Abstract

Psychosocial stress is included in most etiologic models of schizophrenia, frequently as a precipitating factor for psychosis in vulnerable individuals. Nonetheless, the stress-diathesis model has not been tested prospectively in prodromal patients as a predictor of psychosis. The biological effects of stress are mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which governs the release of steroids, including cortisol. The past few decades have witnessed an increased understanding of the neural effects of stress and cortisol, including both normal and abnormal diatheses. As few biological markers have been evaluated as risk factors for psychosis in prodromal patients, the HPA axis and its interaction with intervening life events are apt candidates for study. In this article, we review the HPA axis and its neural effects, present a model for how stress might precipitate psychosis in vulnerable individuals, review the empirical evidence of a link between stress and schizophrenia symptoms, and propose a research design and appropriate statistical models to test the stress-diathesis model for psychosis onset in prodromal patients.

Keywords: Schizophrenia, psychosis, prodrome, stress, cortisol.


The past decade has witnessed major developments in the prediction of psychosis among individuals with subclinical positive symptoms. Measures have been developed to assess "prodromal" symptoms and identify "prodromal" individuals, of whom 40 to 50 percent become overtly psychotic within 1 to 2 years (McGorry et al. 2001; Miller et al. 2001). However, no clear biological markers of risk for psychosis have been established within a prodromal population. Variables identified thus far as having predictive value for psychosis among prodromal individuals have been mostly symptoms and clinical characteristics: that is, Brief Psychiatric Rating Scale scores (total and psychotic), symptoms of depression and anxiety, low global functioning, and duration of symptoms (McGorry et al. 2001). With the exception of maternal age, developmental variables (e.g., retrospective assessments of obstetric complications, developmental milestones, childhood behaviors, premorbid adjustment) have also failed to predict psychosis in prodromal individuals (McGorry et al. 2001). Neuropsychological domains of premorbid intelligence, executive functioning, and memory are also not predictive (McGorry et al. 2001), although new evidence suggests that poor olfactory identification may predict the development of schizophrenia spectrum disorders among prodromal patients (Brewer et al. 2003). Some researchers have found that prodromal individuals who later become psychotic have a higher baseline ratio of left hippocampal volume to whole brain volume than do prodromal patients who do not become psychotic, an unexpected and paradoxical finding that requires further investigation (McGorry et al. 2001; Phillips et al. 2002).

To date, other than brain volumes, few biological markers have been evaluated, either as baseline predictors or as dynamic mediating variables for the emergence of psychosis, in individuals identified as at risk for psychosis. Such studies are important in this high-risk group, as they can shed light on the pathophysiology of the onset of psychosis in vulnerable individuals, which in turn can lead to the development of new treatment and prevention strategies. A reasonable candidate system to evaluate is the stress cascade, including the HPA axis, as stress has been theorized to precipitate a first onset of psychosis in schizophrenia. In fact, preliminary evidence suggests that intolerance to normal stress, a dimension in prodromal scales, may be predictive of outcome (Yung et al. 2003). It has
long been assumed that stress is relevant to the course of schizophrenia, and stress has been included as a “triggering” element in the dominant etiologic models of the disorder. In particular, diathesis-stress models originated in the field of schizophrenia and were subsequently applied to other forms of psychopathology. Although the earliest incarnations of the diathesis-stress model of schizophrenia were primarily focused on the interaction between psychosocial stress exposure and genetic vulnerability, more recent models have encompassed a neurobiological level of analysis (Walker and Diforio 1997). Several of these recent approaches have addressed the biological aspects of the stress response, including elements of the HPA axis, such as cortisol. The HPA axis is an appropriate candidate neural system to study as a risk factor and marker for onset of psychosis and schizophrenia, as cortisol dysregulation characterizes a subset of schizophrenia patients and cortisol levels have been associated with psychosis, cognitive deficits, and schizophrenia-like brain changes across a host of disorders.

There is now evidence that HPA function may be pertinent to the question of psychosis risk in prodromal individuals. Baseline cortisol levels in adolescents with schizotypal symptoms, who may be at risk for psychosis, predict severity of their schizotypal symptoms 1 and 2 years later (Walker et al. 2001) and their risk for conversion to Axis I psychotic disorders (Walker and Walder 2002). These results are consistent with the notion that the HPA axis moderates the expression of psychotic symptoms. This is also parallel to what has been found in other at-risk adolescent samples, as baseline morning cortisol is associated with a 7-fold increase in risk for the onset of major depression within a year in adolescents identified as at high risk for depression (Goodyer et al. 2000). In adolescents with depression, evening cortisol levels have been found to predict chronic depression (Goodyer et al. 2001), recurrence of depression (Rao et al. 1996), and future suicide attempts (Mathew et al. 2003).

The notion that stress is a precipitating factor for psychosis in vulnerable individuals has face validity and resonates for patients and their families. The stress-vulnerability model currently provides the foundation for what is considered state-of-the-art psychological treatment for prodromal patients in clinics worldwide. However, although stressful life events are implicated in psychosis relapse, the contribution of stress to psychosis onset has not yet been studied prospectively (Nuechterlein et al. 1992). However, in a cross-sectional study of young adults who are identified as being at high risk for schizophrenia on the basis of having at least one affected first degree relative, current psychotic symptoms were related in cross-section to recent life events in a dose-dependent relationship, with an estimated effect size of 2.0 (Miller et al. 2001). Prospective studies in adolescents at risk for depression demonstrate the importance of psychosocial stress. Among adolescents at risk for depression, major disappointments and permanent losses predicted the onset of major depression in the ensuing month, with odds ratios of 58.9 (7.0–495.5) and 8.8 (2.02–38.6), respectively (Goodyer et al. 2000).

The stress cascade and its corresponding neurobiology, in terms of activation of the HPA axis and consequent neurobiological effects, are reasonable to explore as both a risk factor for and a marker of evolving psychosis. Namely, how might stress and the HPA axis influence vulnerability to schizophrenia? And how might stress and HPA activity trigger episodes in vulnerable individuals? In this article, we will (1) review the effects of stress and the HPA axis on the brain in both animals and humans, (2) describe how neurodevelopmental pathology might lead to an enhanced vulnerability to psychosis in the context of stress, and (3) describe methodological and statistical approaches to research on stress and the HPA axis in prodromal patients.

