral effects of psychosocial stressors on schizophrenia. More recently, research has been conducted on neurohormonal indicators of stress responsivity, particularly cortisol release resulting from activation of the hypothalamic-pituitary-adrenal (HPA) axis. This article integrates the psychosocial and biological literatures on stress in schizophrenia, and it offers specific hypotheses about the neural mechanisms involved in the effects of stressors on the diathesis. Both the behavioral and biological data indicate that stress worsens symptoms and that the diathesis is associated with a heightened response to stressors. A neural mechanism for these phenomena is suggested by the augmenting effect of the HPA axis on dopamine (DA) synthesis and receptors. Assuming the diathesis for schizophrenia involves an abnormality in DA receptors, it is proposed that the HPA axis acts as a potentiating system by means of its effects on DA. At the same time, DA receptor abnormality and hippocampal damage render the patient hypersensitive to stress. This neural diathesis-stress model is consistent with findings on prenatal factors and brain abnormalities in schizophrenia, and it provides a framework for explaining some key features of the developmental course and clinical presentation.

Diathesis-stress models have dominated theories about the etiology of schizophrenia for almost 30 years. Rosenthal (1970) played a central role in promulgating the notion that the behavioral expression of the biological vulnerability for schizophrenia was influenced by exposure to stress. Although some have questioned the validity of the diathesis-stress model (McGuffin, Asherson, Owen, & Farmer, 1994), it continues to serve as the basis for much contemporary theorizing about the origins of schizophrenia (e.g., Breier, Wolkowitz, & Pickar, 1991; Fowles, 1992; Norman & Malla, 1993a; Nuechterlein et al., 1994; Weinberger, 1987).

But despite the prevailing assumption that stress is relevant to the etiologic process in schizophrenia, the biological factors that mediate the effects of psychosocial stressors on the disorder have received relatively little attention. For the most part, the behavioral and biological aspects of stress responsivity in schizophrenia have been studied separately. The investigators and the paradigms are characterized by virtually no overlap, and thus there is a dearth of work aimed at synthesizing the behavioral and biological levels of analysis. Moreover, the issue of neural mechanisms has received scant attention; only a few authors have speculated on the nature of the diathesis-stress interaction at the biological level (e.g., Benes, 1994; Bogerts, 1989; Breier et al., 1991; Csernansky, Murphy, & Faustman, 1991; Fowles, 1992), and there have been no integrative analy-

ses of the research literature on the hypothalamic-pituitary-adrenal (HPA) axis in schizophrenia. This is noteworthy given the central role that the HPA system plays in the mammalian stress response and the growing body of literature showing the pervasive effects of HPA activation on the central nervous system (CNS).

In this article we address the issue of stress responsivity in schizophrenia, with an emphasis on (a) the parallels between the behavioral and biological responses of patients and (b) the potential interaction between the HPA axis and constitutional vulnerability for schizophrenia, which is presumed to involve an abnormality in dopamine (DA) neurotransmission.

The literature on stress and schizophrenia has focused almost exclusively on psychosocial stressors and has explicitly or implicitly conceptualized them as events that pose a threat to physical or emotional well-being (Norman & Malla, 1993a). In this article, we broaden the conceptualization of stressors to encompass biological insults and adopt the definition of stressors as events or experiences that jeopardize homeostasis (Chrousos & Gold, 1992; Sapolsky, 1992). By definition, then, stressors activate neuroendocrine and autonomic nervous system (ANS) reactions that originally developed to facilitate the organism's capacity to respond to threat (McEwen, 1995). These neuroendocrine and ANS reactions constitute the biological stress response and are typically associated with behavioral changes. In this article, we discuss findings pertinent to both the biological and behavioral aspects of the stress response in schizophrenia.

We begin by briefly reviewing the literature on responsivity to psychosocial stressors in schizophrenia. The results are consistent with the assumptions that exposure to psychosocial stressors exacerbates the symptoms of schizophrenia and that vulnerability to schizophrenia is associated with heightened behavioral responsivity to stressors. We then turn to the question that is the central focus of this article: Is there a neural mechanism to

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explain the effects of stressors on schizophrenia symptoms? Specifically, what stress-induced neural process has the potential for altering the expression of the neural substrate that is presumed to underlay the disorder, namely, overactivation of dopamine pathways? To answer this question, we turn to the biological level of analysis and examine the evidence on HPA dysfunction in schizophrenia, particularly heightened cortisol release and hippocampal damage. The findings are consistent with the conclusions drawn from the psychosocial literature. Finally, we explore the neural mechanisms that might underlie the relation between stress responsivity and the diathesis for schizophrenia. There are complex interactions between the HPA axis and DA neurotransmission, and these interactions may be the critical element in the effects of stressors on the course of schizophrenia. Specifically, although HPA dysfunction characterizes other psychiatric disorders, it is proposed that HPA activation has the additional effect of potentiating the biological and behavioral expression of abnormalities in DA neurotransmission that underlie schizophrenia. We conclude by offering a neural diathesis-stress model of schizophrenia—one which provides a framework for explaining some key features of the illness and for generating testable hypotheses.

Behavioral Evidence for the Effects of Stressors on Schizophrenia

Recent articles have reviewed behavioral evidence of the effects of psychosocial stressors on schizophrenia (Fowles, 1992; Norman & Malla, 1993a, 1994); therefore, a comprehensive overview is not presented here. Instead we briefly summarize the major trends in the findings.

On the basis of their review of the literature on stressful life events and schizophrenia, Norman and Malla (1993a, 1993b) draw two general conclusions. The first is that there is little evidence that schizophrenia patients are exposed to higher levels of postnatal stressors than the general population. This conclusion should be qualified by pointing out that the chief goal of most of this research has been to determine whether stressors play a causal role in both or either triggering or exacerbating the illness. Investigators have therefore been concerned with differentiating stressful events that are a potential consequence of the illness from events that are independent. Thus the conclusion that exposure to psychosocial stressors is not elevated in schizophrenia refers to events that are unlikely to have been induced by the individual's behavior. In this connection, it should be noted that psychiatric symptoms and syndromes are known to interfere with functioning in such a way that they induce subjective stress, as well as stressful interpersonal, occupational, and financial experiences.

The second conclusion drawn by Norman and Malla (1993a, 1993b) is that there is a causal relationship between stressful life events and severity of schizophrenia symptoms. Both retrospective (Birley & Brown, 1970) and prospective studies (Ventura, Nuechterlein, Hardesty, & Gitlin, 1992; Ventura, Nuechterlein, Lukoff, & Hardesty, 1989) have revealed an increase in independent stressful events in the months preceding relapse. In other words, the occurrence of stressful events that are not

attributable to the patient's behavior predicts subsequent worsening of symptoms.

Evidence for a causal relation between psychosocial stressors and symptom exacerbation has also been provided by studies of the interpersonal behavior of patients' family members. These investigations have shown that when patients are exposed to family members who are emotionally intense, express critical comments, or both, the likelihood of relapse is significantly increased (e.g., Barrelet, Ferrero, Szigethy, Giddey, & Pellizzer, 1990; Nuechterlein, Snyder, & Mintz, 1992; Vaughn, Snyder, Jones, Freeman, & Falloon, 1984). Conversely, interventions aimed at reducing critical emotional reactions in family members have been successful in reducing the likelihood of relapse (e.g., Hogarty et al., 1986; Tarrier et al., 1988). In sum, there is consensus in the research literature that psychosocial stress can exacerbate symptoms and trigger relapse.

The role of psychosocial stressors in triggering the initial illness episode is the subject of controversy, and it has not been established that psychosocial stressors are etiologic factors. To date, the evidence suggests that exposure to stressors can exacerbate premorbid behavioral dysfunction and may, at least, hasten the onset of the initial clinical episode. The effects of exposure to stressors in the premorbid period are suggested by the finding that children at high risk for schizophrenia (i.e., offspring of schizophrenic parents) show greater behavioral dysfunction if they are exposed to parental maltreatment (Walker, Downey, & Bergman, 1989). Further, it has been shown that high-risk children who experience care in institutional settings are more likely to subsequently manifest schizophrenia symptoms than are those who remain in the nuclear or extended family (Walker, Cudeck, Mednick, & Schulsinger, 1981). Similarly, one adoption study has revealed that the risk for psychiatric maladjustment is increased in the biological offspring of schizophrenia patients who are reared in dysfunctional adoptive families (Tienari, 1991). Finally, there is evidence that high levels of critical attitudes are predictive of the onset of schizophrenia-spectrum disorders in adolescents (Valone, Norton, Goldstein, & Doane, 1983). An answer to the question of whether the likelihood of a lifetime history of schizophrenia is actually increased by nonoptimal psychosocial environments must ultimately await follow-up assessments of these at-risk participants—assessments that are conducted after all of the participants have passed through the major risk period for schizophrenia.

