

Schizophrenia is (not simply) a neurodevelopmental disorder

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Schizophrenia affects almost 1% of the population at some point in their life. It occurs in all geographic areas in which studies have been done, although the outcome appears to be better in developing countries. In this editorial we will discuss the evidence, from epidemiological, genetic and neuroimaging studies, that suggests that schizophrenia is in part a neurodevelopmental disorder. However, we will also point out that, contrary to some recent statements, this is not the whole story. Figure 1 provides a simplified view of our model.

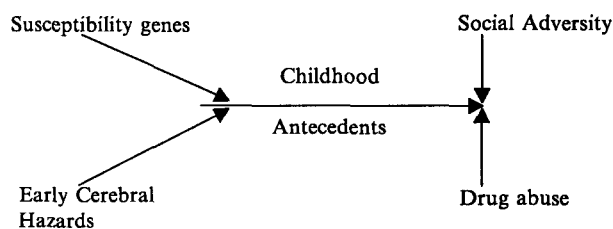


Figure 1. – A model for schizophrenia.

It is often said that the aetiology of schizophrenia is unknown; this is not true since a number of risk factors have been clearly established. These may be crudely divided into A) Biological predisposing fac-

tors which operate during development such as familial/genetic predisposition and early environmental insults, and B) Psychosocial precipitating factors which operate prior to the onset of illness such as social adversity and drug abuse.

BIOLOGICAL PREDISPOSING FACTORS

What is the role of genes?

The most powerful risk factor for developing schizophrenia is having an affected relative (Murray & McGuffin, 1993). The risk of developing schizophrenia rises from 1% in the general population and 2% in the case of second degree relatives, to about 42% in the monozygotic co-twins of schizophrenics (Cardno *et al.*, 1999). Further evidence of a role for genes comes from studies of the unaffected relatives of schizophrenic subjects. Sharma *et al.* (1998) have shown that in families where several members are affected by schizophrenia, the unaffected relatives who appear to be transmitting the disorder show enlarged ventricles, similar to their affected relative. Indeed, the unaffected relatives in such families show a range of minor abnormalities in tests of neuropsychology, eye tracking, neurological signs, and event-related potentials, as well as an excess of mixed handedness. Thus, they appear to show in minor form many of the abnormalities found in schizophrenic subjects (Wickham & Murray, 1997).

There have been many studies applying molecular genetic techniques to schizophrenia in recent years.

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Much of this research has been conducted on multiply affected pedigrees, using a technique known as linkage analysis (the use of a known genetic marker to locate the faulty gene). Attention has recently focused on the chromosomes 6, 22, 13, and more recently 8, but the results have been inconclusive (Gill *et al.*, 1996; Straub *et al.*, 1995). Various candidate genes such as those involved in the dopamine pathway have also been studied but again with contradictory findings. We can conclude that if a major gene existed which explained a large proportion of the variance in liability to schizophrenia, it would have been found by now. It seems more likely that a number of genes of relatively small effect are necessary (Maier & Schwab, 1998)

So, are genes the only cause? It seems not! The concordance between monozygotic twins is less than 50% which suggests the action of some environmental factors.

But which environmental factors?

Doomed from the womb?

Obstetric complications (OCs) have been repeatedly shown to be a risk factor for developing schizophrenia, with an odds ratio of about 2 for OCs in general (McNeil, 1995; McGrath & Murray, 1995). Attention has focused on those complications associated with a risk of hypoxic-ischaemic brain damage (Verdoux *et al.*, 1997), as one of the possible causes for the ventricular enlargement observed in schizophrenic patients (Murray *et al.*, 1985). Also, the reduced hippocampal size observed (Suddath *et al.*, 1990) in schizophrenia has been related to the presence of OCs of the types associated with hypoxia-hyschaemia (Stefanis *et al.*, 1999).

Some authors have contended that OCs could just be the consequence of an earlier impairment of brain growth, as suggested by a reduced birth weight (Rifkin *et al.*, 1994) and smaller head circumference observed in these patients. Another evidence suggesting the operation of some earlier factor is the tendency for schizophrenic subjects to be born in late winter and spring (Torrey *et al.*, 1997); this could be secondary to subtle brain damage in the foetus due to winter viral infection. This has been supported by an association between maternal fever in the latter part of pregnancy and later schizophrenia (Jones *et al.*, 1998). There has been a heated controversy over reports of an increased number of children who later developed schizophrenia born several months after

influenza epidemics (Sham *et al.*, 1992; Kunugi *et al.*, 1995). Others have suggested that exposure to rubella or polio or to maternal malnutrition could all increase the risk of later schizophrenia.

