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REVIEW

STRESS AND NEURODEVELOPMENTAL PROCESSES IN THE EMERGENCE OF PSYCHOSIS

C. W. HOLTZMAN, H. D. TROTMAN, S. M. GOULDING, A. T. RYAN, A. N. MACDONALD, D. I. SHAPIRO, J. L. BRASFIELD AND E. F. WALKER*

Department of Psychology, Emory University, 36 Eagle Row, Atlanta, GA 30322, United States

Abstract—The notion that stress plays a role in the etiology of psychotic disorders, especially schizophrenia, is longstanding. However, it is only in recent years that the potential neural mechanisms mediating this effect have come into sharper focus. The introduction of more sophisticated models of the interplay between psychosocial factors and brain function has expanded our opportunities for conceptualizing more detailed psychobiological models of stress in psychosis. Further, scientific advances in our understanding of adolescent brain development have shed light on a pivotal question that has challenged researchers; namely, why the first episode of psychosis typically occurs in late adolescence/young adulthood. In this paper, we begin by reviewing the evidence supporting associations between psychosocial stress and psychosis in diagnosed patients as well as individuals at clinical high risk for psychosis. We then discuss biological stress systems and examine changes that precede and follow psychosis onset. Next, research findings on structural and functional brain characteristics associated with psychosis are presented; these findings suggest that normal adolescent neuromaturational processes may go awry, thereby setting the stage for the emergence of psychotic syndromes. Finally, a model of neural mechanisms underlying the pathogenesis of psychosis is presented and directions for future research strategies are explored.

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Key words: psychosis, prodrome, stress, hypothalamic–pituitary–adrenal (HPA) axis, brain development, clinical high risk.

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INTRODUCTION

Psychotic disorders are arguably the most devastating of all psychiatric illnesses, and there is now a clear scientific consensus that they involve both structural and functional brain abnormalities. Etiologic models of schizophrenia and other psychotic disorders have undergone significant changes in conjunction with advances in our scientific understanding of brain function and molecular genetics. As the complexities of brain and genetic mechanisms have become more apparent, our conceptualizations of psychosis have also increased in complexity. Nonetheless, stress has been an enduring element in theories and models of the etiology of psychosis, with perspectives on stress broadening to include both psychosocial and biological factors (Walker and Diforio, 1997; Walker et al., 2008). Thus the ‘‘diathesis-stress’’ model, which posits an interaction between preexisting vulnerability and stress,

*Corresponding author. Tel: +1-404-727-0761; fax: +1-404-727-0372.
E-mail address: psyefw@emory.edu (E. F. Walker).

Abbreviations: ACTH, adrenocorticotrophic hormone; AST, associative striatum; BDNF, brain-derived neurotrophic factor; CHR, clinical high-risk; COMT, catechol-*O*-methyltransferase; CRH, corticotrophin-releasing hormone; DA, dopamine; DEX, dexamethasone; DST, dexamethasone suppression test; ESM, Experience Sampling Method; GHR, genetic high risk; GRs, glucocorticoid receptors; HPA, hypothalamic–pituitary–adrenal; HVA, homovanillic acid; Met, methionine; MRs, mineralocorticoid receptors; MTHFR, methylenetetrahydrofolate reductase; MZ, monozygotic; NAPLS, North American Prodrome Longitudinal Study; NMDA, *N*-methyl-D-aspartate; NR1, neuregulin 1; OR, odds ratio; PCP, phencyclidine; POMC, pro-opiomelanocortin; SAM, sympathetic–adrenal–medullary; SIPS, Structured Interview for Prodromal Syndromes; SMST, sensorimotor striatum; Val, valine.

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has maintained a central position in contemporary theories.

Although vulnerability to schizophrenia and other psychotic disorders is assumed to originate from genetic factors and abnormalities in fetal brain development, neuromaturational processes during adolescence are also posited to play an important role in the clinical expression of illness (Feinberg, 1982; Keshavan et al., 1994, 2005; Adams et al., 2000). This is because clinical onset of psychosis typically occurs in late adolescence/early adulthood and is generally conceptualized as a neurodevelopmental disorder (Brennan and Walker, 2001). The notion that adolescent neuromaturational processes are relevant to psychosis has gained ascendance in conjunction with an increasing research focus on the prodromal phase of psychosis. As described below, the prodrome is the period of functional decline and gradual onset of subclinical psychotic symptoms that precedes the first psychotic episode (Addington and Heinssen, 2012). It is viewed as an optimal period for identifying the mechanisms that give rise to psychosis, as well as the most plausible developmental period for future studies of preventive intervention. And most relevant to the present paper, adolescence is also a stage that is being increasingly recognized as a unique period with respect to stress sensitivity (Eiland and Romeo, 2012).

