Review Article

Psychosocial Factors in the Neurobiology of Schizophrenia: A Selective Review

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Abstract

Aim: Various forms of social adversity have been implicated in the development and emergence of psychosis. However, how and when these events exert their influences are not clear. In this paper, we attempt to examine these putative psychosocial factors and place them in a temporal context and propose a neurobiological mechanism linking these factors. Methods: Medline databases were searched between 1966 and 2007 followed by the crosschecking of references using the following keywords: psychosocial, stress, stressors, life events, psychological, combined with psychosis and schizophrenia. Results: While some findings are conflicting, there are a number of positive studies which suggest that factors like prenatal stress, urban birth and childhood trauma accentuate the vulnerability for schizophrenia and other psychoses while other factors like life events, migration particularly being a minority group, and high expressed emotions, which occur later in the vulnerable individual may move the individual towards the tipping point for psychosis. Conclusion: Overall, there is evidence to implicate psychosocial factors in the pathophysiology of schizophrenia. These factors may act via a common pathway, which involves stress-induced dysregulation of the HPA axis and the dopaminergic systems. To establish the causal relationship of the various factors would require prospective studies that are adequately powered.

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Introduction

The architecture of the neurobiology of schizophrenia is complex: it comprises an inherited vulnerability with multiple genes involved, and its interaction with a number of environmental factors. That the onset of psychosis typically occurs during late adolescence and early adulthood is suggestive that additional factors play significant roles along the trajectory from a vulnerability state to the onset of schizophrenia. The current view about schizophrenia is that this represents a progressive developmental pathophysiology of the illness that may result from several factors working individually, or in combination.[1]

There is considerable evidence that a range of social and psychological factors are associated with schizophrenia.[2-5] Some of these psychosocial stressors may occur "early" and accentuate the vulnerability state, and the markers of these early factors are unlikely to change in relation to the onset of psychotic symptoms. Those stressors, on the other hand, that occur "late" could be the "triggers" for the psychotic breakthrough, and their presence or absence may differentiate between at-risk patients who do and do not convert to psychosis.

This paper examines the various psychosocial factors implicated in the trajectory of a vulnerable state to first-break psychosis with the attempt to understand them in the context of the neurobiological changes that occur during this process. We heuristically classify these into early and late factors.

Methods

We conducted a literature review for evidences supporting the role of psychosocial factors in the development of schizophrenia. Medline databases were searched between 1966 and 2007 utilising schizophrenia and psychosis as broad search terms in conjunction with the following keywords: psychosocial, stress, stressors, life events, and psychological. We included a combination of cohort and case-control studies in this review, and incorporated a few meta-analyses.

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Early Factors

Prenatal Stress

Maternal stress during pregnancy has been investigated as a risk factor for the subsequent development of schizophrenia in the offspring. A proxy of this stress is unwanted pregnancy. A prospective study that examined a birth cohort of over 11,000 individuals, found the risk of later schizophrenia among unwanted children was raised compared with wanted children even after adjustment for confounding factors such as sociodemographic, pregnancy and perinatal variables.[6] This, however, was not replicated in another study.[7]

The association between prenatal exposure to war and natural disaster, and the risk of subsequent schizophrenia has also been studied. Selten et al[8] examined the effect of prenatal exposure to the 1953 Dutch Flood Disaster on the risk of schizophrenia in the offspring, and found an increased risk of non-affective psychosis for individuals born in the 9 months after the flood but it was not statistically significant. Offsprings of mothers who were exposed to the stress of the Six-Day War and Yom Kippur War in Israel did not have a higher incidence of schizophrenia in adulthood when compared to the offsprings of mothers not exposed to the stress.[9] Children of women exposed to the 1998 Quebec ice storm were more likely to be born premature, being in an incubator as a newborn, and had more obstetric complications.[10] The same investigators also found that children of women exposed to the stress between gestational weeks 14 and 22 and reported high levels of subjective distress had significantly greater dermatoglyphic asymmetry (a biological marker of schizophrenia), while those mothers who had experienced moderate or high levels of objective stress had children with significantly lower cognitive development (a risk factor associated with schizophrenia).