The Stress Cascade and Its Effects on the Brain

Review of the HPA Axis. The HPA axis is one of the main neural systems mediating the stress response in mammals. It involves three chemical messengers: corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (figure 1). In response to stress, cells in the periventricular nucleus of the hypothalamus release CRH, which stimulates the pituitary to secrete ACTH. In turn, ACTH stimulates the adrenal cortex to release glucocorticoids, specifically cortisol in primates and corticosterone in rats. Of note, CRH is not only a component of the HPA axis that stimulates pituitary release of ACTH but also a neuropeptide for which receptors are located throughout the cortex. CRH has direct effects on the brain, including the locus coeruleus, the periventricular nucleus of the hypothalamus, the bed nucleus stria terminalis (BNST), and the central nucleus of the amygdala (Koob and Heinrichs 1999). Interaction of CRH with the noradrenergic system in these four sites can lead to a feed-forward activation that can result in significant alterations to homeostasis—that is, “allostasis” and possibly psychopathology.

Stress leads to glucocorticoid secretion in both animals and humans. In rats, stressors such as restraint, aversive noise, and separation from conspecifics result in a rise in corticosterone secretion (Sanchez et al. 2001). Similarly, in humans, cortisol release is linked with stress exposure across the life span, from infancy through adulthood.
The Stress Cascade

Figure 1. The HPA axis and the brain

Hypothalamus-Pituitary-Adrenal axis

STRESS
(e.g. threat)

Hypothalamus
Pituitary
Adrenal
Glucocorticoids
Kidney

STRESS

Adrenals

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Kirschbaum et al. (1992). Stressors have consistently been linked over minutes to hours to increases in human salivary cortisol in both naturalistic studies (Smyth et al. 1998; van Eck et al. 1996) and in the laboratory (Hubert and de Jong-Meyer 1989; Wittling and Pfluger 1990; Kirschbaum et al. 1993; McCleery et al. 2000). Of note, laboratory stressors include imagined bereavement, public speaking, and the viewing of disturbing popular movies, such as The Shining.

Glucocorticoids have effects throughout the body, and they are critical to the physiological changes that accompany stress exposure. Furthermore, glucocorticoids are known to affect the brain. Glucocorticoid (GC) receptors are located in various regions throughout the brain, and they provide feedback for regulating the activity of the HPA axis. The hippocampus contains GC receptors, and it is postulated to be the main part of a negative feedback system modulating HPA activation (Sapolsky et al. 1990; Lupien et al. 1998). GC receptors have also been found in the medial prefrontal cortex (Diorio et al. 1993), and 40 to 75 percent of midbrain dopaminergic neurons have GC receptors (Harfstrand et al. 1986).

Glucocorticoids can be measured in cerebrospinal fluid (CSF), urine, plasma, and saliva. The responsivity of the HPA axis can be probed through challenge, through either induced stressors or pharmacological challenge. For example, dexamethasone, a steroid, normally provides negative feedback to the HPA axis, leading to a suppression of cortisol secretion. Failure to suppress cortisol constitutes an abnormal dexamethasone test and indexes a deficit in negative feedback. Physiological challenges, such as glucose tolerance tests, determine the extent to which the HPA axis responds to provocation and can identify individuals who have a hyperresponsive HPA axis, with sustained increases in cortisol.

Effects of Stress and the HPA Axis on the Brain. Chronic stress and persistent elevation of glucocorticoids lead to neural changes and “sensitization” to stress, which may result from feed-forward systems as described above, and/or from changes in the negative feedback system that dampens HPA axis activation, such as neurotoxicity to the hippocampus and a subsequent reduction in GC receptors (Sapolsky et al. 1985; Sapolsky et al. 1990; Sapolsky 1992; Stein-Behrens et al. 1994). Stress has been shown to have a number of effects on the GC receptor–rich hippocampus, including not only cell death (Uno et al. 1989) but also potentially reversible processes, such as atrophy of dendrites on excitatory pyramidal neurons (McEwen and Magarinos 1997), decrease in the generation of new neurons (Gould and Tanapat 1999), reduced expression of neurotrophic factors such as brain derived neurotrophic factor (BDNF) (Vaidya et al. 1999), and suppression of long-term potentiation (Diamond et al. 1994), the biological underpinning of memory. Thus, it is not surprising that rodents exposed to high levels of corticosterone manifest deficits in hippocampal-dependent spatial memory (Luine 1994). The degree of impairment in new spatial learning in rats is correlated with cell loss in the CA3 region of the hippocampus (Arbel et al. 1994).

There is evidence in humans that chronic stress and glucocorticoid elevation may also be toxic to the brain, specifically the hippocampus, as there are interrelationships among stress, cortisol function, hippocampal volume, and hippocampus-dependent cognition in stress-related disorders. In post-traumatic stress disorder (PTSD), which by definition involves a significant stressor, there is prominent reduction in hippocampal volume (Bremner et al. 1997) that is accompanied by deficits in hippocampus-dependent explicit memory. Similarly, in depression, there is hippocampal volume reduction (Bremner et al. 2000), and there are memory deficits that are associated with duration of illness (Sheline et al. 1999). The role of glucocorticoids in these deficits is suggested by found associations between urinary cortisol and cognitive impairments (Rubinow et al. 1984) and between cortisol dysregulation and hippocampus volume reduction (Axelson et al. 1993). However, the causal relationships among these variables cannot be determined by cross-sectional studies, and it has been suggested that a smaller hippocampus could be a marker or risk factor for PTSD or chronic depression, and not itself an effect of stress and glucocorticoid exposure.
More solid evidence that cortisol may mediate neurotoxicity in humans comes from studies in individuals who have high cortisol levels, from either endogenous (Cushing's disease) or exogenous (pharmacological corticosteroids) sources. In Cushing's disease, hippocampal volumes are inversely correlated with plasma cortisol levels ($r = -0.73, p < 0.05$) (Starkman et al. 1992) and positively associated with verbal memory scores corrected for IQ. Of note, these memory deficits (Mauri et al. 1993) and hippocampal volume reductions (Starkman et al. 1999) are both reversible with treatment and normalization of cortisol levels, suggesting that cortisol may have direct and reversible effects on hippocampal volumes and hippocampus-dependent memory in humans. Further, exogenous glucocorticoids have reversible effects on cognition, specifically memory (Wolkowitz et al. 1990; Newcomer et al. 1994; Kirschbaum et al. 1996).

HPA Axis and the Brain in Schizophrenia. Evidence of HPA dysfunction also exists in schizophrenia and includes pathology in the neural target of glucocorticoids, the hippocampus, and associated memory deficits. These may be a consequence of the abnormal neurodevelopmental processes that lead to schizophrenia pathophysiology (i.e., an abnormal hippocampus leads to poor memory and impaired feedback of the HPA axis). We hypothesize that abnormality in the hippocampus may be one feature of the neural diathesis in prodromal patients that puts them at risk of developing psychosis in the context of stress. An impaired hippocampus that results from genetic liability or early environmental exposures could lead to an unrestrained HPA axis response to stress, as the hippocampus is rich in GC receptors that are integral to the negative feedback of the HPA axis. Further stress around the time of onset of first psychosis may affect the hippocampus, but that is not an integral part of our model.