The findings reviewed above concern the main effects of psychosocial stressors on the premorbid course and clinical symptoms of schizophrenia. A separate, but related, question concerns the interactive effects of stressors and vulnerability: Specifically, is vulnerability to schizophrenia associated with heightened behavioral sensitivity to psychosocial stressors? This is translatable into the statistical question of whether there is a significant interaction effect of risk status and exposure to stressors on behavioral outcome. The tentative answer is "yes." One source of support for this assumption is the studies of premorbid stressors described earlier. Walker et al. (1989) found a significant interactive effect of risk status and parental maltreatment on behavioral problems in children. High-risk children were more likely than controls to manifest behavioral problems as a consequence of exposure to parental maltreatment. Similarly,

Tienari (1991) showed that exposure to a nonoptimal rearing environment had a stronger association with adjustment problems in adopted-away offspring of parents with schizophrenia than in control adoptees. Taken together, these significant interaction effects, in combination with the absence of differences between patients and controls in the rate of exposure to independent stressors, are consistent with the diathesis-stress model in that schizophrenia appears to be linked with heightened responsiveness to psychosocial stressors.

But other findings suggest that a discussion of the role of stress in schizophrenia would be incomplete if the prenatal period is not taken into consideration. It has been shown that the rate of schizophrenia is elevated in offspring of women who are exposed to a significant psychosocial stressor (death of spouse) during pregnancy (Huttunen, 1989). Moreover, a host of prenatal and perinatal complications have been shown to be linked with schizophrenia. These include prenatal exposure to viral infection (Mednick & Hollister, 1995), nutritional deficiency (Susser et al., 1996), Rh-factor incompatibility (Hollister, Laing, & Mednick, 1996), and a variety of prenatal and perinatal medical complications capable of producing hypoxia (Brixey, Gallagher, McFalls, & Parmelee, 1993). As described later, there is evidence that these complications have implications for stress sensitivity because of their effects on the HPA axis. In fact, it has been suggested that the maternal stress response may be the mediator of the relation between schizophrenia and the various physical complications of pregnancy listed earlier (Huttunen, Machon, & Mednick, 1994).

Biological Stress Responsivity: The Nature of HPA Axis

The human physiological stress response is complex and involves multiple systems, including the adrenomedullary hormonal system, the sympathetic and parasympathetic nervous systems, and the HPA system. In this article, we focus on the HPA axis for three reasons: (a) activation of the HPA axis represents one of the primary manifestations of the stress response (Cullinan, Herman, Helmreich, & Watson, 1995); (b) as described later, there is evidence that it is dysfunctional in some schizophrenic patients; and (c) certain features of the HPA axis make it a plausible system for mediating the effects of stress on symptoms. Although a detailed discussion of the HPA system is beyond the scope of this article, a brief overview is provided here. The reader is referred to other articles for more in-depth descriptions (Cullinan et al., 1995; Friedman, Charney, & Deutch, 1995; Sapolsky, Armanini, Packan, Sutton, & Plotsky, 1990).

The HPA axis involves three chemical messengers: corticotropin releasing hormone, adrenocorticotrophic hormone and glucocorticoids. In response to stress, cells in the paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH). The pituitary contains receptors for CRH, and when these are stimulated, the pituitary releases adrenocorticotrophic hormone (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. Glucocorticoid receptors (GRs) located in various regions throughout the brain serve to regulate the activity of the HPA axis. The hippocampus contains a particularly high density of GRs, and it is believed to play an important role in the feedback system that serves to modulate the activation of the HPA axis (Sapolsky et al., 1990). The nature of the circuitry, neurotransmitters, and receptor subtypes that are involved in this feedback system are the subject of current investigation (Dallman et al., 1994; Rostene et al., 1995).

Acute and Chronic Stress Exposure

Numerous studies of the effects of exposure to stressors have indexed the biological response by measuring glucocorticoids in plasma, urine, or saliva. We review some illustrative findings from both the human and the experimental animal research on stress and the HPA axis, then turn to a discussion of HPA function in schizophrenia.

In normal human subjects, cortisol release is linked with acute exposure to stressors across the life span. For example, brief maternal separation is associated with an increase in cortisol release in human infants (Larson, Gunnar, & Hertzgaard, 1991) and those who are not securely attached show a more pronounced cortisol response (Spangler & Grossman, 1993). In adults, cortisol release is heightened in response to a variety of stressful experiences (Weiner & Sanchez-Ramos, 1992), including the anticipation of public speaking and examinations (Kirschbaum, Wust, & Hellhammer, 1992).

Habituation to a stressor is reflected in diminished biological and behavioral responses with repeated exposure (Pitman, Ottenweller, & Natelson, 1990). But, under certain conditions, there appears to be a sensitization effect of exposure to stressors. For example, exposure of neonatal rats to stressors of sufficient magnitude not only produces immediate behavioral changes and increases in corticosterone (Stanton, Gutierrez, & Levine, 1988) but also augments subsequent behavioral and biological responses to stressors (Plotsky & Meaney, 1993). Although the data are limited, there appear to be similar effects of repeated stressors on glucocorticoid release in nonhuman primates; disruption of social relationships can result in persistent elevations in cortisol in mother and infant squirrel monkeys (Levine, 1993; Mendoza, Hennessey, & Lyons, 1992). Post, Weiss and Leverich (1994) recently reviewed evidence that stress sensitization occurs in human subjects with depressive disorders.

Several factors appear to play a role in determining whether the glucocorticoid response shows habituation or sensitization in animals; stressors of greater intensity (Pitman et al., 1990), and lower controllability (Prince & Anisman, 1990), are more likely to produce sensitization in rodents. Constitutional factors (strain differences) also determine proneness to sensitization (Shanks, Griffiths, & Anisman, 1994). Similarly, in human infants, stressor intensity and individual differences in neonatal health status appear to influence the likelihood of sensitization (Gunnar, Hertzgaard, Larson, & Rigatuso, 1991; Stansbury & Gunnar, 1994). In a recent study, Kirschbaum and colleagues (Kirschbaum et al., 1995) measured cortisol responses to the repeated (5 days) stressors of public speaking and mental arith-

metic in healthy human subjects. Cluster analysis revealed two subgroups: low responders only showed cortisol elevations on Day 1, whereas high responders displayed significant increases in cortisol levels on all days, with no significant change across days. There was a trend toward increased baseline (prestressor) cortisol levels across days. Further, the high responders showed lower self-esteem and greater depression on self-report measures. The authors conclude that there is a substantial subgroup of adults who do not habituate to repeated stressors, and that these individuals are distinguishable on the basis of personality factors. Clearly, further research is needed to elucidate the nature and determinants of stress sensitization in humans.

It has also been demonstrated that when exposure to stressors persists and heightened glucocorticoid release is chronic, there can be permanent changes in the HPA axis. Most notably, the negative feedback system that serves to dampen HPA activation is impaired (Sapolsky, 1992; Sapolsky et al., 1990; Sapolsky, Krey, & McEwen, 1985; Sapolsky & Plotsky, 1990; Stein-Behrens, Mattson, Chang, Yeh, & Sapolsky, 1994). This is at least in part due to damage to the hippocampus, which shows a reduction in cellular density and GRs. This hippocampal damage has been linked to the neurotoxic effects of excessive glutamate release, which is potentiated by glucocorticoids. Thus there is a cumulative effect of stress, such that persistent exposure impairs the feedback mechanism that dampens the HPA axis, thereby enhancing subsequent stress responses. Although all of the experimental research on the biological and behavioral consequences of chronic stress exposure has been conducted on animals, there is reason to believe that similar processes occur in humans (Uno, Eisele, Sakai, & DeJesus, 1994). For example, it has been shown that hippocampal volume and cortisol levels are inversely correlated in human subjects (Starkman, Gebarski, Berent, & Schteingart, 1992).

The deleterious effects of stress exposure are not restricted to postnatal life. Baseline corticosterone release is elevated in rat pups whose mothers are exposed to stressors (Maccari et al., 1995) or administered stress hormones (Fameli, Kitraki, & Stylianopoulou, 1994) during pregnancy. This effect appears to be mediated by hippocampal damage. The hippocampus is highly susceptible to insults during fetal development, and prenatally stressed rats show reduced hippocampal weight (Szuran, Zimmerman, & Welzl, 1994) and glucocorticoid receptor densities (Maccari et al., 1995). Prenatal exposure to glucocorticoids has similar consequences for nonhuman primates (rhesus monkeys); namely, elevated cortisol (baseline and poststress) and 30% reduction in hippocampal volume (Uno, Eisele, Sakai, DeJesus, 1994). Additionally, research with nonhuman primates has shown that prenatal maternal exposure to stressors or stress hormones can have morphologic and behavioral consequences for offspring. These include dermatoglyphic abnormalities (Newell-Morris, Fahrenbruch, & Sackett, 1989), neuromotor and attentional deficits (Schneider, 1992a), and social impairment (Schneider, 1992b).

