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SUPPLEMENT

Pathways to schizophrenia: the impact of environmental factors

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Abstract

Schizophrenia is an aetiologically complex disorder arising from the interaction of a range of factors acting at various stages of life. Schizophrenic individuals inherit genes that cause structural brain 'deviations' which may be compounded by early environmental insults. As a result some pre-schizophrenic children exhibit subtle developmental delays, cognitive problems, or poor interpersonal relationships. They are susceptible to dysregulation of dopamine, the final pathway leading to the onset of a psychotic illness. Dopamine dysregulation may arise through a process of sensitization, which, in animals, can be caused by repeated administration of dopamine-releasing drugs. It is clear that the same process occurs in humans, and that some individuals are particularly sensitive to the effects of such drugs for either genetic reasons or through early environmental damage. Stress has also been shown to induce dopamine release in animal studies, and epidemiological studies have demonstrated that social stresses can precipitate schizophrenia. Thus, stresses, such as drug use and social adversity, in adolescence or early adult life may propel the neurodevelopmentally impaired individual over a threshold into frank psychosis.

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Introduction

Schizophrenia results from the cumulative interaction of a number of risk factors, some of which are neurodevelopmental. Susceptible individuals appear to inherit a number of deviant traits, each of which is not uncommon in the general population, but which together render them vulnerable to schizophrenia. This genetic vulnerability may be compounded by early insults to the developing brain, such as prenatal and perinatal complications. A proportion of pre-schizophrenic children show slight developmental delays, minor cognitive difficulties and social anxiety, which supports the hypothesis that the disorder is at least in part neurodevelopmental. But what causes such a child or adolescent to go on to become psychotic? This paper provides an overview of current evidence on factors influencing the trajectory to schizophrenia, highlighting illustrative studies, and is not intended to be exhaustive.

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Predisposing factors to schizophrenia

Inheriting 'deviant' traits

Schizophrenia shows a high degree of heritability but no single gene has been found to be responsible, in the same way that no single gene has been identified as being the cause of all coronary artery disease, diabetes mellitus and many other medical disorders (Harrison and Owen, 2003). Rather, these complex disorders are thought to arise from the interaction of many different genes with each other, as well as with environmental factors. Reviewing genetic factors in schizophrenia is beyond the scope of this paper, however, recent interest has focused on two types of genes that provide a plausible pathophysiological mechanism to schizophrenia and are particularly relevant to environmental factors (Harrison and Owen, 2003). These are neurodevelopmental genes, such as neuregulin (Stefansson et al., 2002), and genes associated with dopamine regulation, such as the catechol-*O*-methyltransferase (COMT) gene (Mattay et al., 2003; Shifman et al., 2002). These genes may either operate very early in life or nearer to the onset of psychosis.

Schizophrenic individuals have consistently been reported to have structural brain abnormalities. At

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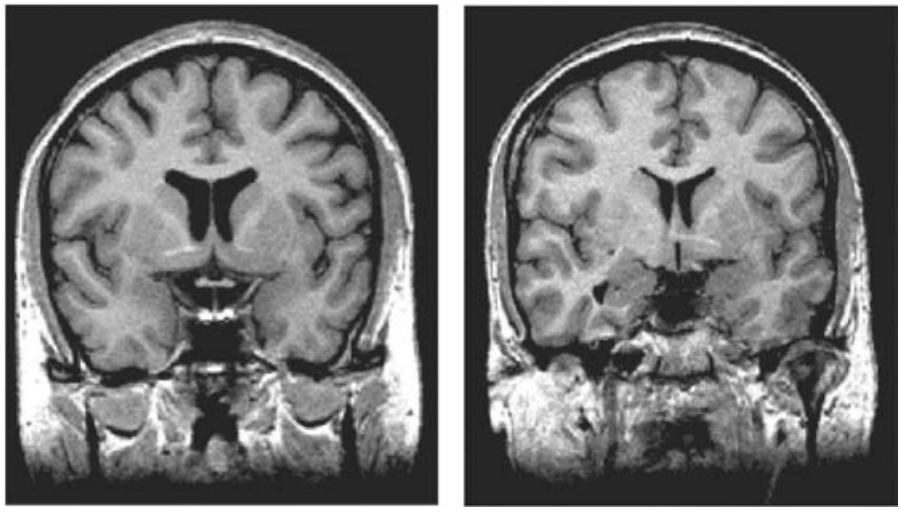

Schizophrenics Controls

Figure 1. MRI scans of schizophrenic and control subjects in the Maudsley Family Study. (Adapted from McDonald et al., 2002.)

least some of the brain abnormalities are inherited. McDonald et al. (2002) performed MRI scans on probands and unaffected relatives from families multiply affected with schizophrenia, which are likely to transmit an elevated genetic predisposition. Unaffected family members displayed similar brain deviations to their schizophrenic relatives, including enlarged lateral ventricles and a reduced cortical volume (Figure 1). Furthermore, a gradient of ventricular enlargement was found amongst the unaffected relatives in proportion to their likelihood of carrying schizophrenia genes, with greater enlargement amongst relatives who were more closely related to the schizophrenic proband. This indicates there is transmission of genes that subtly alter brain development.