HPA axis. Two meta-analyses have demonstrated a significantly higher rate of dexamethasone nonsuppression of cortisol in schizophrenia (Sharma et al. 1988; Yeragani 1990), and dexamethasone nonsuppression has been associated with both negative and cognitive symptoms (Newcomer et al. 1991). There is elevated cortisol secretion in early sleep (van Cauter et al. 1991) and at 4 p.m. in unmedicated schizophrenia patients when compared with controls (Thakore et al. 2002).

Hippocampus. Meta-analysis has demonstrated hippocampal volume reduction in schizophrenia (Wright et al. 2000). Other evidence of hippocampal abnormality in schizophrenia comes from spectroscopic (Deicken et al. 1999) and functional imaging (Heckers et al. 1998; Malaspina et al. 1998) studies. In fact, regional blood flow in the hippocampus is increased in response to exogenous cortisol in schizophrenia patients compared with controls (Ganguli et al. 2002), a regionally specific response that the authors suggest may be evidence of an abnormal brain activation pattern in schizophrenia patients in response to stress. Postmortem studies demonstrate reduced cell size in the hippocampus, as well as abnormal apical dendrites on pyramidal cells in the subiculum (Rosoklija et al. 2000), findings that could be consistent with the known effects of stress and cortisol on apical dendrites in the hippocampus (McEwen and Magarinos 1997). Postmortem studies also show a decrease in GC receptor message in several brain regions in schizophrenia patients compared with normal controls (Webster et al. 2002), including not only layers III to VI of the frontal cortex and layer IV of the inferior temporal cortex but also the dentate gyrus, CA(4), CA(3), and CA(1) regions of the hippocampus. This decrease in GC receptors is consistent with decreased feedback of the HPA axis, resulting in heightened glucocorticoid secretion, as well as differences in cortisol-induced brain activity.

Hippocampus-dependent explicit memory. Cognitive deficits exist in many domains in schizophrenia, including attention, executive function, and working memory. However, a meta-analysis of 70 studies that examined cognition in schizophrenia showed the largest effect sizes across studies for explicit memory, both verbal and nonverbal and both immediate and delayed (Aleman et al. 1999). Cognitive function, specifically hippocampus-dependent verbal memory, is a strong predictor of functional outcome in schizophrenia (Green 1996) and is inversely associated with cortisol levels. Verbal memory deficits exist during the prodrome (Hawkins et al. 2001) and may either be a marker of liability (hippocampal abnormality) or a risk factor itself for psychosis. However, studies by McGorry et al. (2001) have not found verbal memory deficits to be more marked in prodromal patients who will convert to psychosis.

Possible explanations for the associations of these elements in schizophrenia. As in several other clinical disorders, hippocampal, cognitive, and HPA axis measures are interrelated in schizophrenia. However, the questions of timing and causality remain unanswered. Abnormality in the hippocampus could occur primarily in life and represent a marker or risk factor for the eventual development of psychosis and schizophrenia. Another possibility is that there are structural changes in the hippocampus later in life that reflect evolution of symptoms and possibly stress during the prodromal period. In support of this idea, there have been reports of progressive cognitive deficits, including deficits in explicit memory (Hawkins et al. 2001), and hippocampal volume reduction (Pantelis et al. 2001) in the transition from the prodrome to psychosis. Also, high-risk patients have hippocampal volumes intermediate between those of...
normal controls and those of schizophrenia patients (Lawrie et al. 2001), and as mentioned above, one research group reported the counterintuitive finding that larger left hippocampal volume predicted conversion to psychosis among prodromal patients (Phillips et al. 2002).

Therefore, it is not clear whether the structural effects of stress and cortisol on the hippocampus might play a role in the early development of symptoms in schizophrenia, including both the onset of psychosis and cognitive deficits. A model for such effects would involve synaptic reorganization, a process that is increased in adolescence, the period when vulnerable individuals begin to manifest prodromal signs. The synaptic pruning hypothesis is one of the leading models for the development of symptoms in schizophrenia (Feinberg 1982) and is supported by computer modeling (Ruppin et al. 1995; McGlashan and Hoffman 2000), spectroscopic studies (Keshavan et al. 2003), and postmortem studies (reviewed in Harrison 1999). Synaptic pathology could arise in vulnerable adolescents by virtue of an abnormal substrate, resulting from genetic liability or early exposures, and/or an abnormal neuromaturational process, which could be augmented by environmental factors, such as stress. Stress and glucocorticoids can lead to reversible neuroplastic changes (Fuchs and Flugge 1995), such as atrophy of excitatory apical dendrites on pyramidal cells in the hippocampus, and can perturb N-methyl-D-aspartate (NMDA)–dependent synaptic plasticity in the hippocampus (Petrie et al. 2000). Glucocorticoid administration reorganizes dendritic arborization in the medial prefrontal cortex as well (Wellman 2001). Dendritic pathology consistent with stress-induced changes has been found in schizophrenia in both the hippocampal formation (Rosoklija et al. 2000) and the prefrontal cortex (Glantz and Lewis 2001). Such neuroplastic changes could putatively fluctuate with psychotic symptoms, as basal cortisol levels have been observed to do (Sachar et al. 1970).

Nonetheless, although stress may precipitate structural changes in the hippocampus and consequently worsen cognitive deficits during the prodrome, this is not a key element of our model. In our model, we suggest that hippocampal impairment may be part of the abnormal neural substrate in schizophrenia that confers increased likelihood to develop psychosis in response to stress. Many exposures associated with increased schizophrenia risk are particularly injurious to the hippocampus, including obstetric complications (McNeil et al. 2000), head injury (Bigler et al. 2002), and both prenatal and postnatal stress (Avishai-Eliner et al. 2002). Hippocampal abnormality may augment the effects of hypofrontality described below through contributing to decreased feedback of the HPA axis. In a rodent model of schizophrenia, rats with neonatal excitotoxic hippocampal damage show greatly increased mesolimbic release of dopamine in response to stress (Lipska et al. 1993). Stimulation of the prefrontal cortex in nonhuman primates who have a neonatal medial temporal lobe lesion also leads to a phasic increase in subcortical dopamine (Saunders et al. 1998).

Model of the Stress Cascade and Psychosis in Schizophrenia

In addition to structural effects on the brain, there are neurochemical effects of glucocorticoids and stress, and these may be the key to the onset of psychosis in prodromal patients. Stress exposure affects neurotransmitter systems and brain regions that have been implicated in psychosis. Walker and Diforio (1997) proposed that stress exposure may trigger or exacerbate psychotic symptoms by augmenting dopamine activity, particularly in the subcortical region of the limbic circuitry. This idea is supported by animal research that shows that stress can increase dopamine activity via the effects of glucocorticoids. In rodents, stress leads to an increased locomotor response to amphetamine, an animal model for psychosis (Deroche et al. 1992). Adrenalectomy in rodents has the same effect as antipsychotics, leading to a decrease in basal dopamine release in the nucleus accumbens and a reduction in apomorphine-induced locomotor activity (Piazza et al. 1996a, 1996b).