It should be added that physical complications, such as prenatal nutritional deficiency (Butler, Susser, Brown, Kaufmann, & Gorman, 1994; Garcia-Ruiz, Diaz-Cintra, Cintra, & Corkidi, 1993), and hypoxia (Hermans, McGivern, Chen, & Longo, 1993; Nyakas, Buwalda, Kramers, Traber, & Luiten, 1994) are

associated with hippocampal dysgenesis and behavioral abnormalities in animals. Prenatal hypoxia is also associated with heightened fetal corticosteroids (Brooks & Challis, 1992). Although we are not aware of published reports on the effects of prenatal viral exposure on hippocampal morphology, it has been shown that postnatal viral infection is linked with hippocampal changes (Pearce, Steffensen, Paoletti, Henriksen, & Buchmeier, 1996) and increased corticosterone release (Besedorsky, 1989) in rats.

Developmental Changes and Sex Differences in Cortisol Release

The HPA axis is characterized by significant developmental changes. In the rat, corticosterone receptors exhibit a peak in density during puberty, then show a decline through adult development (Meaney, Sapolsky, & McEwen, 1985; Sapolsky et al., 1985). Related to this, Lipska and colleagues (Lipska, Jaskiw, & Weinberger, 1993) have shown that there is a postpubertal onset of hyper-responsiveness to stress in rats who received neonatal excitotoxic hippocampal damage.

There appear to be some parallel developmental changes in human cortisol release. During the first year of life there is a decline in baseline human saliva cortisol (Kiess et al., 1995; Scott & Watterberg, 1995), as well as a decrease in the cortisol response to stress (Ramsay & Lewis, 1994; Stansbury & Gunnar, 1994). This is followed by a gradual increase in baseline levels during middle childhood, then a more marked increase in adolescence (Kiess et al., 1995). The adolescent increase in cortisol level is strongly linked with the stages of pubertal development, suggesting that sexual maturation is associated with heightened activity of the HPA axis. Adult-developmental changes in cortisol release have not been well documented; therefore, it is unknown whether the increases that begin in puberty extend into early adulthood. It has been shown, however, that there is an increase in cortisol release with advanced age (Swaab et al., 1994). This increase has been attributed to age-related degeneration of the hippocampus, which results in a reduction in the negative feedback that serves to dampen HPA activation (Sapolsky, 1992).

It is also of interest to note that there is evidence of a sex difference in cortisol level among normal human subjects, with male participants showing higher cortisol levels than female participants (Davis & Emory, 1995; Frankenhaeuser et al., 1978; Kirschbaum et al., 1992; Lamb, Noonan, & Burrin, 1994; Schaeffer & Baum, 1984). However, some studies, especially those of younger children, do not reveal a sex difference in baseline or stress-induced cortisol release (Lundberg, Westermarck, & Rasch, 1993; Tennes, Kreye, Avitable, & Wells, 1986), suggesting that sex differences may emerge with development. Further, some evidence from animal research and studies of patients with affective disorders indicates that female subjects show more pronounced HPA activation in response to stress than male subjects (Young, 1995). Further research is needed to clarify the nature and extent of sex differences in HPA function.

Cortisol Release and Human Behavioral Dysfunction

Finally, there is an extensive body of literature documenting a relation between cortisol release and a variety of adjustment problems. As Stansbury and Gunnar (1994) point out, however, the findings from studies of children are variable: Some have revealed positive correlations between cortisol levels and social withdrawal (Granger, Stansbury, & Henker, 1994; Granger, Weisz, & Kauneckis, 1994; Scerbo & Kolko, 1994) and depression (Lundberg, Westermark, & Rasch, 1987; Rosenthal, Doherty, & Rosenthal, 1988), whereas other investigators have failed to find evidence of a link between cortisol release and depression (Dahl et al., 1992) or social withdrawal (Tennes & Kreye, 1985) in children. Similarly, among adults, cortisol levels have been found to be positively correlated with measures of clinical and nonclinical depression (Copolov et al., 1989; Dabbs & Hopper, 1990; Heuser, Yassouridis, & Holsboer, 1994) and social inhibition (Dabbs & Hopper, 1990), although recent findings suggest that the positive relation between social inhibition and cortisol may only hold for female participants, with male participants showing an inverse correlation (Bell, Martino, Meredith, Schwartz, Siani, & Morrow, 1993). In summary, it appears that heightened HPA activation is linked with human behavioral dysfunction across developmental stages and that the nature of the relation varies as a function of sample characteristics. It is likely that preexisting constitutional factors determine the nature of the behavioral reaction (e.g., depression, withdrawal or aggression) associated with increased HPA activity (Stansbury & Gunnar, 1994).

Biological Stress Responsivity in Schizophrenia

The findings from research on biochemical indicators of stress responsivity in schizophrenia mirror those from research on psychosocial stressors: The findings suggest that biological indicators of stress are positively correlated with symptom severity and that patients show a unique biological response to stress. It is important to emphasize that the focus here is on the HPA axis such that other neural systems involved in the stress response are only addressed tangentially. Nonetheless, it is important to note that there is extensive evidence from other areas of investigation, including psychophysiology (Fowles, 1992), indicating that at least some schizophrenic patients are hyperresponsive to stress.

Cortisol Release: Baseline Cortisol

Before summarizing the research findings on baseline cortisol in schizophrenia, it is relevant to note that the term *baseline* is used here to refer to measures obtained in the absence of any experimental procedure (i.e., psychological or biological stressor) aimed at challenging the HPA system. In fact, however, participation in a research study, particularly the experience of having blood drawn or urine sampled, may constitute a significant stressor for some individuals. Thus baseline and stress-induced cortisol levels are not completely separable with current paradigms, and heightened baselines may partially reflect heightened stress sensitivity.

Several groups of investigators have found that schizophrenia

patients show higher baseline levels of plasma cortisol (Altamura, Guercetti, & Percudani, 1989; Breier & Buchanan, 1992; Gil-Ad, Dickerman, Amdursky, & Laron, 1986; Lerer et al., 1988; Monteleone, Maj, Fusco, Kemali, & Reiter, 1992; Morphy et al., 1985; Plocka, Matkowski, Lehmann, Kanarkowski, & Rybakowski, 1992; Sora, Nishimon, & Otsuki, 1986; Whalley et al., 1989) and saliva cortisol (Copolov et al., 1989) than normal controls. The finding of heightened baseline saliva cortisol suggests that cortisol levels are elevated in patients with schizophrenia even when the sampling procedures are minimally invasive. Although some studies yielded no significant difference between normal control participants and schizophrenia patients in baseline cortisol, most of the trends were in the direction of higher levels in patients (Breier, Wolkowitz, Doran, Bellar, & Pickar, 1988; Kathol et al., 1992; Nerozzi et al., 1990; Rao et al., 1995; Risch et al., 1992; Roy et al., 1986). Only three studies we are aware of yielded nonsignificantly lower cortisol in schizophrenic patients compared to normal control participants (Brophy, Rush, & Crowley, 1983; Wik, 1995; Wolkowitz, Doran, Breier, Cohen, & Pickar, 1986). Finally, abnormalities in diurnal changes in cortisol release have also been found in patients with schizophrenia, with Van Cauter et al. (1991) reporting higher cortisol throughout the day in patients than in normal control participants, but this only reached statistical significance at night. A reduction in the normative late-day decline was also reported in a study of schizophrenia patients conducted by Kaneko et al. (1992).

Many of the reports on baseline cortisol involve very small numbers of patients (e.g., $n = 5$ in the study by Kathol et al., 1992) and, therefore, very low statistical power for detecting group differences. We computed effect sizes (Cohen's d ; Cohen, 1988) for all of the 11 reports that listed means and standard deviations for the schizophrenia patients and the normal control group (Altamura et al., 1989; Breier & Buchanan, 1992; Breier et al., 1988; Brophy et al., 1983; Morphy et al., 1985; Rao et al., 1995; Risch et al., 1992; Roy et al., 1986; Van Cauter et al., 1991; Wik, 1995; Wolkowitz et al., 1986). (The other reports presented only figures, p -values, or descriptions, thus not providing enough information for a precise determination of effect size.) The result was a mean effect size across studies of .60, which is typically classified as moderate (Cohen, 1988). This is striking in light of the fact that only 4 of the 11 studies that yielded statistically significant cortisol elevations in schizophrenia included enough information to be included in this computation. Thus the averaged effect size of .60 is probably an underestimation. It is also noteworthy that the standard deviation for the schizophrenia group exceeded that of the normal control participants in 8 of the 11 reports. As discussed later, individual differences in symptom severity may be contributing to this elevated within-group variability, as well as to the inconsistencies in study outcomes. (It is unfortunate that information on the patients' current symptom status and the time of day of sampling was not included in enough reports to permit evaluation of the effects of these variables on group differences.)

