Published in final edited form as:
CNS Spectr. 2002 January ; 7(1): 33–42.

Could Stress Cause Psychosis in Individuals Vulnerable to Schizophrenia?

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Abstract

It has long been considered that psychosocial stress plays a role in the expression of symptoms in schizophrenia (SZ), as it interacts with latent neural vulnerability that stems from genetic liability and early environmental insult. Advances in the understanding of the neurobiology of the stress cascade in both animal and human studies lead to a plausible model by which this interaction may occur: through neurotoxic effects on the hippocampus that may involve synaptic remodeling. Of late, the neurodevelopmental model of SZ etiology has been favored. But an elaboration of this schema that credits the impact of postnatal events and considers a role for neurodegenerative changes may be more plausible, given the evidence for gene-environment interaction in SZ expression and progressive structural changes observed with magnetic resonance imaging. Furthermore, new insights into nongliotic neurotoxic effects such as apoptosis, failure of neurogenesis, and changes in circuitry lead to an expansion of the time frame in which environmental effects may mediate expression of SZ symptoms.

INTRODUCTION

Decades ago there was an exploration of the role of life events and stress as etiologic factors in schizophrenia (SZ). Many studies found that patients with first-episode psychosis had a preponderance of recent life events as compared with normals. The climate then was to emphasize psychosocial factors in the development of a number of psychiatric disorders, especially SZ. This too frequently led to the blaming of families and the labeling of mothers as "schizophrenogenic." There was an appropriate backlash to this, with the emergence of activism on the part of patients and their families to destigmatize mental illness and recognize psychiatric disorders as medical and biological disorders.

Since then, powerful technologies have been developed to examine the biological correlates of psychiatric diseases such as SZ, including structural and functional imaging, elucidation of the human genome, and modeling of pathology in animals. Evidence has accumulated in support of biological hypotheses of SZ pathophysiology, such as abnormalities in dopaminergic, glutamatergic,[1] and γ-aminobutyric acid (GABA)[2] function, or an integration of abnormal neurotransmission in all three.[3] Also, disruption of sensory gating[4] has been

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identified as an endophenotype in SZ and disruptions in cortical connectivity through abnormal synaptic pruning[5] have been theorized to be key to the disorder.

With these advances in neuroscience, it makes sense to reevaluate stress as a potential etiologic factor in a host of disorders, including SZ, since the intricate neurobiology of the stress cascade has been elucidated by prominent researchers such as McEwen and Sapolsky. SZ is a heterogeneous illness; it is likely that stressful life events and trauma are neither necessary nor sufficient to cause it. And if stress does play a role in SZ, it is certainly not specific to the illness. But it may be that the vulnerability to SZ entails a sensitivity to the effects of trauma and stressful life events, and that the stress cascade may in some cases reveal a latent susceptibility to psychosis and perhaps also contribute to the cognitive impairments associated with SZ.

In this paper we will (1) describe the basic scientific work on the neurobiological effects of stress and cortisol; (2) illustrate findings that suggest similar mechanisms are at work in SZ; and (3) evaluate the neurodevelopmental and neuropathologic hypotheses of SZ etiology, with sections on gene-environment studies, magnetic resonance imaging (MRI) volumetrics, biologic plausibility, and synaptic pruning hypotheses.

THE STRESS CASCADE: ANIMAL STUDIES

An appreciation of the vulnerability of the hippocampus to stress arose from the postmortem study of vervet monkeys who had been caged in overcrowded conditions and who subsequently died. Upon autopsy, these animals were found to have extensive cell death in the hippocampus.[6] In experimental conditions, Sapolsky and colleagues[7,8] found similar neurotoxicity to the hippocampus as a consequence of severe stress in rodent and primate models, with both necrosis and apoptosis observed. McEwen and colleagues[9,10] expanded upon these findings, noting that across species less severe but chronic stress led to specific atrophy of apical dendrites in the CA3 region of the hippocampus. This same atrophy has been demonstrated in other regions of the hippocampus, specifically CA1 and the dentate gyrus, although to a lesser degree.[11] There is some evidence that this specific mechanism may also operate in the amygdala, but the prefrontal cortex remains unexplored (B. McEwen, PhD, personal communication, 2000).