Prenatal loss of the father has also been examined as a form of prenatal stress. There was a significantly higher number of individuals diagnosed with schizophrenia in a psychiatric hospital whose fathers died before their birth than a control group whose fathers died during the first year of their lives.[11]

The findings from the aforementioned studies are not sufficiently consistent to establish a definite association between prenatal stress and risk of schizophrenia. These studies differ in the definition of prenatal stress, and many of the studies failed to control for confounding variables such as family history, paternal age, and parent's ethnicity. Moreover, there is great inter-individual variability in the perception of stress when confronted with similar events.

Urban Environment

Several epidemiological studies have consistently found an association between exposure to an urban environment and the occurrence of psychosis.[12-14] The risk for a psychotic disorder was linearly associated with the level of urbanicity of place of birth: the incidence of psychotic disorder was found to be the highest in the most urbanised areas.[13] A Swedish study found that subjects born in cities had a higher risk of developing schizophrenia and other non-affective psychoses.[12] Even though the study found that subjects born in main cities were more likely to have experienced obstetric complications and have a higher socio-economic status, controlling for these factors did not reduce the strength in the association between psychotic disorder and urban place of birth.

The effect of urbanicity on the risk of developing psychosis is greater in subjects with a family history of psychosis.[15,16] This had led the authors to conclude that 20% to 30% of individuals exposed to both family history of psychosis and urban life had schizophrenia because of the co participation between these 2 factors.

The timing of exposure appears to be important: the greatest risk for schizophrenia was among subjects who were exposed to the urban environment at birth regardless if they were exposed or not to the same environment at the time of the illness onset. However, those who were not exposed to the urban environment at birth even though they did so later in life did not have an elevated risk for schizophrenia.[17]

Findings from the aforementioned studies have produced compelling evidences that individuals exposed to an urban environment have an elevated risk of developing schizophrenia. A number of environmental risk factors have been hypothesised, and these include the role of social capital,[18,19] stressful life events,[13,14,17] prenatal exposure to infection diseases, poor nutrition, and social isolation.[14]

Childhood Abuse

Several large-scale reviews have established a putative relationship between the childhood abuse and psychosis. A large-scale prospective study reported that child abuse before the age of 16 was a significant risk factor for psychotic symptoms.[20] Another study found that childhood traumatic experiences were associated with a psychotic illness rather than other types of psychiatric illness.[21] However a prospective study of individuals, verified to have been sexually abused in childhood, found that victims of both gender had a significantly higher rate of psychiatric treatment but there was no difference between cases and controls in the rate for schizophrenia and related disorders.[22]

A more recent analysis of the National Comorbidity Survey found that childhood physical abuse was the only significant predictor of psychosis in the total sample after controlling for depression but the odds ratio for rape was only significantly higher for male subjects.[23]

Effects of These Early Psychosocial Factors

It is difficult to integrate the effects of these various factors. Nonetheless, the importance of these events in the pathophysiology of schizophrenia is overall convincing.

One potential causal connection is that these early events (acting singly or an additive manner) alter neurobiological development giving rise to aberrant neural networks, which increases the vulnerability for a psychotic illness. The action of the maturational process on these aberrant networks would facilitate the emergence of psychotic symptoms much later after puberty.

Evidence for altered neurobiological development stemming from early events comes from a study by Chugani et al,[24] which found that Romanian orphans adopted away from orphanages showed significantly decreased glucose metabolism bilaterally in the brain structures when compared to controls. These orphans also showed mild neurocognitive impairment, impulsivity, and attention and social deficits. The dysfunctions of these brain regions are implicated in the development of psychiatric disorders, and may be the result of stress from childhood social deprivation.

Late Psychosocial Factors

Life Events

Brown and Birley[25] examined the rate of life events before the onset of the disorder among the patients diagnosed with schizophrenia, and found that 46% of the patients had at least one life event in the 3-week period just before the onset of the disorder. The study also found that the patients had more life events in the weeks nearest to the onset of the disorder than during the weeks preceding the relapse. This suggests that environmental factors, particularly some sort of crisis or life changes, have a triggering effect on the onset of schizophrenia.