Although a review of the literature on cortisol in patients with other psychiatric disorders is beyond the scope of this article, it is well established that patients with affective illnesses (e.g., major depressive disorder, bipolar disorder) show abnormalities

in cortisol release. Further, of the studies reviewed earlier, most of those that include patients with affective disorders report no significant differences in baseline cortisol between schizophrenia and affective disorder patients (Breier et al., 1988; Copolov et al., 1989; Kathol et al., 1992; Mokrani, Duval, Crocq, Bailey, & Macher, 1995; Risch et al., 1992; Whalley et al., 1989). One exception is the study by Yehuda, Boisoeneau, Mason, & Giller (1993), which showed lower cortisol release in patients with schizophrenia when compared to those with major depressive disorder. As many authors have concluded, elevations in cortisol release appear to be associated with both schizophrenia and affective disorders.

We recently initiated a study of cortisol levels in participants with schizotypal personality disorder (SPD; Walker et al., 1996). SPD is presumed to be part of the schizophrenia spectrum because it occurs more frequently in the biological relatives of schizophrenic patients and it often precedes the schizophrenic syndrome. We found that participants with SPD showed elevated cortisol levels when compared to normal control participants and participants with other personality disorders. These findings suggest that heightened cortisol release is associated with vulnerability to schizophrenia rather than being solely a consequence of psychotic symptoms.

Post-Dexamethasone Cortisol

Dexamethasone is a synthetic glucocorticoid. The dexamethasone suppression test (DST) is typically used with psychiatric patients as a challenge to the HPA axis, with the goal of assessing the integrity of HPA regulation by means of feedback mechanisms. The overwhelming majority of normal control participants show a decrease in cortisol release in response to the DST, but a substantial number of psychiatric patients fail to suppress cortisol release. DST "nonsuppression" is usually defined as a post-DST level that exceeds a standard criterion (Mossman & Somoza, 1989). Yet, baseline cortisol levels are positively correlated with post-DST cortisol levels in psychiatric patients (Aleem, Kulkarni, & Yeragani, 1988; Copolov et al., 1989; Rubin, Poland, Lesser, Winston, & Blodgett, 1987), indicating that DST nonsuppression is associated with preexisting hyperactivation of the HPA axis.

Although it was initially thought that nonsuppression was unique to patients with depressive disorders, it is now well established that a substantial number of schizophrenia patients are DST nonsuppressors. When compared to normal control participants, schizophrenia patients show higher post-DST cortisol levels in saliva (Copolov et al., 1989) and in plasma (Altamura et al., 1989; Hubain, Simonnet, & Mendlewicz, 1986; Sharma et al., 1988; for a review, see Tandon et al., 1991). We are not aware of any published report that has failed to find higher post-DST cortisol in schizophrenia patients when compared to normal control participants. Of course, numerous studies have demonstrated that patients with other psychiatric disorders, especially affective disorders, also manifest heightened DST nonsuppression (e.g., Copolov et al., 1989; Heuser, Yassouridis & Holsboer, 1994). Thus, schizophrenia is not uniquely associated with abnormalities in regulation of the HPA axis;

however, as discussed below, schizophrenia appears to be associated with a unique neural response to HPA activation.

The Relation Between HPA Activation and Clinical Features of Schizophrenia

Several studies have demonstrated an association between cortisol release and symptom severity in schizophrenia. In cross-sectional studies, baseline cortisol levels are positively correlated with ratings of positive psychotic symptoms in nonmedicated (Rybakowski, Linka, Matkowski, & Kanarkowski, 1991) and medicated (Franzen, 1971) schizophrenia patients. We are aware of only two studies that have examined the longitudinal covariance between symptoms and cortisol. Franzen (1971) measured serum cortisol in 10 patients while they were on medication, then withdrew medication for 5 weeks and measured cortisol again at the end of this period. Increases in cortisol over the 5-week period were associated with increases in ratings of psychotic symptoms. In a longitudinal study of 4 nonmedicated patients, Sachar, Kanter, Buie, Engle, and Mehlman (1970) measured daily urinary cortisol over a 2-3-month period. They found that cortisol levels were significantly higher (250%) immediately preceding psychotic episodes when compared to periods of recovery. During psychotic periods, mean cortisol levels fell midway between preepisode and recovery levels. This is consistent with the assumption that elevated cortisol release precipitates symptom exacerbation, rather than being solely a consequence of it.

Higher post-DST cortisol levels have been found to be associated with more severe negative symptoms (Kaneko et al., 1992; Keshavan, Brar, Ganguli, & Jarrett, 1989; McGauley, Aldridge, Fahy, & Eastment, 1989; Newcomer, Faustman, Whiteford, Moses, & Csernansky, 1991; for a review of this research, see Tandon et al., 1991) and positive symptoms (Kaneko et al., 1992) in schizophrenia. Moreover, the relation of pre- and post-DST cortisol levels with schizophrenia symptoms is not affected by level of depression (Schatzberg & Rothschild, 1988; Sharma et al., 1988), suggesting that the findings are not attributable to mood disorder in some schizophrenia patients. After reviewing the literature, however, Tandon et al. (1991) conclude that the strength of the association of cortisol levels with symptoms is greater for negative than positive symptoms. Given that many of these studies were conducted with currently or previously medicated patients, this differential relation may be due to the greater reduction in positive than negative symptoms produced by antipsychotics. Alternatively, the results may reflect differences in the neurohormonal substrates of the two symptom dimensions.

Consistent with the findings on symptom severity, cortisol release has been shown to be related with a variety of indicators of prognosis in schizophrenia. Patients who show higher cortisol levels when on neuroleptics manifest a poorer clinical response to medication suspension (Kuks & Folkerts, 1995). Among medicated patients, higher levels of CRH are associated with poorer premorbid adjustment (Forman, Bissette, Yao, Nemeroff, & van Kammen, 1994). Other studies reveal that poorer cognitive performance (Newcomer et al., 1991), greater premorbid impairment and ventricular enlargement (Tandon et al.,

1991), poorer prognosis (Kaneko et al., 1992; Tandon et al., 1991) and movement abnormalities (Aleem et al., 1988) are associated with higher post-DST cortisol in schizophrenia. Similarly, our studies of participants with SPD revealed a positive correlation between dyskinetic movements and cortisol levels (Walker et al., 1996). This is consistent with the documented relation between stress and exacerbation of dyskinesia in neurological patients and suggests that both the motor and psychiatric features of schizophrenia are stress sensitive.

Drug Effects on Cortisol Release

As might be predicted from the earlier findings, it has been shown that antipsychotic medications reduce cortisol release in schizophrenia patients. A reduction in pre- and post-DST cortisol is produced by typical antipsychotics (Rybakowski & Linka, 1991; Wik, 1995; for a review of the studies, see Tandon et al., 1991), and the atypical antipsychotic, clozapine, reduces the cortisol response to m-chlorophenylpiperazine (m-CPP) challenge (Breier, Kirkpatrick, & Buchanan, 1993). Three studies that failed to yield a statistically significant reduction in cortisol release following neuroleptics nonetheless reported trends in the direction of a decrease in cortisol (Copolov et al., 1989; Roy et al., 1986; Wolkowitz et al., 1986). As would be expected on the basis of these results, neuroleptic withdrawal produces an increase in cerebrospinal fluid (CSF) CRH (Forman et al., 1994). We are aware of no studies to date that have used an ABA design to determine whether cortisol or CRH returns to premedication levels following medication withdrawal.

Given the evidence that antipsychotic medication reduces symptoms, we examined the studies on baseline cortisol to determine whether there was a relation between medication status (on or off medication) and effect size for diagnostic group differences. This yielded effect sizes of .56 and .65 for studies of patients on ($n = 6$) and off ($n = 5$) drugs, respectively. Although not significantly different, the trend is consistent with other reports.

Studies of clinical responses to biologically induced stress in schizophrenia have yielded convergent results in that drugs that increase cortisol release also worsen the symptoms of schizophrenia. Acute caffeine administration significantly increases ratings of symptom severity and cortisol in schizophrenia patients (Lucas et al., 1990). Similarly, m-CPP increases both cortisol and ratings of positive and negative symptoms (Iqbal et al., 1991).

In the research on baseline and post-DST cortisol described earlier, the absolute level of cortisol release was the dependent measure. In contrast, several research groups have examined the magnitude of the change in cortisol release in response to biological challenges. The results have been mixed. When compared to normal control participants, schizophrenia patients have been reported to show a larger and more persistent cortisol response to growth hormone releasing hormone (GHRH; Nerzozzi et al., 1990) and naloxone (Wolkowitz et al., 1986) but not in response to infusion of CRH (Roy et al., 1986), 2-deoxyglucose (2-DG) challenge (Breier, Davis, Buchanan, Moricle, & Munson, 1993) or the administration of apomorphine (Mokrani et al., 1995). Kathol et al., (1992) found that

schizophrenia patients showed a greater cortisol response to the induction of hypoglycemic stress by means of insulin than did normal control participants and depressed patients, although the difference between the control participants and schizophrenia patients did not reach significance.