This neurotoxic process (the stress-induced atrophy of dendrites in regions of the hippocampus) was determined to be mediated through the effects of glucocorticoids, as high doses of cortisol had the same effects as chronic restraint stress. McEwen and colleagues[12] also found that pretreatment with a number of agents protected the hippocampus against these toxic effects of stress and cortisol. These agents include phenytoin, benzodiazepines, and, interestingly, tianeptine (a serotonin [5-HT] reuptake enhancer marketed in France and now available in other countries, such as Venezuela). Their known pharmacologic actions shed some light on the putative biochemical mechanisms of stress-induced changes in the hippocampus. As phenytoin blocks glutamate release and antagonizes sodium channels, this was thought to be the mechanism for neurotoxicity, and further studies have pointed to the role of glutamate.[13,14] Benzodiazepines likely work through their interactions with GABA receptors. Interestingly, tianeptine blocks toxicity but selective serotonin reuptake inhibitors do not, implicating 5-HT as an active factor in stress-induced dendritic atrophy.

Of note, although phenytoin can lower glucocorticoid levels through its activation of metabolizing hepatic enzymes, this mechanism is unlikely to explain its neuroprotective effects, as such effects persist even in the context of very high levels of cortisol. Furthermore, phenytoin likely has a specific regional protective effect in the brain, as it fails to prevent stress-induced changes in body weight and adrenal weight, as well as glucocorticoid-induced reduction of the thymus.

Much of the neurochemistry underlying the neurotoxicity of stress and glucocorticoids to the hippocampus has been elaborated. High levels of cortisol accelerate energy loss[15] and inhibit glucose transport,[16] causing the hippocampus to be energetically limited and vulnerable to damage. Excitatory amino acids, particularly glutamate, accumulate in the synapse, where they activate glutamate receptors and pathologically mobilize free calcium in the postsynaptic neuron.

Of further interest, the neurotoxic effects of stress and cortisol on the hippocampus in rats is reflected in cognitive and behavioral changes, specifically memory deficits such as poor maze performance. Under stress, the degree of hippocampal cell loss in rats is correlated with cognitive deficits: the degree of impairment in new learning of maze escape behaviors is related to the extent of damage to the CA3 region of the hippocampus.[17] These findings, along with neuroanatomic studies[18,19] of patients with temporal lobe epilepsy, confirm that the hippocampus is vital to short-term memory.

THE STRESS CASCADE: TRANSLATION TO HUMAN STUDIES

Allostasis

Emphasizing translational research, McEwen[20] is interested in studying the implications in humans of his work on the biologic mechanisms of the stress cascade in animals. He has coined the phrase “allostatic load” to describe how an organism changes and adapts to chronic stress. Allostasis represents a new reorganization and not simply the maintenance of a condition, which would better be described by the term “homeostasis.” Allostasis is “maintaining stability through change” and describes adaptation rather than a return to a set point. Homeostasis describes factors such as oxygen tension and pH, whereas allostasis can describe the autonomic nervous system (variations in heart rate and blood pressure) and hormonal fluctuations in the hypothalamic-pituitary-adrenal (HPA) axis. The brain adapts to chronic stress through the interaction of local neurotransmitters and systemic hormones to produce structural and functional changes, which include the suppression of neurogenesis in the dentate gyrus and remodeling of dendrites in the hippocampus. Permanent damage to the hippocampus only occurs when stress overwhelms the organism’s resources for adaptation and stress hormones are excessive. Synaptic remodeling that results from less severe stress is in part reversible. Adaptive strategies have a cost to the body either when they are called upon too often or when they are inefficiently managed—this is what is meant by “allostatic load.” An association between stress and illness is not unique to SZ, nor to psychiatric illnesses per se. For example, psychological stress is associated with relapse or exacerbation in a variety of medical illnesses, including ulcerative colitis, genital herpes, asthma, vaginal candidiasis, multiple sclerosis, psoriasis, and “tension-type” headaches.[21] A likely model for these illnesses and SZ is that psychological stress potentiates expression of illness in individuals who are at risk for illness onset or relapse. That is, an underlying vulnerability (exposure to infectious agents, reactive airways, abnormal neural substrate, etc.) interacts with “allostatic load” to lead to disease expression.