Ventura et al[26] conducted a prospective longitudinal study, and found that among the psychotic patients who relapsed, there were a higher number of life events in the 1-month preceding the relapse than in the same month during the non-relapse period. However, over half of the patients who experienced a psychotic relapse did not have a major life event in the month preceding the relapse, which suggests the role of other environmental factors.

Another study by Hirsch et al[27] provided conflicting evidence, having found no difference in the average rate of life events between the most recent period prior to relapse of schizophrenia and the other preceding time period.

Preliminary findings from the Edinburgh High-Risk Project found no differences in the number of life events of a high-risk group of people for psychosis and that of a group of healthy controls and first-episode psychosis patients,[3] while another cross-sectional study also did not find that life events predicted the onset of psychosis.[28]

In conclusion, there are mixed findings to the hypothesis that life events can trigger the onset or relapse of schizophrenia. The retrospective nature of most of the studies makes it impossible to elucidate the causal direction of these events and the onset of psychosis as the validity of the recalled events and its frequency could be questioned.

Migration/Minority Status

Studies have consistently found an elevated risk of schizophrenia and other psychotic disorders among migrant groups. Specifically, numerous studies have found high rate of schizophrenia among people of African-Caribbean origins who are resident in the United Kingdom.[29-31] Selten et al[32] reported a similar elevated incidence rate of schizophrenia among immigrants from Surinam, the Antilles, Morocco, and other non-Western countries, while Zolkowaska et al[33] demonstrated a higher incidence of schizophrenia among immigrants to Sweden from East Africa, and Cantor-Graae et al[34] have also found an increased risk for schizophrenia among immigrants to Denmark from Australia, Africa, and Greenland.

A meta-analysis of 18 studies[35] concluded that first- and second-generation migrants (defined as persons with a foreign birthplace and persons with one or both parents born in a foreign country respectively) had a mean relative risk of 2.9 in developing schizophrenia. The study also found that persons who migrated from developing countries had a greater risk of developing schizophrenia than for persons who migrated from developed countries. Migrants from countries whereby the majority of the citizens were classified as blacks also had a higher relative risk of developing schizophrenia compared to migrants from countries whereby the majority were white or non-white/non-black.[35]

There appears to be significant heterogeneity in the risk across the different migrant groups. Fearon et al[36] found that the rates of schizophrenia among Asian migrants residing in the UK are only modestly raised and not to the same extent as for their African-Caribbean and Black African counterparts. The possibility of a higher rate of obstetric complications among these migrant groups, which could have led to the higher incidence of schizophrenia, was refuted by a study, which found that White psychotic patients were more likely to have a history of obstetric complications than an African-Caribbean population.[37]

A number of factors have been suggested to explain the elevated rate of schizophrenia among migrant groups. Odegaard[38] suggested that individuals who are already genetically predisposed to develop this disorder are more likely to emigrate. This was refuted by Selten et al,[39] who found that the incidence of schizophrenia among the

immigrants from Surinam remained elevated even though he enlarged the denominator by adding the resident population of Surinam.

Social isolation and discrimination by the migrant groups could possibly explain the elevated rates of schizophrenia[35,40] as suggested by an increase in the incidence of schizophrenia where the migrant group formed the minorities.[41,42] Incidence studies conducted in the islands where majority of the migrants came from, specifically Jamaica,[43] Trinidad,[44] and Barbados,[45] also did not find an elevated rate of schizophrenia among the host population. This is further supported by animal studies that showed social isolation and social subordination are associated with changes in the dopamine system characterised by an increase in basal dopamine levels and enhanced dopamine release to amphetamine.[46-48]

High-expressed Emotion

Expressed emotion has been extensively studied, and has been found to be a robust and significant predictor of relapse (effect size of r = 0.3) in schizophrenia.[49]

However, the role of expressed emotions in precipitating a first break psychosis has been hardly studied. In a long-term follow-up study of adopted-away offspring of mother with schizophrenia-spectrum disorder and adopted-away offspring without this genetic risk, Tienari et al[50] found that the rearing-family environment was a significant predictor of schizophrenia-spectrum disorder only in adopted-away individuals at high-genetic risk but not in those at low-genetic risk. O'Brien et al[51] studied the impact of the family environment on the symptoms and social functioning of adolescents at imminent risk for onset of psychosis, and found that higher levels of caregiver emotional involvement, positive remarks, and warmth was associated with significant improvement in the adolescent symptoms and social functioning 3 months after the start of the study.