We are aware of only one study of schizophrenia patients' cortisol responses to a physical stressor (Breier et al., 1988). Breier et al. (1988) examined cortisol changes in response to lumbar puncture and found no differences between schizophrenia patients and controls in the magnitude of the response.

Several methodologic factors should be taken into consideration when evaluating the results of research on cortisol responses to biologic stressors. First, as noted above, the dependent variable is typically the pre- or postexposure change in cortisol release. As is the case with many psychophysiological variables, researchers have observed an inverse relation between baseline level and the magnitude of the increase in cortisol following biologic challenge (Wolkowitz et al., 1986). In all seven of the studies on cortisol response change cited earlier, the schizophrenia sample showed a higher baseline cortisol level than normal control participants, although not always statistically significant. Given the tendency for schizophrenia patients to have higher baseline cortisol, the use of change scores presents obvious measurement problems for studies using biologic challenges (e.g., corticosteroids, 2-DG, etc.). Statistical correction for baseline is needed in diagnostic group comparisons of cortisol change. To date, we are not aware of any studies that have employed this covariance procedure. Second, as described earlier, there are normative sex and age differences in cortisol release, and many studies in this area have not matched samples on these variables. Third, the attenuating effects of antipsychotic medication on the HPA axis are not taken into consideration in many studies of the cortisol response in schizophrenia (Kraus, Grof, & Brown, 1988). Thus diagnostic group differences may be undetected or underestimated when some or all of the patients in the sample are on drugs. Finally, diagnostic group differences in diurnal variation in cortisol, mentioned earlier, suggest that time of day of assessment influences the magnitude of group differences obtained.

Although the role of DA in the biological stress response is discussed in greater detail later, it is relevant to point out here the evidence that the DA response to stress may be greater in schizophrenia patients. Breier, Davis, et al. (1993) used a glucose-deprivation paradigm in which 2-DG is administered as a challenge that constitutes a perturbation to the central nervous system, similar to external stressors. Although baseline plasma homovanillic acid (HVA), a DA metabolite, was not elevated in schizophrenia patients, they manifested a significantly greater increase in plasma HVA in response to infusion of 2-DG when compared to normal control participants. There was a positive correlation between cortisol and HVA increases for both normal control participants and schizophrenia patients, and both groups showed a significant increase in cortisol release following 2-DG. However, the increase in cortisol was no greater in schizophrenic patients than in normal control participants. Along these same lines, an investigation by Wolkowitz, Doran, Breier, Roy, and Pickar (1989) revealed that schizophrenia patients showed a more pronounced pre- and post-DST increase in plasma HVA

than did patients with affective disorders. Both of these research groups conclude that the nature of the corticosteroid effect on DA may be syndrome specific, with schizophrenia patients showing more pronounced DA release than other psychiatric patients.

Hippocampal Abnormalities in Schizophrenia

Because the hippocampus plays a pivotal role in the modulation of the HPA axis, structural abnormalities in this region would be expected to be linked with HPA dysfunction. Over two decades ago, Mednick (1970) proposed that obstetrical complications might contribute to risk for schizophrenia by damaging the hippocampus. Although he based this well-reasoned hypothesis on careful analysis of findings from animal research, without the benefit of data from research using in vivo neuroimaging technology, subsequent neuroimaging studies have provided confirmation. Several research groups have found a reduction in the volume of the hippocampus in schizophrenia patients (Bogerts, Meertz, & Schonfeldt-Bausch, 1985; Breier, Buchanan, Elkashef, Munson, Kirkpatrick, & Gellad, 1992; Jeste & Lohr, 1989; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990; Waldo et al., 1994). Postmortem studies have revealed signs of cellular irregularities, including reduced cellular densities and irregular interconnections (for a review, see Bogerts & Falkai, 1995). In contrast, it should be mentioned that volumetric studies of the striatum indicate enlargement of these regions in schizophrenic patients (for an overview, see Walker, 1994). Thus, the reduced hippocampal volume is not attributable to generalized atrophy.

The study of monozygotic twins (MZ) who are discordant for schizophrenia provides one of the most powerful methodologies for identifying nongenetic potentiating or moderating factors. In MZ twin pairs who are discordant for schizophrenia, the affected twins show hippocampal reductions, especially in the anterior portion, when compared to the nonaffected co-twins (Suddath et al., 1990). It is of further interest that Suddath et al. found that hippocampal volume was smaller in the affected twin in 14 out of 15 cases, suggesting that this abnormality is not uncommon in schizophrenia. The predominance of volumetric reduction in the anterior region is intriguing in light of the results of lesion studies that show that modulation of cortisol levels in the rhesus monkey is subserved more by the anterior than the posterior hippocampus (Regestein, Jackson, & Peterson, 1986).

In this connection, there are some striking parallels between the factors that produce hippocampal damage and hyperactivity of the HPA axis in animals and the findings on prenatal correlates of schizophrenia. Table 1 lists, across the top, the prenatal factors that have been shown to be associated with schizophrenia. (References for the studies are cited in previous sections of this article.) As indicated, all have been linked with hippocampal abnormalities in animals. Also listed in the table are some other biological and behavioral abnormalities that have been described in animals exposed to these factors. It is striking that the same morphologic and behavioral characteristics have been observed in schizophrenia patients; namely, dermatoglyphic (Bracha, Torrey, Bigelow, Lohr, & Linington, 1991), neuromo-

Table 1
Prenatal Correlates of Schizophrenia and Some of Their Demonstrated Biological and Behavioral Effects on Animals

Effects demonstrated in animal research	Prenatal correlates of schizophrenia			
	Psychosocial stress	Viral infection	Nutritional deficiency	Hypoxia
Hippocampal abnormalities	X	X	X	X
Heightened glucocorticoid release	X	X		X
Dermatoglyphic abnormalities	X			
Neuromotor deficits	X			
Behavioral abnormalities	X	X	X	X

tor (Walker, Savoie, & Davis, 1994), attentional and interpersonal abnormalities (Neumann, Grimes, Walker, & Baum, 1995; Walker, Grimes, Davis, & Smith, 1993). Thus, Mednick's (1970) proposal that prenatally induced, hippocampal damage may be associated with schizophrenia appears to be substantiated by more than two decades of subsequent research.

Summary

Taken together, findings from neuroendocrine and neuroanatomical studies of schizophrenia show substantive parallels to those on the effects of psychosocial stressors: Specifically, the results suggest a dysregulation of the stress response (i.e., hippocampal damage, higher baseline and post-DST cortisol), as well as stress-induced exacerbation of symptoms (i.e., positive relations of cortisol with symptom severity and prognosis).

We now turn to the question of neural mechanisms. At the biological level, how is exposure to psychosocial stress translated into a worsening of schizophrenia symptoms? We know that hyperactivity or reactivity of the HPA axis is not, in itself, sufficient to explain psychotic disorders; there is extensive evidence that dysfunction of the HPA axis is associated with other psychiatric conditions (Chrousos & Gold, 1992; Yehuda et al., 1993). Presumably, the role of the HPA axis in schizophrenia lay not in its main effect, but in its interaction with a preexisting neuropathology.

The Organic Diathesis for Schizophrenia

Researchers in the field have offered a variety of theories regarding the neuropathology underlying schizophrenia. Most of these theoretical formulations focus on a specific neurotransmitter system (e.g., glutamate, serotonin, dopamine) as the critical element in pathogenesis. Amidst these varied theoretical models, however, the dopamine system has been the primary focus of interest (Davis, Kahn, Ko, & Davidson, 1991). As Davis et al. (1991) note, there are two main reasons why dopamine has played a leading role in theories about the neural origins of schizophrenia. First, it is well established that DA

agonists can induce psychotic symptoms in at least some humans. Second, DA antagonists can reduce or eliminate psychotic symptoms; all currently used antipsychotic medications have DA antagonistic properties. These two facts have contributed to the general notion that schizophrenia involves hyperactivity of DA neurotransmission.

For purposes of the present discussion, we adopt the notion that overactivation of DA pathways is the critical feature of the neuropathology in at least some cases of schizophrenia. This overactivation might emanate from elevated DA receptor densities or regionally specific increases in DA release. Drawing on this assumption, we consider how, at the biological level, stress exposure might alter the expression of the organic liability for schizophrenia.

As numerous writers have argued, it is likely that there is more than one etiologic process in schizophrenia, and similar behavioral outcomes and neural circuitry malfunction could result from abnormalities in different neurotransmitter systems. Thus in addition to the DA model of schizophrenic neuropathology, we briefly consider a contemporary model of glutamatergic abnormality in schizophrenia, and the manner in which this abnormality might be exacerbated by stress.