EVIDENCE OF THE STRESS CASCADE IN HUMAN CONDITIONS

McEwen’s work has inspired a number of researchers to explore whether these elements (stress→cortisol→hippocampal toxicity→memory deficits) may play a role in a number of human conditions, including Cushing’s disease, normal human aging, and psychiatric disorders such as posttraumatic stress disorder (PTSD), depression, and SZ. In humans, functioning of the HPA axis may be evaluated in many ways, including (1) basal serum, salivary, or urinary levels of cortisol and (2) challenge tests, among the simplest being the dexamethasone suppression test (DST), which assesses the negative feedback of the HPA axis by the

corticosteroid dexamethasone, which normally leads to a lowering of endogenous cortisol levels.

Cushing's disease is a medical condition in humans that is analogous to the experimental exposure of animals to glucocorticoids, as it is marked by high levels of endogenously released cortisol. In Cushing's disease, hippocampal volumes are inversely correlated with plasma cortisol levels.[22] As in other disorders, these reductions in hippocampal volumes are also correlated with lower scores in verbal memory.

Healthy aging individuals with increasing/high cortisol levels (measured annually) were found to have impairments in explicit memory.[23] In an analogous study, another group with increasing/high cortisol was found to have a 14% reduction in hippocampal volume; the annual rate of cortisol increase correlated negatively with hippocampal volume.[24] Hippocampal size is also inversely related to delayed memory performance in normal human aging.[25]

In PTSD, combat veterans have deficits in hippocampus-dependent memory measures like the Wechsler Memory Scale and the Selective Reminding Test (these deficits correlate with reduction in right hippocampus volume).[26,27] Adult survivors of childhood abuse also have similar memory deficits and decrements in hippocampal size.[28]

In depression, an abnormal DST is common and has been found to be inversely correlated with hippocampal size.[29] Also, in depression, baseline levels of cortisol in the urine are correlated with cognitive impairment.[30] Middle-aged patients with chronic refractory depression have smaller hippocampi than do age-matched healthy controls,[31] and among depressed patients the total lifetime duration of depression (but not age) correlates with smaller bilateral hippocampal volumes and lower verbal memory scores.[32] Patients with depression have a statistically significant 16% smaller left hippocampus than controls.[33] These volumetric studies suggest either that depressive episodes are toxic to the hippocampus (perhaps through cortisol) or that individuals with smaller hippocampi are more vulnerable to developing depression.

Of interest, psychosis is a common phenomenon in the conditions described above (except of course for normal human aging) and psychotic symptoms in these conditions have been linked to serum cortisol levels. For example, there are case reports of psychosis occurring in Cushing's disease that remits with lowering of the endogenous hypercortisolemia by treatments such as cortisol receptor antagonists, like mifepristone,[34,35] and adrenalectomy.[36] In fact, psychosis is the presenting symptom in some cases of Cushing's disease.[37-39] Exogeneous corticosteroid treatment for a number of disorders, such as asthma[40] and inflammatory bowel disease,[41] may also lead to psychosis,[42,43] which can likewise remit with lowering of the dose of corticosteroids.[40] PTSD, a psychiatric illness defined at least in part by the occurrence of stress and trauma, has been found to have rates of psychosis as high as 40%.[44] Depressive episodes are frequently accompanied by psychotic symptoms. In fact, a meta-analysis of 14 studies demonstrated that dexamethasone nonsuppresssion is significantly more common in cases of major depression with psychosis than in cases without psychosis.[45] Several of the studies reviewed, such as one by Schatzberg and colleagues,[46] found higher levels of cortisol in major depression with psychotic features. Newer reports confirm this finding of significant rates of dexamethasone non-suppression in major depression with psychosis.[47]

STRESS AND SCHIZOPHRENIA

These key elements of the stress cascade—stress, cortisol, hippocampus, and cognition—have all been found to be abnormal in SZ. Further, associations have been found among these elements in SZ. Therefore, it is plausible that the stress cascade plays a role in the expression of SZ.