The neural diathesis of schizophrenia may entail a special vulnerability to develop psychosis in the context of stress. Abnormal functioning of the prefrontal cortex may lead to a hyperresponsivity to stress by subcortical dopaminergic neurons that do not have normal inhibition from the prefrontal cortex. Moghaddam (2002) writes: "A primary dysregulation in executive functioning of the PFC can lead to abnormal regulation of stress-related circuitry in regions downstream from the PFC, such as in the amygdala, ventral striatum or hippocampus, and produce an altered response to stress that elicits behavioral disruptions that are mechanistically distinct from those seen during normal conditions (p. 776)."

One model of psychosis in schizophrenia suggests that cortical dopaminergic dysfunction leads to a disinhibition of excitatory glutamate projections to subcortical dopaminergic neurons, specifically in the nucleus accumbens (ventral striatum) (Finlay and Zigmond 1997; Krystal et al. 1999). Dopamine neurons coming in to the prefrontal cortex hold projection glutamatergic pyramidal neurons under tonic inhibition. If these inhibitory dopaminergic afferents are disabled, heightened glutamatergic activity renders the nucleus accumbens hyperresponsive to stressful experiences (Deutch et al. 1990). The nucleus accum-
bens is posited to be relevant to the attribution of incentive salience; Heinz (2002) has theorized that "stress-induced or chaotic activation of dopamine release may attribute incentive salience to otherwise irrelevant stimuli and thus be involved in the pathogenesis of delusional mood and other positive symptoms (p.13)." Further, King et al. (1997) speculate that "a disruption in the interaction between these mesocortical dopaminergic neurons and dopaminergic neurons projecting to the nucleus accumbens shell is involved in those symptoms of schizophrenia that are influenced by stress (p. 141)." Support for this model comes from animal studies: the depletion of dopamine in the medial prefrontal cortex leads in rodents to increased basal and stress-induced dopamine efflux in the nucleus accumbens (Deutch et al. 1990; King et al. 1997).

As for prodromal or clinically at-risk patients, we hypothesize that hypofrontality, as reflected in negative symptoms and deficits in executive function, can set the stage for increased susceptibility to developing psychosis in the context of stress. As mentioned, this diathesis may be augmented by abnormality in the hippocampus, such that there are fewer G(1) receptors, disrupted feedback to the HPA axis, and prolonged cortisol secretion in response to stress. As in other disorders, disturbance of baseline diurnal cortisol in schizophrenia is assumed to reflect both cumulative effects of stress and trait characteristics, and may therefore predict conversion to psychosis in prodromal patients. Furthermore, it is likely that psychosocial stress interacts with the neural diathesis over time to produce surges in cortisol secretion that will trigger or exacerbate psychotic symptoms.

What May Constitute Stress Vulnerability in Schizophrenia?

Persons with schizophrenia do not appear to experience more stressful life events than normal controls, but they do report greater subjective stress (Norman and Malla 1993; Walker and Diforio 1997). Stress vulnerability is enhanced in patients with schizophrenia, such that they respond with more negative emotions to everyday stressors than do controls (Myin-Germeys et al. 2001). Of interest, family members of these schizophrenia patients demonstrate a stress sensitivity lower than that of patients but higher than that of controls (Myin-Germeys et al. 2001). This suggests that stress reactivity may be associated with liability for psychotic disorder as well as the expression of the illness. This liability may very well have a genetic component, as it is at least partially shared by family members. Although there is no established association between any purported schizophrenia susceptibility gene and reactivity to psychosocial stress, there is evidence that earlier stress exposure might increase stress vulnerability.

Postnatal Stress. Sensitivity to stress and consequent behavioral changes may result from stress early in development (Levine 1993; Plotsky and Meaney 1993; Coplan et al. 2001). Rodent and primate models of early adverse experience demonstrate long-term changes in neuroendocrine responses to stress, cognition, brain morphology, and emotional and behavioral regulation (Sanchez et al. 2001). Further, early stress in rodents can reprogram the brain to have increased stress-induced dopamine release in the nucleus accumbens (Cabib et al. 2002), a model for psychosis. In fact, adrenalectomy in the rat leads to decrease of dopamine in the nucleus accumbens shell, both at baseline and in response to mild stress, an effect reversed by corticosterone (Barrot et al. 2000).

Experience of earlier trauma may predispose individuals to develop psychosis. Although the effect of early trauma as a risk factor for psychosis has not yet been studied in prodromal patients per se, general population surveys show that a history of childhood abuse predicts development of psychotic disorders in individuals who endorse any psychotic symptoms at baseline, controlling for potential confounds, and that this relationship is dose dependent (Janssen et al. 2002). Of interest, PTSD involves rates of psychosis as high as 30 to 40 percent (David et al. 1999; Hamner et al. 1999), and the psychosis in PTSD can resemble that of schizophrenia (Mueser and Butler 1987; Butler et al. 1996). In one study, at least 75 percent of veterans with PTSD and psychosis had some hallucinations and delusions that were not combat related (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999). Also, as compared with schizophrenia patients, combat veterans with PTSD and psychosis have similar global Positive and Negative Syndrome Scale (PANSS) ratings (Hamner et al. 1999).
increased responsivity to stress. through modification of the HPA axis and hence an by which these exposures increase schizophrenia risk is (Walker et al. 1981) or by adoptive families that are "dysfunctional" (Tienari et al. 1994) or show "communication deviance" (Wahlberg et al. 1997) are more likely to succumb to schizophrenia. Early adversity may, therefore, interact with genetic liability to lead to schizophrenia.

A caveat is that this relationship between early trauma and liability to psychosis may not be causal. Childhood behavioral problems are a common precursor of schizophrenia and could contribute to the occurrence of early trauma. Also, genetic factors may account for this relationship, such that families with a history of mental illness may be characterized by less stability, lower socioeconomic status, and higher rates of abuse, as well as more offspring with psychiatric disorders. Therefore, early trauma could be a marker of risk for psychosis, not a risk factor in and of itself. Also, any causal relationship might not be direct (e.g., early trauma could lead to an increase in behaviors, such as drug use, that can increase risk for psychosis).

