Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Genetic liability, prenatal health, stress and family environment: Risk factors in the Harvard Adolescent Family High Risk for Schizophrenia Study

Deborah J. Walder [a,b,c,*], Stephen V. Faraone [d,e], Stephen J. Glatt [d,e], Ming T. Tsuang [f,g], Larry J. Seidman [c,h,**]

[a] Brooklyn College, Department of Psychology, United States
[b] The Graduate Center of The City University of New York (CUNY), United States
[c] Harvard Medical School, Department of Psychiatry at Beth Israel Deaconess Medical Center, United States
[d] SUNY Upstate Medical University, Department of Psychiatry and Behavioral Sciences, United States
[e] SUNY Upstate Medical University, Center for Neuropsychiatric Genetics, Biomedical Sciences Program, Neuroscience and Physiology, United States
[f] Center for Behavioral Genomics and Institute of Genomic Medicine, Department of Psychiatry at University of California — San Diego, United States
[g] Harvard Institute of Psychiatric Epidemiology and Genetics, Harvard School of Public Health, United States
[h] Harvard Medical School, Department of Psychiatry at Massachusetts General Hospital, United States

ARTICLE INFO

Article history:
Received 8 January 2014
Received in revised form 6 April 2014
Accepted 11 April 2014
Available online xxxx

Keywords:
Stress
Psychosis
Relatives
Obstetric complications
Neurodevelopment
Family environment

ABSTRACT

Objectives: The familial ("genetic") high-risk (FHR) paradigm enables assessment of individuals at risk for schizophrenia based on a positive family history of schizophrenia in first-degree, biological relatives. This strategy presumes genetic transmission of abnormal traits given high heritability of the illness. It is plausible, however, that adverse environmental factors are also transmitted in these families. Few studies have evaluated both biological and environmental factors within a FHR study of adolescents.
Methods: We conceptualize four precursors to psychosis pathogenesis: two biological (genetic predisposition, prenatal health issues (PHIs)) and two environmental (family environment, stressful life events (SLEs)). Participants assessed between 1998 and 2007 (ages 13–25) included 40 (20F/20M) adolescents at FHR for schizophrenia (FHRs) and 55 (31F/24M) community controls. 'Genetic load' indexed number of affected family members relative to pedigree size.
Results: PHI was significantly greater among FHRs, and family cohesion and expressiveness were less (and family conflict was higher) among FHRs; however, groups did not significantly differ in SLE indices. Among FHRs, genetic liability was significantly associated with PHI and family expressiveness.
Conclusions: Prenatal and family environmental disruptions are elevated in families with a first-degree relative with schizophrenia. Findings support our proposed 'polygenic neurodevelopmental diathesis–stress model' whereby psychosis susceptibility (and resilience) involves the independent and synergistic confluence of (temporally-sensitive) biological and environmental factors across development. Recognition of biological and social environmental influences across critical developmental periods points to key issues relevant for enhanced identification of psychosis susceptibility, facilitation of more precise models of illness risk, and development of novel prevention strategies.

1. Introduction

Over the last few decades it has become firmly established that schizophrenia has early neurodevelopmental origins (Lewis and Murray, 1987; Weinberger, 1987) that later manifest in illness expression through disruptions of normal neuromaturational processes (Walker and Bollini, 2002). Biological susceptibility is reflected in 1) behavioral (family, twin, adoption) genetic studies yielding heritability estimates of approximately .65–.70 (Gottesman and Shields, 1967), confirmed by national population-based and registry studies in Denmark (Wray and Gottesman, 2012) and Sweden (Lichtenstein et al., 2009) and 2) elevated rates of perinatal complications in schizophrenia (Cannon, Jones et al., 2002; Cannon, van Erp et al., 2002). Increasingly, molecular genetic origins are being tested with large-scale consortia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), pointing to complex polygenic influences involving many common single nucleotide variants and rare events such as copy number variants. Perinatal complications

* Correspondence to: D.J. Walder, Department of Psychology, Rm 5315 James Hall, Brooklyn College, 2900 Bedford Avenue, Brooklyn, NY 11210, United States. Tel.: +1 718 951 5000; fax: +1 718 951 4814.
** Correspondence to: L.J. Seidman, Massachusetts Mental Health Center, 75 Fenwood Road, Boston, MA 02115, United States. Tel.: +1 617 754 1238; fax: +1 617 754 1250.
E-mail addresses: DWalder@brooklyn.cuny.edu (D.J. Walder), lseidman@bidmc.harvard.edu (L.J. Seidman).

http://dx.doi.org/10.1016/j.schres.2014.04.015
0920-9964/

and genetics represent two important risk domains given that they exert effects early, impacting brain development. Robust evidence of structural and functional brain abnormalities in nonpsychotic, biological relatives between 8 and 30 years of age (Thermenos et al., 2013) supports the notion that disrupted neurodevelopment precedes onset of frank psychosis. For example, gray matter volume abnormalities exist in youth at familial high-risk (FHR) compared to controls (Rosso et al., 2010), with greater volume reduction over time associated with increasing symptoms and cognitive deficits in those who develop schizophrenia (McIntosh et al., 2011). Prefrontal cortex alterations and smaller hippocampal volume are the most consistently reported neuroimaging findings in FHR youth, observed in pre-teen, teenage and adult relatives (Boos et al., 2007; Thermenos et al., 2013).

In contrast to neurobiological studies of schizophrenia patients and their relatives in family studies, relatively less attention has been paid to environmental influences, particularly the social environment. Environmental factors are emphasized in contemporary conceptualizations of schizophrenia, most prominently in the 'diathesis–stress' model (Zubin and Spring, 1977). Accordingly, biological vulnerability presumably interacts with environmental risk toward precipitating psychosis (Tsuang, 2000). Despite high heritability, concordance for schizophrenia in monozygotic twins is only around 0.50 (Cardno and Gottesman, 2000). This phenotypic discordance implicates environmental factors, which are important because they are likely more malleable than genetic risk factors, particularly in the context of new approaches to early intervention and prevention strategies for psychosis.