Stress

An early study found that 46% of 50 patients with acute-onset SZ had been exposed to stressful life events in the preceding 3 months as compared to only 14% of 325 controls; the difference was most pronounced in the 3 weeks leading up to hospitalization.[48] A meta-analysis of the literature showed significantly higher incidence of recent life events in SZ patients as compared with healthy controls in 43% of all studies reviewed; it was noted that stressors and severity of symptoms covaried over time in SZ.[49]

Evidence of an association between life events and SZ symptoms does not necessarily imply causation. It may be that simply by virtue of having SZ (or vulnerability to SZ) an individual is more prone to experience major life events. However, when patients are their own controls (relapse versus baseline) or when relapsing patients are compared with non-relapsing patients, an association of life events and relapse persists.[50-53] A preponderance of life events has been found in the weeks to months leading up to relapse.[50,53] Of interest, in a prospective study Sachar[54] found that cortisol levels increased by 250% immediately preceding psychotic exacerbation and then decreased to a level between that of preepisode and recovery.

Cortisol

Studies demonstrate that diurnal rhythms of cortisol are disrupted in SZ, with the common finding that cortisol remains abnormally elevated in the late evening.[55] Basal cortisol levels have been found to be inversely correlated with memory and frontal tasks—both for SZ patients and controls.[56] Cortisol regulation is also disrupted in a subset of patients. A meta-analysis of 46 studies yielded an overall rate of 26.4% of DST nonsuppression in SZ as compared with 5% in controls.[57] In SZ, DST nonsuppression has been linked to negative and cognitive symptoms, but not to depressive symptoms.

The Hippocampus

There is abundant evidence that the hippocampus is abnormal in SZ. A meta-analysis of 18 studies showed a bilateral reduction of volume in the hippocampus of 4%.[58] A number of investigators have reported that hippocampal volumes in SZ are inversely correlated with measures of memory.[59-61] Magnetic resonance spectroscopy (MRS) studies suggest that neuronal integrity is compromised in the hippocampus in SZ, as low *N*-acetyl-aspartate (NAA) has been consistently found.[62,63] Positron emission tomography studies also implicate the hippocampus as a site related to hallucinations. [64] Postmortem studies provide evidence that there is synaptic and hence circuitry abnormalities in both the hippocampus and the prefrontal cortex.[65] Intriguingly, cognitive and MRI volumetric assessments of twins discordant for SZ suggest that hippocampal abnormality is more prevalent in the affected twin, suggesting nongenetic influences.[66-68]

Cognition: Hippocampus-Dependent Explicit Memory

A meta-analysis of 70 studies that examined cognition in SZ showed a consistent moderate-to-large effect size across studies for memory impairment, specifically recall. Impairment was present in hippocampus-dependent verbal and nonverbal memory, both immediate and delayed.[69] Explicit memory (which is hippocampus-dependent) is selectively and more severely impaired than other cognitive domains in SZ, including in first-episode patients, who have a selective deficit in learning and memory, against a background of diffuse dysfunction.[70]

SCHIZOPHRENIA: EARLY OR PROGRESSIVE NEURODEVELOPMENTAL DISORDER?

The consideration of postnatal stress as a factor in SZ etiology and expression is counterintuitive to the prevailing early neurodevelopmental hypothesis of SZ. In this section, the strengths and weaknesses of this hypothesis will be explored along with evidence that supports the role of later events in SZ risk.