**Prenatal Stress.** In rodents, prenatal stress is associated in the adult offspring with behavioral changes, persistent elevations in HPA axis activity, and changes in GC receptor density (Takahashi et al. 1992; Henry et al. 1994; Lordi et al. 2000; Szuraz et al. 2000). Maternal stress or corticosterone administration also increases amphetamine-induced locomotor behavior in the adult offspring, a rodent model for psychosis (Diaz et al. 1995; Henry et al. 1995; Koenig et al. 2001). In nonhuman primates, prenatal stress leads to impaired attention, neuromotor abnormalities, decreased locomotion, and hyperreactivity to stress in the adult offspring (Schneider et al. 2002). Prenatal stress in primates also leads in offspring to increased levels of dihydroxyphenylacetic acid (DOPAC), a dopamine metabolite, in the CSF, suggesting increased dopamine activity.

In longitudinal research on humans, schizophrenia has been linked with exposure to several forms of prenatal maternal stress, including the death of the father during pregnancy (Huttunen and Niskanen 1978), unwanted pregnancy (controlling for maternal depression) (Myhrman et al. 1996), and exposure to war and disasters, such as the 1940 invasion of Holland (van Os and Selten 1998), the nuclear attack on Nagasaki, and tornadoes (reviewed in Koenig et al. 2002). Elevated rates of schizophrenia are also related to maternal depression during pregnancy (Jones et al. 1998) and maternal malnutrition, obesity, and infections (influenza, rubella). It is noteworthy that these maternal conditions are known to be associated with hypercortisolemia (Walker and Diforio 1997; Koenig et al. 2002). It has been hypothesized that a potential mechanism by which these exposures increase schizophrenia risk is through modification of the HPA axis and hence an increased responsivity to stress.

**Why Adolescence?**

Although the vulnerability to schizophrenia likely originates during fetal development, it is not until adolescence and early adulthood that the prodromal phase and first episode of psychosis typically emerge (Bunney and Bunney 1999). Many neuromaturational processes take place following the onset of puberty, and one or more of these may be related to the emergence of the prodromal phase of schizophrenia and the subsequent onset of psychosis.

Normal adolescents have a progressive decrease in gray matter, which may reflect synaptic reorganization, and an increase in white matter, which is consistent with myelination of cortical fiber pathways (Giedd et al. 1999). In addition, neuromaturation is apparent in functional activity, with evidence of enhanced activity in the frontal cortex (Thatcher et al. 1987; Anokhin et al. 2000), as well as decreases in metabolic demand (Chugani et al. 1987). Taken together, these findings evidence support the idea of greater cortical organization and functional efficiency with development. Furthermore, puberty is marked by hormonal surges and increased activation of the hypothalamic-pituitary-gonadal and HPA axes (Walker et al. 2001). These neural and hormonal changes may unmask a latent vulnerability to psychosis and schizophrenia. Myelination could lead to greater excitatory inputs that are unrestrained because of GABAergic dysfunction (Benes 2000). Also, cortisol may be neurotoxic to inhibitory GABAergic cells in the hippocampal formation, which may already be compromised from abnormal developmental processes.

**Baseline Cortisol as a Risk Factor for Psychosis in Prodromal Patients**

There is a diurnal rhythm to cortisol secretion, with a surge around the time of waking and then a steady decrease throughout the day (figure 2). Abnormality in the diurnal rhythm can consist of either elevated cortisol levels at any time of day or persistence in secretion, resulting in a less pronounced slope of decline and hence elevated cortisol levels later in the day. Studies have explored the associations of these disturbances with demographic and behavioral characteristics.

**Baseline Cortisol and Psychosocial Stress in Children.** Evidence suggests that, in children, relatively higher baseline cortisol values, especially in the morning, seem to be related to lower socioeconomic status (Lupien et al. 2000) as well as to disturbance in living situation. In a 9-year study in the Caribbean (Flinn and England 1997), mean cortisol levels were higher for children who lived with only their mother or lived with either half-siblings or more distant relatives. This could reflect chronic stress, the accumulation of more frequent acute stressors, or poor
Figure 2. Serum cortisol profiles for boys and girls during pubertal development.

Values shown are mean ± standard error of the mean. The areas under the curve (AUCs) for the girls were 4,383 ± 199; 4,642 ± 393; 3,694 ± 234; 3,809 ± 274; and 4,058 ± 375 at pubertal stages 1-5, respectively. The AUCs for the boys were 4,201 ± 110; 3,715 ± 123; 3,561 ± 219; 3,037 ± 219; and 3,662 ± 171 at pubertal stages 1-5, respectively. There was a significant difference (p < 0.05) between boys and girls at pubertal stage 2 (by Mann-Whitney U test). Reprinted with permission from Knutsson et al. (1997).

Baseline diurnal cortisol has marked intraindividual stability in normal children over an average of 1 year, consistent with a traitlike feature (Knutsson et al. 1997) that is independent of age, weight, height, and pubertal stage. The free cortisol response to awakening involves a mean cortisol increase of about 50 percent within the first 30 minutes after awakening (Wust et al. 2000). This free cortisol response also has remarkably high intraindividual stability over time, with correlations up to 0.63, and appears to be unrelated to age, use of oral contraceptives, smoking, time of awakening, sleep duration, or even use of an alarm clock.

Cortisol and Psychosis

Cross-Sectional Associations. HPA axis function has been linked to the expression of psychotic symptoms in psychiatric disorders. Among depressive disorders, psychotic depression is associated with a higher rate of dexamethasone nonsuppression than is depression in the absence of psychosis (Nelson and Davis 1997; Duval et al. 2000), and higher levels of baseline cortisol (Schatzberg et al. 1983). Among patients with PTSD, those with psychotic symptoms have higher levels of corticotropin releasing factor (CRF) in CSF than do those without psychotic symptoms, again suggesting that psychotic symptoms may be associated with heightened activity of the HPA axis (Sautter et al., in press). In patients with schizophrenia and other psychotic disorders, cortisol levels are positively correlated with ratings of positive, disorganized, and overall symptom severity (Walder et al. 2000).
HPA function may also be related to psychosis expression among individuals with equivalent genetic liability for psychosis. In a recently published study, concordance for neurohormones such as epinephrine, norepinephrine, and several dopamine metabolites was examined in monozygotic (MZ) twins discordant for psychosis (Walker et al. 2002). In healthy MZ twin pairs, these tend to be concordant, but in discordant MZ twin pairs, there was no concordance for epinephrine, norepinephrine, or cortisol. This finding suggests that the expression of psychotic disorders (as opposed to simple liability) is associated with functional changes in the noradrenergic systems and HPA axis.

Longitudinal Associations. Increases in endogenous and exogenous cortisol in humans are associated with heightened risk for psychosis. Psychosis can be the presenting symptom in Cushing’s disease (Saad et al. 1984; Gerson and Miclat 1985; Hirsch et al. 2000), and case reports indicate that there is a remission of psychosis in Cushing’s disease with correction of the endogenous hypercortisolemia (Johnson 1975; van der Lely et al. 1991; Chu et al. 2001). Steroid treatment may also lead to psychosis (Brown and Suppes 2000; Patten and Neutel 2000), which remits with lowering of the dose (Lee et al. 2001).