In conclusion, findings from the above studies have demonstrated the association between family environment and risk for the onset of psychosis or psychotic relapses. However, more studies addressing the same research question should be done, and the studies' results should be replicated to further strengthen the association between family environment and risk for schizophrenia.

A Psychosocial-biological Model for Schizophrenia

The common biological mechanism that is possibly involved is the activation of the hypothalamic-pituitary-adrenal (HPA) by these various psychosocial stressors, and the subsequent release of glucocorticoids. The hippocampus, which has a high density of glucocorticoid receptors, is part of the feedback system that modulates the activation of the HPA axis. Stressors of sufficient magnitude can produce a sensitisation effect. When exposure to stressors persists and heightened glucocorticoid release is chronic, there can be permanent changes in the HPA axis such that corticosterone release is augmented, of which high levels would have damaging effects on the hippocampus.[52]

In fact, hippocampal volume reduction is one of the most consistent structural abnormalities found in schizophrenia.[53] Functional neuroimaging studies have complemented evidence from post-mortem and behavioural studies, showing regionally specific abnormalities of the hippocampus and of memory function in schizophrenia.[54] The hippocampus carries out crucial working memory function in childhood right up to the time that the prefrontal cortex reaches functional maturity and takes over this function. Diamond[55] has postulated that the onset of psychotic symptoms is related to disruption of the transfer of the crucial working memory functions. Damage of the hippocampus (and/or the prefrontal cortex) from the effects of psychosocial stressors early in one's life would prevent this transfer.

A marker of heightened HPA activity is the increased volume of the pituitary, which has been reported by Pariante et al[56] in a group of ultra-high risk patients for psychosis, as well as those with first episode of psychosis compared to non-psychotic controls. In the acute phase of the psychosis, the increased pituitary volume could represent a consequence of the distress and arousal associated with the psychotic experience. Alternatively, it could represent an increased activation of the stress response preceding the development of psychosis, for an increased susceptibility to daily life stress, an increased level of independent stressors, or both.[57,58] There could also be a parallel process that stress would induce by influencing the rate of dopamine activities. Specifically, stress elevates not only the release of cortisol and dopamine. Repeated social defeat in animal studies leads to activation of the mesolimbic dopamine system,[59,60] which is associated with psychosis in humans.

Walker and DiForio[61] argued that the stress-induced dysregulation of the HPA axis and dopaminergic systems result in a hypersensitive state. As these dopaminergic systems are important in interpretation of stress and threat-related stimuli, this state could lead to anomalous conscious experiences like heightened perception, and psychotic experiences like delusions and hallucinations.[62] Kapur[63] has proposed that the mesolimbic dopamine system provides salience to a mental event from a stimulus, and the over-activity of this system would result in an aberrant salience being assigned to what would be otherwise an event and stimuli of no importance.

Overall, the impact of psychosocial stressors in the aetiology of schizophrenia is undoubtedly present but the

differential significance of each of the individual putative factors is not clear. The construct of each of the stressor is complex and multi-dimensional. We have just proposed a possible mechanism whereby these factors would contribute to the manifestation of psychotic disorders. Any model that seeks to conceptualise the role of psychosocial stressors in the neurobiology of schizophrenia has to take into consideration the role of other risk factors such as genetic, early environmental insults to the brain, and drugs like cannabis. The model would also have to consider the possible differential effects of these diverse factors on the temporal course of the disorder. Clarifying the effect of these factors and the nature of their interaction would require a prospective study that is sufficiently powered.

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