Do Early Processes Lead to Schizophrenia Expression or Simply Schizophrenia Vulnerability? The Possibility of an Additional Postnatal Hit

The leading hypothesis of SZ etiology is that SZ is a neurodevelopmental disorder in which the abnormality is established by processes that occur either prenatally or around the time of birth. Certainly, the extensive literature linking SZ risk to genetic factors, prenatal infectious exposures, and obstetric complications clearly implicates early processes in the later development of SZ. Also, the demonstration of a number of abnormalities in children who will go on to develop SZ—neuromotor, attentional, and behavioral—makes it clear that early abnormal neurodevelopmental processes play a role in SZ risk. Although these risk factors and phenotypic variables are clearly related to SZ etiology, they may not be sufficient to cause the illness. About 15% of children of individuals with SZ go on to develop the illness themselves, which means that 85% do not. An important role for environmental factors (prenatal or postnatal) is highlighted by mean SZ concordance rates of only 48% in identical twins and equivalent risks of SZ in offspring of discordant monozygotic twins.[71] Plus, neither early exposures nor phenotypic markers are specific for SZ. Both prenatal infectious exposures and obstetric complications have been linked to other disorders: prenatal rubella is associated not only with SZ but also with mental retardation. And the very early phenotypic variables (ie, clumsiness, poor attention, shyness) associated with later SZ are nonspecific. It may be that the aforementioned risk factors and phenotypic variables may be more related to SZ vulnerability and that, at least for some individuals, an additional postnatal hit is necessary for disease expression.

Evidence That Postnatal Events Increase Risk for Schizophrenia, Including Gene-Environment Interactions

In fact, postnatal events have been associated with increased SZ risk, including rearing environment, separation from a parent, and traumatic brain injury (TBI).[72] High-risk children are more likely to develop SZ if they are exposed to parental maltreatment or live in institutional settings.[73,74] The adopted children of affected biological mothers are similarly more likely to develop SZ if their adoptive families are “dysfunctional.”[75] In 1997, Wahlberg and colleagues[76] determined that biological children of mothers with SZ were more likely to develop the illness themselves if their adoptive families had “communication deviance.” Furthermore, patients with SZ have been found to have a 4-fold increased rate of early parental loss (death or separation) compared to controls, particularly if parental loss occurred before 9 years of age.[77] (Of note, the odds ratio of approximately 4 was similar to that for bipolar disorder and depression, suggesting a nonspecific effect of psychosocial stress interacting with vulnerabilities to different psychiatric illnesses). As for TBI, among members of SZ pedigrees, who presumably have high genetic vulnerability, TBI further increased their risk for SZ by 2.89-fold.[78]

It can be argued that these associations of SZ expression with postnatal events do not necessarily imply etiology. For example, odd children may elicit changes in their rearing environment, pre-SZ individuals may be more likely to incur TBI because of motor incoordination, and parental loss may reflect genetic vulnerability that a parent and child share. However, in our studies of SZ and TBI we have found that patients with prior TBI had better

cognition than those who did not,[79] which suggests that some SZ patients with a history of TBI may not have developed the illness had they not incurred the TBI. TBI may be a postnatal hit in some cases of SZ.

Neuroanatomic Evidence for Schizophrenia as a Progressive Neurodevelopmental Disorder

There are now a host of longitudinal MRI volumetric studies that demonstrate that an active, ongoing process is occurring beyond the onset of psychosis in at least a subset of SZ patients, and perhaps prior to onset as well. The most consistent finding in longitudinal studies of first-episode patients is ventricular enlargement in both childhood-onset SZ[80] and adult-onset SZ.[81-84] Longitudinal reduction in brain volumes for first-episode patients (as compared with controls) has been observed for total brain,[84] frontal lobes[85] and the hippocampus.[86] Also of interest, preliminary evidence suggests that neurodegenerative changes may occur shortly before psychosis onset. Although both first-episode and chronic SZ patients have been found to have smaller bilateral hippocampal volumes than normal controls, one study found that high-risk patients do not have smaller hippocampi, including those that went on to develop psychosis.[87] One longitudinal study has found that high-risk patients who went on to develop psychosis had larger volumes when they were at risk and smaller hippocampal volumes after psychosis onset. In sum, the observation of progressive changes in the brain in new-onset SZ makes a simple, static early neurodevelopmental lesion model unlikely.