Longitudinal studies show a relationship between temporal fluctuations in cortisol and symptoms in psychotic patients. Sachar et al. (1970) measured daily urinary cortisol in four young adult patients over a 2- to 3-month period and found that cortisol levels were significantly higher (250%) immediately preceding psychotic episodes when compared with periods of recovery. Levels during episodes fell midway between the pre-episode and recovery periods. Similarly, Franzen (1971) withdrew medication from ten schizophrenia patients for 5 weeks and found that increases in cortisol release were associated with subsequent increases in psychotic symptoms. Cortisol levels are decreased with the successful treatment of psychosis with clozapine (Hatzimanolis et al. 1998; Markianos et al. 1999).

Could Elevated Cortisol in Psychosis Reflect Psychosocial Stress? Of interest, in a sample of inpatients admitted for an acute episode of psychosis, pretreatment plasma cortisol levels were correlated with the severity of recent stressors, even when controlling for demographic and clinical factors, such as age, sex, marital status, diagnosis, age of onset, and duration of psychotic symptoms. This finding suggests that the relationship between HPA function and psychotic symptoms could be initiated by experience of psychosocial stress (Mazure et al. 1997).

Psychosocial Stress as a Trigger for Psychosis

Stress is associated with relapse or exacerbation of a number of medical illnesses, such as asthma, ulcerative colitis, and multiple sclerosis (reviewed in Corcoran et al. 2001). It is associated with outcome in myocardial infarction, melanoma, and breast cancer (reviewed in Leserman et al. 1999). Of interest, in a prospective study, cumulative mean life events (and cumulative mean cortisol) were associated with conversion to AIDS among HIV-positive men, with an increase of 4 points on a life events scale reflecting a doubling of risk for AIDS (Leserman et al. 2000). Correspondingly, the risk for AIDS was doubled for every 5 microgram/deciliter increase in cortisol. The relationships between stress and cortisol with the onset of AIDS persisted even when controlling for a host of relevant factors, including baseline CD4 count and viral load, antiviral medication exposure, and health habits.

Stress can worsen symptoms and precipitate relapse across a wide range of psychiatric conditions, including postpartum psychosis, affective illness, and alcohol dependence (reviewed in Corcoran et al. 2001). Although the role of stress in psychosis onset has not yet been examined in prodromal patients, several studies have found a relationship between stress and relapse of psychosis.

Life Events and Relapse. Stress exposure, specifically life events, increases in the weeks to months leading up to relapse (Malla et al. 1990; Hultman et al. 1997). When patients are their own controls (relapse vs. baseline), or when “relapsing” patients are compared with “nonrelapsing” patients, an association of life events and relapse is observed (Ventura et al. 1989; Malla et al. 1990; Hultman et al. 1997). Schizophrenia patients have significantly more stressful life events during the 3 weeks preceding a relapse than they do during other time periods (Brown and Birley 1968; Day et al. 1987). This has been confirmed in prospective studies (Ventura et al. 1989). In a 1-year followup of schizophrenia patients, a proportional hazards regression model showed that life events made a significant cumulative contribution over time to the risk of relapse (Hirsch et al. 1996): 23 percent to 41 percent of the relapse risk could be attributed to life events, depending on the extent of exposure. Prospective studies reduce the problem of recall bias, although causality remains an issue, as symptoms may begin to exacerbate prior to relapse and may lead a patient to incur more life events (Ventura et al. 1989). Also, worsening symptoms may be a great source of stress, as psychotic and other symptoms can be frightening and interfere with functioning (Walker and Diforio 1997).
Coping and Antipsychotics. Coping strategies and antipsychotic medications may protect against stress-induced psychosis relapse in schizophrenia. In a prospective study, relapse was correlated with fewer cognitive resources and less coping ability only in the absence of major life events (Pallanti et al. 1997). Effective coping may act as a buffer between stressors and relapse (Hultman et al. 1997). As neuroleptics can lower HPA activity, it is expected that antipsychotic medications may protect against the psychotogenic effects of stress. In fact, among patients who relapsed in one study, those on medication experienced a significantly greater number of stressful life events prior to relapse than did those who were not on medication (Nuechterlein et al. 1992, 1994). These results suggest that neuroleptics may raise the threshold for psychosis, so that more stress is required to trigger relapse (Nuechterlein et al. 1994).

Daily Hassles and Expressed Emotion. In addition to life events, there are more subtle everyday factors that might be associated with illness, such as daily stressors or hassles (Fowles 1992; Norman and Malla 1993). Also, expressed emotion (EE), which refers to family members’ negative emotional reactions to patients, may be relevant as a stressor in psychosis relapse in schizophrenia (Nuechterlein et al. 1992). Schizophrenia patients returning to families with high criticism and emotional involvement levels have about a 50 percent chance of relapse, compared with 15 percent in patients returning to low-EE families (Vaughn and Leff 1976; Butzlaff and Hooley 1998). Family interventions designed to minimize EE are effective in preventing relapse (Leff et al. 1982; Leff 1994), and low EE can buffer the effects of stressful events (Nuechterlein et al. 1994). As with life events and psychosis, the direction of causality cannot be assumed as a patient’s symptoms and behavior likely affect the behavior of the family toward the patient (Fowles 1992). In fact, the bidirectionality of the patient/family interaction is now assumed (Barrowclough and Parle 1997).

Is the Connection Between Life Events and Psychosis Stronger Earlier in the Illness? Stressful events may be more relevant for the onset of psychosis than for relapse in schizophrenia patients, similar to what has been found in major depression (Ghaziuddin et al. 1990) and bipolar disorder (Post 1992). In a cross-sectional study of 32 male schizophrenia inpatients, those with fewer than four episodes had significantly more recent life events than did those with more episodes (Castine et al. 1998). There is a neurobiological basis for expecting that external stressors may have greater triggering potential for the first episode of psychosis than for relapse. Laruelle (2000) has proposed a model of sensitization of subcortical dopaminergic pathways in schizophrenia, which suggests a progressive enhancement of dopamine response under repeated stress exposure, such that provocation of the dopaminergic system by stress may be different in early schizophrenia. Laruelle (2000) theorizes that sensitization drives the prodromal and initial phases of illness in schizophrenia, with increases in subcortical dopamine activity culminating in the expression of psychosis. This sensitization is self-perpetuating and eventually becomes independent of the environmental factors responsible for its initiation. Sensitization is under maturational, genetic, and environmental influences—that is, perinatal anoxia and prenatal stress (reviewed in Laruelle 2000). Of note, in animals, sensitization is heterogeneous and state dependent, which is consistent for a process that may underlie psychotic symptoms in schizophrenia. An example of exogenous sensitization in humans is the stress-induced psychotic symptoms seen in individuals with a history of methamphetamine psychosis (Yui et al. 1999).