By way of background, it is important to note that recent advances in our understanding of genetic and environmental mechanisms conferring risk for psychosis do not appear to correspond with current nosological distinctions among psychotic disorders. Rather, evidence suggests that schizophrenia and other psychotic disorders share genetic (Craddock et al., 2009) and environmental risk factors, such as prenatal complications (Buka and Fan, 1999) and cannabis use (Moore et al., 2007). In addition, as described below, there is evidence that similar neurobiological processes are involved in the adverse effects of stress exposure on all diagnostic categories of psychosis.

In this paper, we discuss research on diagnosed psychotic patients, emphasizing studies that shed light on the emergence of psychosis by focusing on individuals who manifest clinical risk syndromes. We begin with an overview of research findings on the role of psychosocial stress and trauma in psychosis. Then we turn to the biological aspects of the stress response, with an emphasis on the hypothalamic–pituitary–adrenal (HPA) axis. As one of the primary neural systems governing the stress response, this system has been the focus of most research on biological aspects of stress in psychosis. We therefore examine its function and development, as well as the role it may be playing in psychotic disorders. While evidence indicates that the HPA axis is hyperactive in psychotic disorders, findings also suggest how it might be involved in the neuropathology underlying these illnesses. Specifically, activation of the HPA axis is postulated to contribute to the development of aberrant brain structural changes and to augment abnormal function of dopamine (DA) brain circuitry linked with the emergence of psychosis. Sensitivity to these effects may be amplified by early exposure to stress that sensitizes stress responsivity. Below we discuss a model of these mechanisms and offer suggestions for future research strategies.

PSYCHOSOCIAL STRESS AND PSYCHOSIS

Until relatively recently, the research examining associations between stress and psychosis has largely focused on stressful life events (e.g. loss of a family member, parental divorce, serious illness, birth of a child, etc.), with particular attention to events that are uncontrollable and relatively independent of the patient's illness (Phillips et al., 2007). Cross-sectional studies have not provided consistent evidence that patients diagnosed with schizophrenia or other psychotic disorders experience more of these stressful life events than healthy or psychiatric controls (for reviews, see Phillips et al., 2007; Walker et al., 2008). While several longitudinal designs have revealed a significant increase in the number of life events preceding psychotic relapse (Malla et al., 1990; Hultman et al., 1997; Mondelli et al., 2010a), at least one study failed to replicate these findings (see Phillips et al., 2007).

There also appears to be a threshold effect, such that when the number of stressful life events exceeds the threshold, symptom onset or exacerbation occurs. For example, a longitudinal population study revealed that recent negative life events increased the risk of psychotic symptom presentation, but only in the group with exposure to ten or more negative events (Lataster et al., 2011). Further, the individual's perception of the event as stressful, undesirable, and/or uncontrollable is also relevant (Horan et al., 2005; Renwick et al., 2009). This is illustrated in a study by Horan et al. (2005) in which schizophrenia patients actually reported lower rates of life events than healthy controls, yet they appraised both positive and negative life events as less controllable and more poorly managed, and rated positive life events as less desirable.

Psychosis also appears to be associated with greater emotional reactivity to stressors, as indexed by self-report measures of reactivity, arousability, and anxiety (Docherty et al., 2009). Furthermore, scores on emotional reactivity moderate the relationship between stressful life events and psychotic symptoms, such that life events were found to lead to symptom exacerbation primarily in patients who scored high in emotional reactivity (Docherty et al., 2009). Taken together, these results suggest that there are differences among psychotic patients and that their responses to stress should be taken in consideration in attempting to understand associations between stressful life events and psychosis.

More recently, some researchers have broadened the focus to examine the impact of minor stressors, or ''daily hassles'' (e.g. rushing to meet a deadline, transportation problems, etc.) on patients with psychoses. These studies have generally shown that patients with psychosis report a range of daily stressors and that ratings of self-reported daily stressors are positively