Neuropathologic Evidence for Schizophrenia as a Progressive Neurodevelopmental Disorder

Arguments for the early neurodevelopmental hypothesis include the finding that gliosis is rarely found in postmortem studies of SZ, and that since gliosis occurs only after the second trimester in humans, the primary abnormal events in SZ must have occurred before this time. However, we now know that there are many mechanisms of postnatal neuroplasticity that have no relationship to gliosis, including apoptosis, synaptic pruning/growth, neurogenesis (or its failure), and myelination/demyelination. Margolis and colleagues[88] have suggested that SZ could result from a “graded apoptosis.” Apoptosis, or programmed cell death, is initiated by caspases, which are activated by excitatory amino acids, such as glutamate, as well as calcium influx. Activation of caspases can also lead to synaptic loss and remodeling.[89] The stress cascade is known to affect both synaptic modeling and neurogenesis in the hippocampal formation, so it could have late (or early) effects in SZ that also would not result in gliosis.

Stress and the Synaptic Pruning Hypothesis of Schizophrenia

In SZ there is reduced neuropil, which implicates abnormalities in axons, dendrites, and synapses[46] that could occur at any stage of development, without accompanying gliosis. In fact, a leading theory of SZ pathophysiology is the theory of abnormal synaptic pruning, first articulated by Feinberg in 1982.[90] Support for the “developmentally reduced synaptic connectivity” hypothesis of SZ etiology comes from both computer modeling[5] and neuropathologic findings.[91] Stress could plausibly reduce synapses through its effects on dendrites of pyramidal cells in the hippocampus.

Arguments Against the Role of Stress in Schizophrenia Pathophysiology

Leaders in the field of SZ research have considered the idea that stress could contribute to SZ symptoms through synaptic remodeling in the hippocampus, given the consistent finding of reduced size of pyramidal neurons, which could result from the effects of glucocorticoids on neuropil. In 1999, Weinberger[92] considered and rejected this idea, arguing that SZ is not characterized by gliosis, dramatic reduction of the hippocampus, cortisol abnormalities, or increased expression of the NR1 subunit of the *N*-methyl-D-aspartate receptor (which can be seen with stress). In fact, stress-induced dendritic atrophy can occur unaccompanied by gliosis

or dramatic volume reductions of the hippocampus,[93] cortisol abnormalities are seen in a subset of patients with this heterogeneous disorder,[21] and NR1 "knockdowns" in mice provide a convincing animal model of SZ[94] (so that *N*-methyl-D-aspartate receptor subunit abnormality may be a primary feature of SZ that would not change with stress).

CONCLUSION

The prevailing hypothesis of SZ etiology is that it is primarily an early neurodevelopmental disorder. However, the heterogeneity of the illness, its long latency to expression, and its fluctuating course suggest that SZ may be a progressive neurodevelopmental disorder in which early pathologic factors, such as genetic vulnerability, prenatal insults, and obstetric complications, create an abnormal neurobiological substrate that is more vulnerable to the development of SZ symptoms. Events that may trigger actual onset of SZ include both (1) maturational processes, such as programmed cell death and synaptic remodeling, and (2) postnatal environmental insults, such as psychosocial stress, TBI, and perhaps even substance abuse. A mechanism by which development unmasks latent vulnerability is plausible, and has its correlates in other brain functions, such as vision, in which later cortical development can mediate the expression of an initial insult. For example, deprivation of patterned visual input in human infants, who can only detect global contour but little detail, leads to later deficits in the adult-like expertise in processing of faces.[95] However, there is also evidence that postnatal environmental factors increase the risk of SZ, as has been reviewed in this paper. It is not parsimonious to assume that a brain that is vulnerable to developing SZ is a brain that is immune to environmental insults that may plausibly increase that risk. Lieberman[96] argues that the neurodevelopmental theory, taken to its logical extreme, suggests both inevitability and therapeutic nihilism, which he has phrased as "doomed from the womb."