How to Study the HPA Axis

Glucocorticoids can be measured in CSF, urine, plasma, and saliva. Each of these measures has advantages and disadvantages. Plasma and serum samples can be assayed for CRH and ACTH, as well as cortisol, so that all levels of the HPA axis can be probed. As yet, this is not true for saliva, in that saliva assays for CRH and ACTH are not available. However, serum samples are highly labile and require immediate freezing, unlike salivary cortisol, which is more stable (Kirschbaum and Hellhammer 1994; Clements and Parker 1998). Plasma and serum samples may also be distorted by the HPA axis response to venipuncture. Serum sampling is not the method of choice in longitudinal studies, especially for children and adolescents, as studies show significant sample attrition for repeat phlebotomies, and the more impaired teens are more likely to decline further participation (Susman et al. 1997). Cortisol can also be measured in 24-hour collections of urine. However, many individuals are reluctant to collect urine over the period of a day, and it is difficult for researchers to assess whether all urine was in fact collected.

HPA activity can be measured under baseline or stress-induced conditions, as well as repeatedly over time to index changes. It should be kept in mind, however, that samples collected in the laboratory or the clinic do not necessarily represent “baseline” levels in the natural environment. This is especially true of the samples collected.
immediately following the individual's arrival in the research setting, as novelty augments HPA activity. It is therefore advisable to obtain multiple measures, including fluid samples collected after the research participant is acclimated to the setting.

Functional properties of the HPA axis can be tested by administering CRH or ACTH to determine the responsivity of the pituitary and adrenal glands, respectively. Sensitivity to GC-mediated negative feedback can also be tested using the synthetic glucocorticoid dexamethasone in the dexamethasone suppression test. Dexamethasone should suppress the HPA axis in normal individuals through negative feedback action. Individuals with impaired feedback will demonstrate no suppression, or an early release from suppression.

Salivary Cortisol Assessment. Among the simplest and most reliable ways to measure baseline and stress-induced HPA activity is through salivary cortisol assay, using radioimmunoassay, which has been employed as an index of the HPA axis in more than 400 studies (Silver et al. 1983; Schwartz et al. 1998; Netjek 2002. Saliva samples are typically obtained in specimen tubes, and a common method is to instruct subjects to place a cotton roll in their mouth on the order of minutes, until it is saturated. This is nonintrusive and generally well tolerated.

Salivary cortisol is a reliable indicator of free cortisol in plasma, which is considered to be the biologically active hormone. Salivary and serum cortisols have been correlated in both children and adults (Burke et al. 1985; Bober et al. 1988; Woodside et al. 1991). Saliva cortisols are also significantly correlated with 24-hour urine cortisols, as was demonstrated in a patient with Cushing’s disease who had daily salivary cortisol assessment and 24-hour urine samples for 725 days (Hermus et al. 1993).

Further, salivary cortisol levels are unaffected by salivary flow rate (Netjek 2002), and it appears that smoking, eating, consuming caffeine, consuming alcohol, and exercising strenuously have only short-term and very modest effects on salivary cortisol levels (Snyth et al. 1998). Salivary cortisol is responsive to stress exposure and demonstrates the expected circadian rhythm.

The time frame of the response of salivary cortisol secretion to stressors ranges from minutes to hours. Activation of hypothalamic paraventricular neurons leads to ACTH secretion by the anterior pituitary within 10 minutes. Then it takes 15 to 20 minutes after the onset of ACTH release for cortisol secreted by the adrenal cortex to reach the acinar cells of the parotid gland. Peak post-stimulus salivary cortisol has been observed to occur about 20 to 30 minutes after stress onset (Kirschbaum and Hellhammer 2000). Salivary cortisol has a half-life of approximately 1 hour (van Eck et al. 1996), and cortisol levels return to baseline within 1 to 2 hours after the termination of a stressor.

Because activity of the HPA axis shows a diurnal rhythm, it is critical to consider time of day in collection of samples for assay (Halbreich et. al. 1985a, 1985b), and efforts should be made to standardize time of collection across subjects. Cortisol is highest in the morning and then gradually declines over the course of a day, with a brief postprandial small peak after lunchtime. Multiple sampling throughout the day can illustrate the diurnal pattern. Psychopathology is often associated with a less steep decline and hence elevated cortisol values in the afternoon and evening. Although traditionally it has been recommended that baseline diurnal cortisol rhythm be assessed over a few days, high interreliability of cortisol levels across 3 days was demonstrated in a study of normal children and children with PTSD, suggesting that 1 day of assessment may be sufficient (Carrion et al. 2002).

There are several variables that can influence cortisol secretion, and efforts should be made to document or standardize in research protocols, including age, gender, season, phase of menstrual cycle, sleep-wake cycle patterns and eating, activity, caffeine use, and cigarette smoking. Salivary cortisol levels should be obtained while in a sitting position, as postural changes can alter measures.

Research Design and Statistical Approaches

Survival Analysis. A prospective cohort study can be conducted of prodromal patients, with the sample stratified into above-median and below-median baseline levels of cortisol. This can be a proxy for exposure, and rates of “failure” (conversion to psychosis) can be estimated for the two groups. The data for subjects who either drop out of the study or complete the study without conversion to psychosis would be considered “censored.” Kaplan-Meier curves could be compared for the two groups (low-cortisol and high-cortisol) and log rank tests would be used to determine whether they had significantly different risks for psychosis. The hypothesis that intervening life events are associated with the onset of psychosis also can be addressed through survival analysis techniques, specifically through the use of Cox proportional hazards models. Survival analyses can include intermediate measurements of life event exposure and cortisol measures. These can be entered into the model as cumulative means, as in a study of stress and cortisol in HIV+ patients (Leserman et al. 2000), if it is hypothesized that cumulative exposure is relevant to psychosis risk, which is consistent with McEwen’s concept of allostasis. Alternatively, if major life events are seen as triggers, the occurrence of any major life events at a current or previous time point could be entered into the model as a potential variable of import. Using survival analyses and Cox proportional
hazards models, potential confounds such as drug use and medication exposure can be incorporated into statistical models.

**Time Series Analysis and Special Statistical Methods for Longitudinal Data.** Although survival analysis is very useful for studying predictors of outcome in a cohort, it cannot be used to analyze dynamic processes and interplay among multiple factors over time. In the following paragraphs, we will briefly describe analytic procedures that are ideally suited for studying biobehavioral processes in the prodrome, such as those involving psychosocial stress exposure, HPA axis activity, and the development of psychotic symptoms. These procedures fall under the general rubric of time series analysis, which is used to test hypotheses based on temporal data involving measurement of the same variable(s) at multiple time points (Boeker et al. 2002). Time series analysis can be applied to research designs involving one or more variables, and with single subjects or multiple subjects.