Environmental insults

Many studies have shown that early environmental 'insults', such as prenatal infections and nutrition, maternal substance misuse, early life stressors, and obstetric complications, are more common in people with schizophrenia than the general population (Cannon et al., 2002a; Hulshoff Pol et al., 2000; Lieberman et al., 2001). Recent studies investigating the effects of these factors on brain development provide evidence for the interaction between genetic and environmental factors acting early in life. For example, McDonald and colleagues (McDonald et al., 2002; Schulze et al., 2003) examined the impact of obstetric complications on brain development in schizophrenic probands, their unaffected relatives, and controls. Obstetric complications of moderate severity in the control subjects did not have a large effect on brain development. However, in non-psychotic but predisposed relatives from multiply affected families, the left hippocampal volume was decreased in those who had suffered an obstetric insult but normal in those who had not. The schizophrenic group was even more sensitive to obstetric insult: there was greater decrease in left hippocampal volume and increase in lateral ventricular volume in those who had suffered obstetric complications compared to those who had not. This suggests that early environmental factors may produce a more detrimental effect on the brains of individuals carrying a genetic predisposition to schizophrenia than those who do not.

In animal studies, perinatal damage has also been shown to lead to a labile dopamine system vulnerable to sensitization. Moore et al. (1999) suggested that developmental disruption of the temporal cortex can result in dysregulation of the dopaminergic inputs to the striatum, increasing the response to novelty, mild stress or psychotomimetics. In a similar way, early environmental factors appear to interact with genetic predisposition to schizophrenia, increasing the risk that an individual will develop dopamine dysregulation and resultant psychosis in adolescence or later.

Neurocognitive impairments

Many studies have suggested that children who go on to develop schizophrenia may be different from their peers and display some developmental deviations, such as mild social, motor and cognitive dysfunctions (Cornblatt et al., 1999; Erlenmeyer-Kimling, 2001). However, these deviations are not sufficiently

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specific or sensitive to enable identification of 'at risk' individuals early in childhood (Lieberman et al., 2001).

To find a better predictor of psychosis, the Dunedin Birth Cohort Study assessed the development of 1037 children every 2 yr from the ages of 3–15 yr, and then again at ages 18, 21 and 26 yr (Cannon et al., 2002b; Moffitt et al., 2001). They were assessed in great detail by neurologists, psychologists and social workers, and a child psychiatrist interviewed the children at age 11 yr. Ninety-six per cent of the cohort was again interviewed at age 26 yr, using a standardized interview schedule to obtain DSM-IV diagnoses (APA, 1994). A total of 3.7% were found to meet criteria for schizophreniform disorder, which is characterized by the same symptoms as schizophrenia but the criteria for symptom duration are shorter (1 month vs. 6 months). Schizophreniform disorder was examined rather than severe schizophrenia partly because of the low base rate of schizophrenia in general population samples, and because many studies have previously focused on children of schizophrenic parents or on frank schizophrenia.

One study focused on whether individuals with schizophreniform disorder also showed developmental impairments (Cannon et al., 2002b). Not surprisingly, obstetric complications (such as neonatal insults, being small for gestational age and, in particular, hypoxia) were found to increase the risk of psychosis. Individuals who developed schizophreniform disorder had shown early in their life (aged 4–7 yr) poorer motor development, poorer receptive language and a lower IQ (Cannon et al., 2002b). Many of the symptoms of schizophrenia involve language systems: for example, thought disorder is expressed as disordered language, and auditory hallucinations are a misinterpretation of inner language. Therefore, it is not surprising that individuals who have difficulty in understanding language early in life are more prone to the language-based symptoms of schizophrenia. However, although motor or cognitive abnormalities increased the risk of subsequently developing schizophreniform disorder, they were not powerful predictors – increasing the risk by only 2- to 3-fold.