Two high-risk paradigms have evolved to identify precursors of psychosis. The clinical (or ultra) high-risk paradigm involves ascertainment of youth with subclinical psychotic symptoms. The FHR approach selects nonpsychotic biological relatives to assess liabilities expressed across a range of phenotypes presumably reflecting vulnerability. Hallmark phenotypes (e.g., odd thinking, smaller hippocampi, stress sensitivity) can be studied at different ages in FHR studies to evaluate developmental effects, and in different subpopulations (higher vs. lower genetic loading) to study subgroup expression. The latter approach captures an important proportion of individuals at heightened risk while avoiding confounds associated with illness and assumes a cumulative, non-specific, polygenic liability of genetic and environmental risk factors.

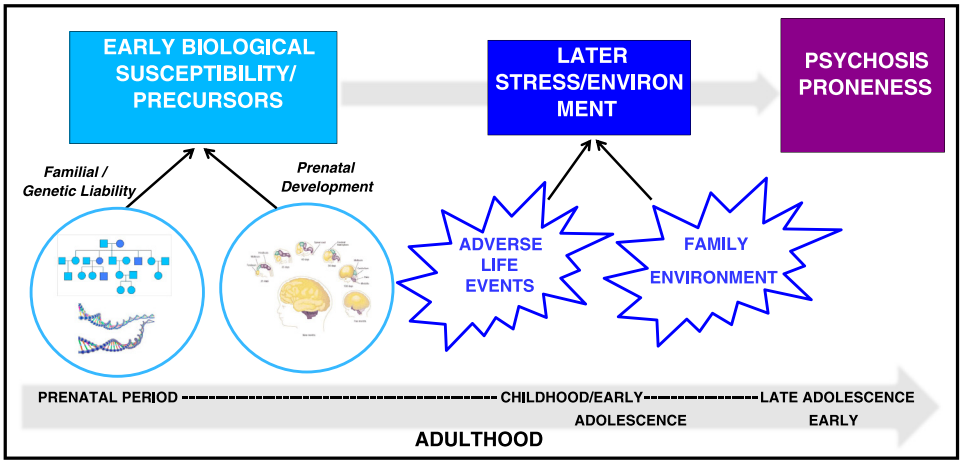
Previously, we demonstrated that compared to controls, Harvard Adolescent FHR youth have neurocognitive difficulties (Seidman et al., 2006; Phillips et al., 2011; Seidman et al., 2012; Scala et al., 2013), more physical anhedonia (but not magical ideation or perceptual aberration) and more social difficulties and reward dependence (Glatt et al., 2006; Rosso et al., 2010), the latter of which were associated with higher genetic loading (Glatt et al., 2006). We did not report on key environmental variables that may influence these outcomes, such as perinatal health issues and later life stressors.

In the present paper, we propose a 'polygenic neurodevelopmental diathesis–stress model' that targets four early developmental perturbations demonstrated to play a role in psychosis vulnerability in a temporally-sensitive manner, not previously examined together in a FHR context. We examine two classes of biological precursors (genetic predisposition/loading; prenatal health issues (PHIs)) and two classes of social–environmental factors (family environment; stressful life events (SLEs)) (see Fig. 1).

Regarding biological precursors, first, prevailing genetic hypotheses utilize polygenic models wherein many susceptibility genes of small effect (and a few rare genes with larger effects), rather than single major genes, predispose to schizophrenia (Gottesman and Shields, 1967). We utilize a proxy measure of genetic loading (Glatt et al., 2006) to approximate polygenic liability. Second, obstetric complications are one of the strongest predictors of psychosis risk. Evidence indicates higher rates of adverse prenatal events across the psychosis spectrum, such as prenatal maternal viral exposure, malnutrition, stress, and complications of pregnancy and delivery (see Cannon, Jones et al., 2002; Cannon, van Erp et al., 2002; Walder et al., 2012). Surprisingly, we are aware of only one FHR study that evaluated PHI (Gilbert et al., 2003); accordingly, high-risk offspring (compared to controls) had a higher frequency of birth complications.

Stressful life events occurring during development are strongly implicated in psychosis risk. Literature demonstrates 1) relationships among major life events, daily stressors and symptomatology in schizophrenia (Norman and Malla, 1993) and 2) social environmental context modulates impact of stressful life events (Ventura et al., 1989). Undesirable life events are linked with prodromal symptoms, and daily stressors predict increased positive prodromal symptoms (Tessner et al., 2011). Strikingly few studies have examined the influence of stressful life events among youth at FHR for psychosis (Binbay et al., 2012). The one study we are aware of found that social disadvantage increases risk more for FHR offspring than non-risk offspring (Wicks et al., 2010).

Finally, family environment plays a pivotal role in psychosis. Negative family environment contributes to poor prognosis (Myin-Germeys et al., 2001) and increases risk independent of family history of psychosis (González-Pinto et al., 2011). Patient exposure to hostile, critical and emotionally over-involved attitudes by relatives (Lukoff et al., 1984)



Note: Genetic liability converges with prenatal health issues and later developmental stressors during childhood and adolescence towards enhanced psychosis susceptibility.

Fig. 1. Polygenic neurodevelopmental model.

Please cite this article as: Walder, D.J., et al., Genetic liability, prenatal health, stress and family environment: Risk factors in the Harvard Adolescent Family High Risk for Schizophrenia Study, Schizophr. Res. (2014), http://dx.doi.org/10.1016/j.schres.2014.04.015