Lieberman[96] has proposed instead that SZ may result both from early neurodevelopmental events and later limited neurodegenerative processes, which may be most active in the early stages of illness and associated with the onset of psychotic symptoms. This would be consistent with the findings of progressive ventricular enlargement and ongoing reduction of brain volumes in a subset of patients with SZ. An understanding of the neuropathologic mechanisms occurring with the onset of psychosis (and concurrent cognitive symptoms) and the roles of both developmental processes and environmental factors in this process is key to developing novel treatment strategies, both pharmacologic and nonpharmacologic.

In this paper, we have presented a model whereby stress can play a role in SZ pathophysiology through its effects on synaptic organization and cortical connectivity; it should be noted, however, that other mechanisms may be at work. For example, stress may simply lead to psychosis through the activation of dopaminergic transmission, a theory advanced by Schatzberg in the 1980s.[97] In healthy individuals, cortisol has been found to increase serum levels of homovanillic acid, a key dopamine metabolite.[98] Walker[99] has reported that cortisol increases dopamine metabolism in the nucleus accumbens and raises plasma dopamine metabolites, and hypothesizes that this may be a mechanism whereby stress precipitates psychosis. In an animal model of SZ, rats with neonatal hippocampal excitotoxic damage show greatly increased mesolimbic release of dopamine in response to stress.[100] Also, stress precipitates flashbacks to psychosis in individuals with a history of methamphetamine psychosis.[101]

Another mechanism by which stress may contribute to SZ pathophysiology is through excitotoxic injury to vulnerable inhibitory GABA-ergic interneurons in the hippocampus, a model advanced by Benes in 1999.[102] Interestingly, it has been proposed that *N*-methyl-D-aspartate receptor hypofunction could lead to reduced GABA transmission and thus enhanced

glutamatergic excitotoxicity that contributes to SZ.[103] The effects of stress could also be mediated by excitatory inputs of the amygdala to the hippocampus.[2]

It may be that early neurodevelopmental events or genetic liability create a sensitivity to stress, and that this may be an important component of vulnerability to SZ. Mednick and Schulsinger[104] found that environmental factors such as early parental separation and severe social disruption during pregnancy were associated with later SZ risk in offspring. Huttunen and Niskanen[105] also found that maternal stress was linked to later SZ risk. Mednick and colleagues[106] studied a cohort of children in Mauritius who had a high genetic risk of SZ and found that autonomic nervous system abnormalities were predictive of later serious mental illness. Later studies have confirmed the presence of failure of habituation of autonomic nervous system activity and abnormal skin conductance in patients and individuals either genetically or clinically at risk.[107,108] In another study, Mednick and colleagues found that early environmental enrichment was associated with improved psychophysiologic orienting and arousal mechanisms 6-8 years later in children, demonstrating that these variables, although being at least partly genetic in origin, could be ameliorated through early intervention.[109]

More prospective longitudinal studies of at-risk and prodromal individuals are currently needed. These studies require close follow-up and evaluation, especially around the time of onset of psychosis. A common perception is that psychosis onset follows a major life event or transition, This is one of many hypotheses that must be explored, as it has important implications for prevention and treatment and may help elucidate the neurobiological mechanisms underlying the important transition to psychosis. Given the evidence in both animals and humans that environmental enrichment can have neuroprotective effects on the hippocampus and normalize deficits in arousal and focus that are also seen in SZ, it may be warranted to pilot psychosocial interventions such as stress reduction in individuals identified as at risk for SZ.

Acknowledgments

The authors thank Bruce McEwen, PhD, for his contribution to this article.

Disclosure: This work has been supported in part by the National Alliance for Research on Schizophrenia and Depression.

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