The interview at age 11 yr was the best predictor of whether a child would go on to develop schizophreniform disorder in adulthood (Poulton et al., 2000). Children, interviewed by a child psychiatrist, were asked questions about quasi-psychotic phenomena, such as:

'Have other people ever read your mind?'
'Have you ever had messages sent just to you through the TV or radio?'
'Have you ever thought that people are following you or spying on you?'
'Have you heard voices other people cannot hear?'

The cohort was categorized on the basis of responses to these questions. The strong-symptom group consisted of children who answered 'yes, likely' to two symptoms or 'yes, definitely' to one symptom, and children who answered 'yes, likely' to one symptom were assigned to the weak-symptom group. When the 13 children in the strong-symptom group were examined at age 26 yr, the risk of schizophreniform disorder was increased 16 times compared to the rest of the population. Twenty-five per cent of the strong-symptom group and 9% of the weak-symptom group went on to develop schizophreniform disorder. Of the control subjects (those who answered negatively to all quasi-psychotic symptoms at age 11 yr), less than 2% had developed schizophreniform disorder by the age of 26 yr. Thus, the presence of quasi-psychotic symptoms at age 11 yr is a more powerful predictor of later psychosis than cognitive or psychomotor problems.

As well as exhibiting neurocognitive impairments, children who go on to develop schizophrenia tend to be socially anxious. These children tend to set themselves apart from their peers and begin to experience odd thoughts that may include strange ideas about what other children are doing or of particular messages being sent to them. But what triggers the development of psychosis in adolescence or later?

Precipitants to the development of psychosis

Drugs that release dopamine, such as cannabis, amphetamines and cocaine, can increase the risk of psychosis and exacerbate psychosis in those already ill. Stress can also induce dopamine release in animals and epidemiological studies have demonstrated that social stresses can precipitate schizophrenia (Bebbington et al., 1993).

Drug use

Psychoactive drug use has become very common in many countries, and may be a factor in the trend towards a lower age of onset of schizophrenia (Di Maggio et al., 2001). Cannabis is the drug most commonly used by people with psychoses, and they often report taking the drug as a type of self-medication – the reasons given include counteracting the negative effects of their medications or to feel better (Hambrecht and Hafner, 1996). Most studies report a positive association between cannabis use and

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psychotic disorders, although there are many cultural, and social factors that may affect this relationship (Hall and Degenhardt, 2000). There are a number of potential explanations for this (Degenhardt and Hall, 2002):

- common factors such as personality disorder could explain the co-occurrence;
- cannabis could cause psychosis;
- cannabis could precipitate psychosis in vulnerable individuals;
- cannabis could prolong psychosis in people with an established psychotic disorder;
- people with psychosis may be more likely to become regular cannabis users because of factors such as self-medication, or social situation and stress.

Recent longitudinal studies support the theory that cannabis precipitates psychosis in some vulnerable people, indicating that cannabis is a factor on the pathway to schizophrenia. For example, the Dunedin Birth Cohort Study (Moffit et al., 2001) obtained information regarding drug use at ages 15 and 18 yr. Consumption of cannabis at age 15 yr was associated with a 4-fold increase in the risk of schizophreniform psychosis by age 26 yr (Arseneault et al., 2002). Even after excluding individuals who had quasi-psychotic symptoms at age 11 yr, the rest of the cohort still had a 3-fold increased risk of developing schizophreniform psychosis with cannabis use. This study is the first to show that adolescent cannabis users are at increased risk for experiencing schizophreniform psychosis as adults, over and above childhood psychotic symptoms antedating their cannabis use. These findings are consistent with cohort studies in Sweden, Germany and The Netherlands (Andreasson et al., 1987; Hambrecht and Hafner, 2000; van Os et al., 2002). Evidence of a dose–response relationship, with increasing cannabis use associated with increasing risk of psychosis, further supports the importance of cannabis on the pathway to psychosis (Andreasson et al., 1987).

The observation that particular individuals are susceptible to developing psychosis when they use a dopamine-releasing drug while others can use the same drug without experiencing psychotic symptoms supports the multifactorial integrative model of psychosis. The contribution of some of these factors, genetic and personality variables, to the risk of psychosis associated with drug use has been examined in methamphetamine users as the symptoms of methamphetamine psychosis are similar to the positive symptoms of schizophrenia.

Chen and colleagues investigated 445 methamphetamine users (Chen et al., In Press). Of the regular users, 121 never developed psychosis; 143 experienced a psychosis lasting less than 1 month; and the psychosis lasted more than 1 month in 20 users. A total of 140 occasional abusers (<20 times per year) never developed psychosis. Childhood schizoid/schizotypal traits were associated with an increased likelihood of developing a methamphetamine psychosis in adulthood amongst regular users. If a person was not schizotypal in childhood, they could use methamphetamine without becoming psychotic. However, the more an individual was considered schizotypal in childhood, the more prolonged the resulting psychosis was.