Dopamine Activity in Schizophrenia

In their review of the literature on DA abnormalities in schizophrenia, Davis et al. (1991) provide a synthesis of the key trends in the findings. As they note, there is fairly consistent evidence from studies of plasma and CSF that baseline DA is not elevated in schizophrenia patients, as a group, when compared to normal control participants. At the same time, as Davis et al. point out, several investigators have shown that DA metabolites are positively correlated with symptom severity. This has led theorists to postulate that the key feature of DA transmission in schizophrenia is either a regional DA imbalance in the brain (e.g., Davis et al., 1991; Weinberger, 1987) or an abnormality in receptors (e.g., Csernansky et al., 1991), possibly an increase in the density of DA receptors of the D2 subtype (Seeman, Hong-Chang, & Van Tol, 1993; Wong et al., 1986). (DA receptors that are not linked to adenylate cyclase are classified as D2 receptors.)

The notion of a regional imbalance in DA activity is clearly articulated in the models proposed by Davis et al. (1991) and Weinberger (1987). Both suggest that decreased prefrontal DA activity results in enhanced DA activation in subcortical regions, particularly the mesolimbic system. This proposal is based, in part, on the results of animal research that suggest that prefrontal DA activity serves to modulate subcortical DA activation. Davis et al. (1991) suggest one potential mechanism in this effect; namely an increase in DA-D2 receptor binding produced by lesions of prefrontal DA pathways. Although the research literature on DA-D2 receptor densities in schizophrenia has been fraught with controversy, a number of confirmatory reports have been published (for a review, see Tune et al., 1993).

Support for the notion that an increase in subcortical DA-D2 receptor activity is involved in schizophrenia is also provided by research on movement abnormalities. It is well established that abnormalities of movement are associated with schizophre-

nia, and recent findings suggest that these abnormalities predate the onset of clinical symptoms of schizophrenia (Walker et al., 1994). Our studies using home movies of infants revealed a higher rate of dyskinetic movements in preschizophrenic infants when compared to their healthy siblings (Walker et al., 1994). Several groups of investigators in the field of movement disorders have hypothesized that these dyskinetic syndromes are due to overactivation of DA pathways in the striatum (Alexander, Crutcher, & DeLong, 1990), particularly the D2-mediated pathway (Gerfen, 1992). Drawing on these models, Walker (1994) proposed how DA-D2 receptor overactivation might disrupt the striatal-cortical neural circuitry and produce both movement abnormalities and psychotic symptoms. Thus, on the basis of this neural circuitry model, the presence of idiopathic dyskinesia in schizophrenia is consistent with the reports of elevated DA-D2 receptor densities.

As described earlier, there is evidence of a positive correlation between cortisol level and subclinical dyskinesia in both schizophrenia patients and participants with SPD. These findings are consistent with the long-standing observation that stress exacerbates hyperkinesia (Kalachnik, Young, & Offerman, 1984). Moreover, they suggest a link between HPA activation and DA neurotransmission. Assuming that an abnormality in DA neurotransmission is the key neuropathological feature in some cases of schizophrenia, we now turn to the question of how activation of the HPA axis might exacerbate this abnormality.

The Association Between Activation of the HPA Axis and Dopaminergic Neurotransmission

On the basis of suggestive findings that glucocorticoids increase DA activity in the mesolimbic system, Schatzberg et al. (1985) proposed that the presence of psychotic symptoms in some depressed patients is a secondary consequence of hypercortisolemia in a subgroup who are especially sensitive to DA activation. More recently, Breier et al. (1991) proposed that schizophrenia patients show unique alterations in DA activity in response to stressors, although they did not implicate the HPA system. Subsequent studies have revealed that the relation between glucocorticoids and DA is more pervasive and complex than was originally assumed. Although much of the literature supporting this relation is based on animal studies, the findings from research on humans are generally consistent. As is shown, the literature suggests there are effects of the HPA axis on DA synthesis, reuptake and receptor sensitivity. We review some pertinent findings here, then explore their implications for DA models of schizophrenia.

Of course, stress is associated with changes in multiple neurotransmitter systems, including gamma-aminobutyric acid (GABA), serotonin and glutamate, as well as DA. Although discussion of these other systems is beyond the scope of this article, we briefly consider the effects of stress on glutamatergic neurotransmission because this system has recently received attention from investigators in the field.

Stress exposure elevates cortisol and DA release. It has been repeatedly demonstrated that both cortisol and DA release are increased by exposure to stress (Antelman & Chiodo, 1984; Grossman, 1993; McMurray, Newbould, Bouloux, Besser, &

Grossman, 1991; Sorg & Kalivas, 1995). This has been demonstrated in numerous animal studies as well as in research on humans. Similarly, the biochemical induction of stress responses in human subjects enhances both cortisol and DA (Breier et al., 1988; Krystal et al., 1994; Wolkowitz et al., 1989).

Evidence for a causal effect of HPA activation on DA release is provided by experiments in which corticosteroids are directly administered. In animals, corticosterone administration results in heightened DA metabolism in the *nucleus accumbens* (Mittleman, Blaha, & Phillips, 1992; Rothschild et al., 1985) and the caudate (Wolkowitz, 1994), suggesting that cortisol release triggers subcortical DA activity. Corticosterone also augments the rate of DA-mediated locomotion (Wolkowitz, 1994). Similarly, Wolkowitz and others (Rothschild et al., 1984; Schatzberg et al., 1985) have shown that acute corticosteroid challenge significantly raises plasma HVA in normal human subjects. More specifically, recent research indicates that the induction of heightened cortisol release in humans is followed by a rise in HVA that peaks several days later (Schatzberg et al., 1995).

There is a relation between the magnitude of cortisol release and DA activity. Consistent with this evidence, the results of human research indicate a link between the magnitude of cortisol release and DA activity. It has been shown that cortisol release and DA activity are related in normal human subjects (McMurray, Newbould, Bouloux, Besser, & Grossman, 1991), as well as in patients with schizophrenia and affective disorder (Breier, Davis, et al., 1993; Rothschild et al., 1987; Schatzberg & Rothschild, 1988; Schatzberg et al., 1987). Breier, Davis, et al. (1993) report correlations of .50 (schizophrenia patients) and .64 (normal control participants) between the magnitude of the increases in cortisol and DA release following challenge. Schatzberg et al. (1987) found that the pre-DST cortisol-DA correlation was .48 and the post-DST cortisol-DA correlation was .56 in a mixed group of patients with affective disorders.

Both DA administration and stress can produce sensitization. It is well established that administration of DA agonists, such as methamphetamine (MAP), augments sensitivity to subsequent DA agonism (for a review, see Akiyama, Kanzaki, Tsuchida, & Ujike, 1994). In rats, this sensitization effect is manifested behaviorally in the form of increased stereotypies, locomotion, and responsivity to novel environments. Akiyama et al. (1994) point out several aspects of MAP-induced sensitization that have potential relevance to schizophrenia: (a) It appears to involve an increase in DA release and DA receptor sensitivity and density; (b) it is associated with heightened responses to stress; and (c) it can be blocked by DA antagonists.

More recently, exposure to stress has been demonstrated to have sensitization effects similar to that of stimulants (see Sorg & Kalivas, 1995, for a review). Both prenatal and postnatal exposure to stress can enhance the behavioral response of rats to DA agonists. For example, exposure of rats to restraint stress during pregnancy accelerates the development of behavioral sensitization in the offspring (Henry et al., 1995). Similarly, postnatal exposure to stress produces a heightened behavioral response to DA agonists (Piazza, Deminiere, LeMoal, & Simon, 1990). The biological induction of HPA activation appears to have the same effect. Administration of CRH or corticosterone induces behavioral sensitivity to DA antagonism (Cador, Cole,

Koob, & Stinus, 1993; Deroche, Piazza, Maccari, LeMoal, & Simon, 1992). Conversely, blocking stress-induced corticosterone secretion reduces the subsequent behavioral response to DA agonists (Deroche et al., 1993).

Consistent with the assumption that augmentation of the HPA axis produces heightened sensitivity to DA, Lipska and colleagues (Lipska et al., 1993) have shown that lesions of the hippocampus in neonatal rats produce an increased behavioral response to DA agonists following pubertal maturation, though not before. This heightened DA reactivity is reduced by administration of the DA antagonist haloperidol (Lipska, Jaskiw, & Weinberger, 1994). The investigators have proposed that this phenomenon may serve as an animal model of developmental neuropathology in schizophrenia.