When applied to single variables, time series analysis can address questions about temporal trends in the data, including linear and nonlinear aspects. When applied to multiple variables, the concomitant time series approach answers questions about the relationships among variables measured simultaneously, or at successive time points. When data from multiple subjects are available, moderating variables can be incorporated to test for the effects of individual differences, demographics, or clinical factors. In this article, we have repeatedly noted that in cross-sectional and even longitudinal studies, it can be difficult to discern causal relationships among variables. As causal relationships can be inferred through the evaluation of temporal sequence, time series analysis is a useful way to begin to address this question.

To examine relationships of HPA activity, psychosocial stress, and the development of psychotic symptoms in the prodrome, concomitant time series analysis offers major advantages. It can provide information about the interrelations among variables while taking into consideration linear and nonlinear trends that can obscure the true relation between two factors over time. Concomitant time-series methods correct for serial dependencies in time series data, such as autocorrelation and linear trending, which spuriously inflate the cross-series association and bias standard errors for significance tests. Autocorrelation refers to the fact that, in repeated measures within individuals, observations are more similar to one another than would occur by chance. If autocorrelation is not accounted for, there would be an artificial deflation in error variance, an increase in the test statistic, and hence an increase in the probability of making a type I error. As for linear trending, this is demonstrated by the positive correlation observed by two independent variables that both happen to have upward, parallel temporal trends.

Effect sizes can be derived for the relationship between two variables in a time series. The within-person effect sizes would typically be standardized regression coefficients from time series regression equations. The effect sizes can then be subjected to further analyses to test for differences among individuals or groups. Researchers have employed concomitant time series procedures to study individual differences in relations among variables that are hypothesized to be causally interrelated. In prodromal subjects, this procedure would allow researchers to identify individuals who seem to be more stress-sensitive, such that they show a stronger association between stressful events and positive symptoms. Similarly, this strategy would allow the investigator to answer questions about group or individual differences in the strength of the relation between psychosocial stress and positive symptoms—that is, are prodromal patients with more elevated baseline cortisol levels more likely to develop psychotic symptoms after stress exposure?

Biological processes occur in real time, and behavioral effects are not expected to be immediate. Cross-correlational techniques are often used in conjunction with time series analysis to explore delayed effects. The cross-correlation coefficient indexes the strength of the simple linear relationship (if any) between successively time-lagged measurements in two paired and equally spaced time series (Veldhuis et al. 1994). This allows the investigator to answer questions about the temporally lagged effects of one factor on another. For example, increases in cortisol may be associated with the emergence of psychosis. If the increase in cortisol precedes the worsening of symptoms leading to psychosis onset, it may be causal. However, if cortisol increases follow the worsening of symptoms leading to psychosis, it may reflect the stress of having psychotic symptoms. Likewise, testing cross-correlations among time-lagged measures of life events and symptoms can help determine whether more life events precede (and then may trigger) psychotic symptoms, or if increased rates of life events follow the worsening of psychotic symptoms.

Cross-correlation is performed for paired variables considered simultaneously (zero time lag) and at various time lags between the sampling intervals. Imagine a study in which the researchers measure levels of cortisol and psychotic symptoms weekly, over a period of 3 months. In the data analysis, cortisol levels in time series A can be correlated pairwise with psychotic symptoms (series B) measured simultaneously (zero lag), later (positive lag), or earlier (negative lag). Error estimates for the cross-correlation coefficients can be derived from the pooled intrasam-
ple variances, based on the total series length \((n)\) and the number of lag units \((k)\) considered. The statistical significance of a coefficient at any given lag time can be tested against the null hypothesis that the \(z\) score distribution of coefficient values is normal with a mean of zero and a standard deviation of one with a statistic, such as the Kolmogorov-Smirnov.

As with any statistical procedure, the required number of subjects and observations will depend upon the nature of the data and the hypotheses to be tested. For some time series applications, there is only a single subject. This would be the case if the researcher is interested in testing predictions about the temporal trends in a particular variable (e.g., symptoms), or the relation among variables (e.g., symptoms and stress) over time. The number of observations required depends upon the reliability of the measure and the nature of the expected temporal trends. For variables that can be measured with a fairly high level of reliability (i.e., low error variance), fewer observations are needed. For example, biological variables from assays may be more reliable than self-report measures of symptoms or stress. The predicted temporal pattern will also play a role in determining the number of observations. As a case in point, if a variable of interest is expected to show a monthly cycle of fluctuation, daily sampling for at least 30 days would be necessary. In one study of a single subject, we detected significant lagged relations between symptoms and stress with only 30 observations. Of course, the more observations available, the greater the statistical power for detecting temporal patterns and lagged relationships.

When the investigator is interested in applying time series analysis to the study of group or individual differences, the required number of subjects can be determined by a power analysis. Again, as with other parametric procedures, the sample size needed for time series will be largely determined by the reliability of the dependent variable and the frequency with which it is measured.

### Conclusion

Our conceptualization of the diathesis-stress model of schizophrenia has been transformed by the revolution in behavioral neuroscience. Experimental research on animals has elucidated the pervasive effects of stress and adrenal hormones on brain structure and function. Gradually accumulating findings from studies of human subjects indicate that these effects extend across species and that stress may have relevance for a range of human disorders, both physical and mental. Understanding the role of stress as a potential trigger in schizophrenia, with a full appreciation of what basic science tells us, has tremendous implications for developing novel pharmacologic and nonpharmacologic approaches to intervention. As it stands, antipsychotics are the only medications that have been systematically tested in prodromal patients. In one published double-blind placebo-controlled study, olanzapine led to improvement of subclinical positive symptoms over 6 to 8 weeks but was also associated with a mean weight gain of ten pounds (Woods et al. 2003). Clearly, there is a need for consideration of medications that may have fewer side effects. In the future, for example, CRH receptor antagonists, such as R121919 (Heinrichs and Tache 2001), may be candidate treatments in the schizophrenia prodrome.

At the same time, it is important that research on the biobehavioral course of the prodromal process be expanded. In particular, there is a need for longitudinal studies that combine neuroendocrine and behavioral measures, so that the biobehavioral and interactional processes can be charted. There is strong empirical evidence to support the notion that the biological response to stress, especially activation of the HPA axis, is capable of triggering a downstream cascade of neurochemical events that can precipitate or exacerbate psychosis. If researchers are able to shed greater light on this chain of events, it may be possible to develop effective strategies for preventive intervention.

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