Methamphetamine users who developed psychosis were also distinguished from those who did not by having relatives with a greater morbid risk of schizophrenia (Chen et al., In Press). Individuals who had no family history of schizophrenia could abuse dopamine-releasing drugs without developing psychosis. However, the greater the predisposition to schizophrenia, the more likely an individual would have prolonged psychosis from these drugs. This suggests that a factor is being transmitted within the family that makes these individuals vulnerable to the psychotogenic effects of the drug.

The findings of Chen et al. support the idea that dopamine sensitization is critical to the development of schizophrenia. In individuals who are particularly sensitive to dopamine, arising from either genetic reasons or through early environmental damage, repeated use of methamphetamine or cannabis may augment the sensitization of the dopamine system, to a point that it becomes dysregulated, and resulting in psychosis.

Social stress

There is considerable evidence that a range of social and psychological factors, such as stressful life events, ethnicity and childhood trauma, are associated with schizophrenia (Miller et al., 2001; Read and Ross, 2003). The role of social isolation has attracted considerable recent interest. Several studies have demonstrated that being born and raised in an urban area increases the risk of psychosis compared to a rural birth and upbringing. Indeed, the incidence of schizophrenia was found to be nearly 2-fold higher in South London, a deprived inner city area, than in Dumfries, a quiet, rural area of Scotland (Allardyce et al., 2000). While cities may be considered more stressful to live in for many reasons, the factors contributing to the increased incidence of schizophrenia were unclear. Social isolation had previously been

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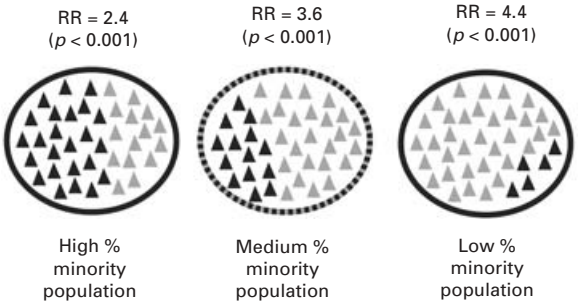

Figure 2. Risk of schizophrenia in non-white ethnic minorities according to their proportion in their local area. RR, Incidence rate ratio. (Adapted from Boydell et al., 2001.)

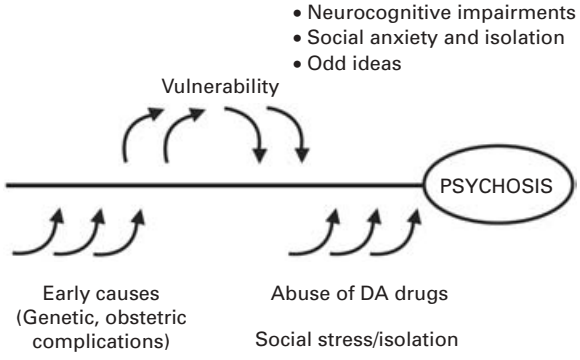

Figure 3. The developmental origins of schizophrenia.

proposed to be associated with the increased risk of psychosis observed in migrants (Bhugra, 2000; Harrison et al., 1988; Selten et al., 2001) and South London has a large, non-white, ethnic minority population (Allardyce et al., 2000). Hence, Boydell et al. (2001) investigated the incidence of schizophrenia among people from non-white ethnic minorities in neighbourhoods where they constituted a smaller proportion of the total population. The incidence of schizophrenia increased significantly as the proportion of minorities in the local population fell. The incidence rate ratio ranged from 2.4 in areas where the minorities formed a larger proportion of the local population to 4.4 in the areas where they formed a smaller proportion (Figure 2). This suggests that social isolation and the lack of social support for people living in an alien environment may be factors contributing to schizophrenia. These data are supported by animal studies that show social isolation, and social subordination are associated with changes in the dopamine system characterized by an increase in basal dopamine levels, and enhanced dopamine release to amphetamine (Hall et al., 1998, 1999; Morgan et al., 2002).

Conclusion

The aetiology of schizophrenia involves the interaction of many factors, which may act from very early development onwards (Figure 3). An inherited genetic vulnerability may be compounded by early environmental insults. Stresses in adolescence or early adulthood, such as drug use and social isolation, may then propel the neurodevelopmentally impaired individual over a threshold, resulting in frank psychosis.

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