HPA activation augments DA synthesis and receptors. Administration of corticosterone significantly increases the rate of whole-brain DA synthesis in laboratory animals (Iuvone, Morasco, & Dunn, 1977). The findings of recent investigations indicate that this increase in DA synthesis is due, in part, to the effects of corticosteroids on tyrosine hydroxylase (TH), the chief enzyme in catecholamine biosynthesis. Glucocorticoids increase TH levels (Ortiz, DeCaprio, Kosten, & Nestler, 1995) as well as the transcription rate of the TH gene, levels of TH messenger RNA (mRNA; Fossom, Sterling, & Tank, 1992) and levels of TH enzyme protein (Tank, Ham, & Curella, 1986).

Several lines of research suggest that activation of the HPA axis can alter DA receptors. Henry et al. (1995) found that prenatal stress exposure produced no change in DA-D1 receptors, but elevated D2 receptors and decreased D3 receptors in the *nucleus accumbens* of rats. However, these receptor effects were not observed until the animals reached adulthood. Postnatal exposure of rats to stress also alters DA receptors, although the nature of the effect has been shown to vary by strain (Cabib & Puglisi-Allegra, 1991), suggesting a role for individual differences in the neural consequences of stress exposure. Adrenalectomy reduces the concentration of both D1 and D2 receptors in rat striatum, and glucocorticoid administration increases binding of DA to both of these receptor subtypes (Biron, Dauphin, & DiPaolo, 1992).

Behavioral sensitization to stimulants also appears to be mediated by DA receptor changes, and there is evidence that D2 receptors are a primary site of this effect. Rats that have been behaviorally sensitized to DA agonists show an elevation in D2, but not D1, receptors (Peris et al., 1990). Conversely, D2, but not D1, agonists enhance the behavioral response to stimulants (Fontana, Post, Weiss, & Pert, 1993). It should be noted, however, that there is also evidence that DA-D1 receptors are altered by repeated DA agonism (Henry & White, 1991), and there appear to be complex reciprocal influences among DA receptor subtypes; therefore, further research is needed to specify the role of receptor subtypes in sensitization.

On the basis of their finding of a developmentally linked effect of prenatal stress on DA receptors, and other evidence, Henry et al. (1995) suggest that changes in DA receptors are due to long-lasting alterations following stress exposure. Specifically, they suggest that stress of sufficient magnitude permanently alters the modulation of the HPA axis, such that corticosterone release is augmented and hippocampal glucocorticoid receptors

are changed. Thus long-standing hypersecretion of corticosterone may serve to enhance DA receptor densities, as well as DA release.

DA can enhance HPA activation. The DA system and HPA axis may act in a synergistic fashion. As previously described, DA antagonists reduce cortisol release in schizophrenia patients. Similarly, depletion of DA through lesion of the ventral tegmental area results in a decrease in both baseline and stress-induced corticosterone in rats (Casolini et al., 1993). In normal human subjects, it has been shown that DA agonists produce a significant increase in cortisol release (Mokrani et al., 1995), and this may be a specific consequence of DA-D2 agonism (Schilling, Adamus, & Pulluk, 1992). Taken together, these findings suggest that individual differences in stress sensitivity are partially determined by differences in the DA system (Cabib & Puglisi-Allegra, 1991).

Glutamate and Schizophrenia

Recently the potential role of abnormalities in the glutamate transmitter system has received greater attention from researchers. Before turning to a general discussion of the merits of our neural diathesis-stress model for understanding the clinical characteristics of schizophrenia, we briefly consider how the HPA axis might interact with abnormalities in glutamate neurotransmission. To date, a model developed by Olney and Farber (1995) constitutes the most comprehensive proposal of the likely mechanisms linking glutamate with schizophrenia. They focused on the N-methyl-D-aspartate (NMDA) receptor, which is a specific subtype of glutamate receptor present in both cerebral cortex and hippocampus, as well as other regions. Agents (e.g., phencyclidine and ketamine) that block NMDA receptors produce and exacerbate psychotic symptoms. Olney and Farber proposed that NMDA receptor hypofunction characterizes individuals at risk for schizophrenia and that early adulthood is the period of maximal sensitivity to the neurodegenerative changes that this can produce in the human brain. They also noted evidence that this neurotoxic effect can be induced in utero through excessive exposure to glutamate, which can cause a degeneration of neurons that express a high level of NMDA receptors. Among the neurodegenerative changes that NMDA hypofunction can produce is damage to regions that have been shown to be abnormal in schizophrenia: the cingulate and entorhinal cortices, hippocampus, and amygdala. The authors also pointed out that this hypothesis is compatible with DA involvement in schizophrenia, in that DA receptors inhibit the release of glutamate such that DA hyperactivity may contribute to NMDA receptor hypofunction.

The role of glutamate and other excitatory amino acids in the biological stress response has received less attention than has the DA system (Horger & Roth, 1995). Nonetheless, there is recent evidence that NMDA receptor blockade (ketamine) produces a significant increase in both plasma cortisol and DA metabolites, but not methoxyhydroxyphenylglycol (MHPG) or norepinephrine (NE), in human subjects (Krystal et al., 1994). Krystal et al. point out that the effect of NMDA blockade on cortisol is consistent with the finding that NMDA receptors in the hypothalamus modulate hormone release. Thus NMDA

receptor hypofunction is expected to result in HPA hyperactivation and enhanced behavioral response to stress.

But what of the effect of stress on NMDA receptor function? It has been shown that exposure to stress produces an increase in glutamate release, and this is triggered by glucocorticoid secretion (Horger & Roth, 1995). Glutamate binding with NMDA receptors appears to play a role in the modulation of DA neurotransmission. Although the nature of this effect is still the subject of inquiry, there is evidence that in response to stress, NMDA receptors mediate an increase in medial prefrontal cortex DA activity and a decrease in striatal DA. Thus NMDA receptor hypofunction could produce a reversal of this cortical-subcortical DA activation balance and result in the pattern of cortical-subcortical DA imbalance proposed by Weinberger (1987) to be responsible for schizophrenia.

A Neural Diathesis-Stress Model

The research findings reviewed previously provide a point of departure for the formulation of a model. Activation of the HPA axis appears to have the potential for augmenting DA neurotransmission. Thus, to the extent that DA overactivation represents either the primary abnormality in schizophrenia or a downstream consequence of some other primary factor, activation of the HPA axis can be viewed as a mediator of the relation between stress and symptom exacerbation. Further, activation of the HPA axis may have the potential for altering DA neurotransmission in a manner that persists beyond the duration of the stressor (i.e., by increasing DA synthesis or receptors), and this suggests that it can also be viewed as a moderator of the expression of the diathesis. In other words, the strength of the association between biological vulnerability and psychiatric outcome may vary as a function of the level or persistence of HPA activation. Such an effect is suggested by the significant interaction effect of risk status and stressors in the studies of high-risk offspring described earlier. (For a more detailed discussion of variables that have both mediator and moderator status in causal models, see Baron & Kenny, 1986.)

The augmenting effects of DA on HPA activation and the evidence of hippocampal damage in schizophrenia also offer an explanation for the heightened behavioral sensitivity to stressors manifested by schizophrenia patients. Additionally, both would account for the elevated baseline and post-DST cortisol in schizophrenia.

In sum, the research findings discussed in this article point to a dynamic interaction among neurotransmitter systems that has significant implications for behavioral development. Drawing on these findings, our general working model posits that some cases of schizophrenia (and SPD) involve an abnormality in striatal DA receptors (e.g., the regional distribution, density, affinity, subtype ratio, or some combination thereof) that results in a heightened sensitivity to DA. The expression of this biological diathesis is moderated by the HPA axis due to the augmenting effects of cortisol on DA activity. At the same time it is likely that there is a reciprocal effect such that the diathesis influences HPA activation and thus renders the individual hyperresponsive to stress.

Figure 1 illustrates the neural diathesis-stress model and in-

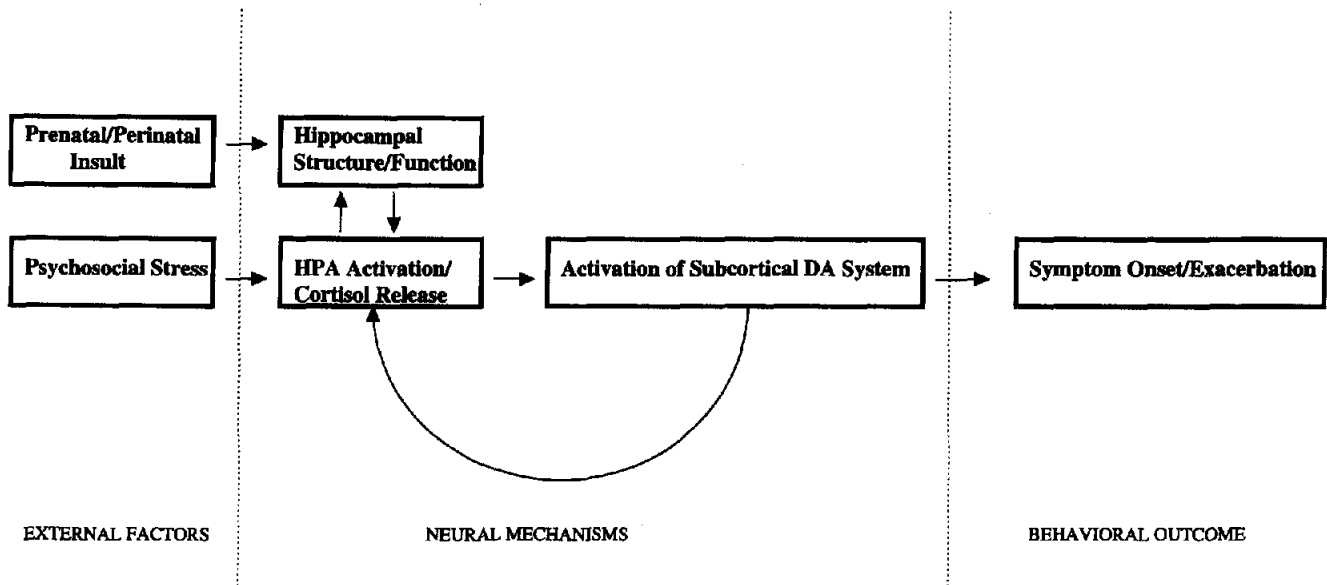


Figure 1. Neural mechanisms in the effects of stressors on individuals who are vulnerable to schizophrenia. HPA = hypothalamic-pituitary-adrenal; DA = dopamine.

corporates the effect of pre- and perinatal stress on the HPA axis. The figure is intended to show the pathways that are of primary relevance to the model, but it is not assumed to be exhaustive. For example, DA activity is influenced by factors other than the HPA system. Also, psychiatric symptoms can have evocative effects such that they increase the likelihood of exposure to stressors, and poor coping skills would be expected to amplify the impact of daily stressors on schizophrenia patients and vulnerable individuals.

This neural diathesis-stress model offers a framework for explaining several other key findings and features of schizophrenia. First, the model proposed here provides an integrative heuristic for explaining the interaction effect of obstetric complications with genetic liability in predicting psychiatric outcome (Cantor-Graae, McNeil, Sjoström, Nordström, & Rosenlund, 1995; Eyster-Zorrilla, & Cannon, 1995). Particularly noteworthy in this regard is the study by Eyster-Zorrilla and Cannon (1995), which demonstrated that the presence of familial schizophrenia was associated with cortical abnormalities in adult participants, whereas the interaction of familial schizophrenia with exposure to obstetric complications predicted ventricular enlargement. Ventricular enlargement is presumed to reflect a reduction in the volume of periventricular regions, such as the hippocampus. As noted, it is well established that prenatal complications can produce hippocampal damage in the fetus and that this damage can render the organism hypersensitive to stress in postnatal life (e.g., Altmann, Gutowski, & Wiegand, 1994; Butler et al., 1994; Szuran et al., 1994). If the inherited vulnerability to schizophrenia does involve an abnormality in DA receptors, such as that described earlier, then prenatally acquired hippocampal damage might serve to increase the likelihood of eventual schizophrenia in individuals predisposed to the disorder.

Second, the model offers an explanation for the gradually

escalating behavior problems observed in preschizophrenic participants and the modal age at onset of the prodromal phase in late adolescence (Neumann et al., 1995). As noted, it has been shown that human cortisol release gradually increases with age throughout childhood, then shows a very rapid rise in adolescence. Research with animals reveals a pubertal change in glucocorticoid receptors. These maturational changes in the biological response to stressors could be one of the critical factors that moderates the expression of premorbid behavioral deficits, making adolescence-early adulthood the peak risk period for onset of behavioral dysfunction. Consistent with the notion that HPA activity modulates the developmental expression of the diathesis, Nasrallah and Olson (1996) recently reported that hippocampal abnormalities in schizophrenia are associated with younger age at onset of illness.

Third, the facilitative effects of HPA activation on DA activity offers an explanation for the apparent worsening of the prognosis when schizophrenia is not treated with neuroleptics. It has been shown that the longer the period between illness onset and the initiation of antipsychotic treatment, the worse the course and long-term outcome (Wyatt, 1995). As stated above, there is evidence that antipsychotics blunt HPA activation. Antipsychotics may, therefore, serve a protective function by dampening the biological stress response associated with psychotic episodes. A reduction in the cortisol elevations associated with psychosis also decreases the consequent likelihood that hippocampal or other systemic changes will occur. Thus the shorter the duration of the nonmedicated period of illness, the less likely the patient is to sustain permanent changes in the HPA axis: changes that could serve to increase stress sensitivity and symptom severity.

Finally, the HPA axis may be involved in the gender differences that have been observed in schizophrenia (Walker & Lew-

ine, 1993). As noted, although the research findings are mixed, there is evidence of heightened cortisol levels in human male participants. Assuming HPA activation can serve to trigger or exacerbate behavioral dysfunction in vulnerable individuals, this might contribute to the greater premorbid behavioral dysfunction, earlier onset of symptoms, and poorer prognosis found in male patients.

Directions for Future Research

The research reviewed in this article offers substantive evidence that schizophrenia is a stress-sensitive disorder at both the biological and behavioral levels. The well-established relation between HPA activation and DA neurotransmission provides the groundwork for a neural diathesis-stress model of schizophrenia. At the same time, this model generates some important and answerable questions for further research.

First, what are the relations among hippocampal morphologic abnormalities, cortisol release, glucocorticoid receptor characteristics, and sensitivity to psychosocial stress in schizophrenia? Are they intercorrelated in the manner predicted by the model? To date, we are aware of no studies that have addressed any component of these inter-relations. Of particular theoretical interest are the biological correlates of patients' behavioral responses to conflictual interaction with family members. Granger, Weisz, and Kauneckis (1994) have shown that adolescents with internalized behavior problems show significant elevations in cortisol in response to conflictual family interactions. Similar research on participants with schizophrenia-spectrum disorders is needed.

Second, further research is needed on the relation of various pharmacologic agents with the behavioral and biological stress response in schizophrenia. Does baseline or post-DST cortisol or both predict responsivity to various kinds of pharmacologic agents in a manner that would suggest specific treatment regimens? Related to this, is the length of nonmedicated illness episodes associated with indicators of HPA activation or hippocampal morphology?

As mentioned, some investigators report that post-DST cortisol level is more strongly associated with negative than with positive symptoms of schizophrenia, although others find generalized relations between cortisol and symptom severity. Thus, a third issue in need of clarification is the specificity of the link between cortisol release and symptoms. It has been suggested that negative symptoms, such as withdrawal and affective blunting, partially reflect the patient's compensatory effort to reduce stress and, thereby, positive symptoms (Walker & Lewine, 1988). Therefore patients with the most severe negative symptoms may be those who are most stress sensitive.

Fourth, longitudinal studies are needed to clarify the nature of developmental changes in the HPA system, especially the HPA response to stress and its relation with symptoms. Prospective studies including both high-risk and nonhigh-risk children would be especially informative with respect to clarifying the link between the HPA system and symptom onset. As previously described, both of the published longitudinal studies on the covariance of symptoms and cortisol release in schizophrenia patients indicate that heightened cortisol predicts symptom ex-

acerbation (Franzen, 1971; Sachar et al., 1970). These are very salient findings, and they point to the importance of in-depth studies aimed at elucidating this phenomenon and at identifying the patient characteristics that predict sensitivity to stressors.

Finally, there is a need to explore new paradigms in biochemical research on schizophrenia and other psychiatric disorders. The model proposed here assumes that symptoms emerge as a function of interactions among multiple neural systems. It is likely that these interactional patterns differ among individuals. Thus, within-subject, longitudinal studies of multiple neurochemical indices in schizophrenia patients may be illuminating. Specifically, such research holds promise for identifying neurochemical profiles that are linked with symptom changes and for elucidating individual differences in the nature of these neurochemical profiles. This dynamic longitudinal approach would represent a significant departure from the cross-sectional paradigms that have dominated research on neurochemical aspects of psychiatric disorders.

In conclusion, we acknowledge several limitations of this article. We have essentially restricted our focus to the DA system as the organic substrate for schizophrenia, although other neurotransmitters have been proposed as candidates in the etiology of the disorder. Knowledge of these other neurotransmitters in schizophrenia is relatively limited, however, and their associations with psychotic symptoms and stress responsivity are less well established. Further, we are limited by the extant data on behavioral and biological consequences of stress exposure in schizophrenia patients. Thus some key features of the neural diathesis-stress model proposed here have not been tested. But the dearth of empirical research that addresses the biobehavioral aspects of stress responsivity in schizophrenia has been due, at least in part, to the lack of a theoretical framework that can generate testable hypotheses. We hope that the hypotheses proposed here will stimulate integrative research aimed at elucidating the nature of the diathesis-stress interaction at both the biological and behavioral levels.

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