A parsimonious way of making sense of the numerous reports of prenatal risk factors is that a range of illnesses in the mother may slightly impair the cortical development of her baby, and that this in turn increases the risk of later schizophrenia. It is probable also that cerebral insults and infections in early childhood increase the risk (Cannon & Murray, 1998)

A lonely childhood?

Longitudinal cohort studies and studies of high-risk children have all reported an excess of minor social and cognitive deficits pre-dating the onset of the schizophrenic illness. Children destined to develop schizophrenia show deficits in attention, in visuo-perceptual tests and in language acquisition. They are more likely to show delayed neuro-motor development, including retarded skeletal growth. Even as early as age 4, they tend to be more likely to play alone and, during adolescence, they show a lack of confidence and tendency to social withdrawal and anhedonia (Jones *et al.*, 1994; Cannon *et al.*, 1999).

These premorbid changes are seen by many as the expression of the same underlying brain abnormality which will later produce frank psychosis. However, this is not proven, and it is also possible these childhood characteristics act as independent risk factors. Such a model would suggest that preschizophrenic individuals proceed on a course of increasing deviance with an accumulation of risk factors pushing them towards the threshold for the development of frank psychosis (figure 2).

Category	Specific	Effect Size
Genetic*	MZ Twin	45
	DZ Twin or Sibling	5
Early Environmental ¹	Obstetric Complications	2
	Maternal Infection	2
	City birth	1.4
	Late-winter/Spring birth	1.1
Late Environmental ¹	Immigrant status	4
	Chronic Cannabis Abuse	2
	Adverse Life Events	1.5

* Relative Risk, ¹ Odds Ratios

Figure 2. – Risk factors for schizophrenia (from Cannon & Jones, 1996).

Hand preference is an index of functional lateralization which has been repeatedly studied in schizophrenic subjects. An excess of non-right handedness (ambiguous handedness or ambidexterity) (Cannon *et al.*, 1995), but not of pure left-handedness, has been reported in schizophrenic subjects. Ambiguous handedness has also been observed in pre-schizophrenic children (Crow *et al.*, 1996), in people who score highly on measures of psychosis proneness and in subjects with schizotypal traits (Chapman & Chapman, 1987; Kim *et al.*, 1992). It has also been reported in a variety of neurodevelopmental disorders as dyslexia, mental retardation and autism (Orr *et al.*, in press).

In general, right-handed subjects have a more asymmetrical brain than those who are left or mixed-handed. The excess of mixed handedness in patients with schizophrenia may correspond to the lack of hemispheric asymmetry observed in their brains. Crow (1997) proposes that this loss of normal asymmetry is genetic. According to his theory, mixed-handedness would reflect a less completely lateralised pattern and should be found in excess also among the unaffected relatives of schizophrenic subjects. In support of this hypothesis is the finding of an abnormal hemispheric asymmetry not only in schizophrenic patients from families with several affected members, but also in those healthy relatives who appear to be transmitting the disorder (Sharma *et al.*, in press).

Is it better to be female?

Schizophrenia affects both sexes but much recent research suggests that severe schizophrenia is more common in males (Castle *et al.*, 1993). There is also a different age-of-onset with male subjects presenting, on average, approximately five years before female subjects. The difference in age of onset between male and female subjects disappears when the patients come from families multiply affected with the disorder (that is heavily genetically loaded). This observation suggests a role for environmental factors in bringing forward the age of onset in males.

Onset is not the only difference between the two sexes. Female schizophrenics are in general more advantaged. They show better premorbid functioning, better social adjustment, and better outcome (i.e., a more schizoaffective picture) (Foerster *et al.*, 1991a, b). Some studies suggest that they also show less

structural abnormalities than male subjects. Males are at increased risk of neurological and neuropsychological damage than their female counterpart (Castle & Murray, 1991). Murray (1994), observing that neurodevelopmental disorders such as autism, dyslexia, conduct disorder and hyperactivity are more common in males, postulates that the early onset observed in male could be the consequence of a greater vulnerability of the developing male brain to environmental insult.

In a comparison of MRI images from schizophrenics and normals, matched for gender and handedness, it was observed that only male schizophrenics showed a reversed hemispheric asymmetry (Bullmore *et al.*, 1995). This is particularly interesting considering that males are generally more severely affected by the illness and show more pronounced structural abnormalities. It is intriguing to suggest that left-sided damage during brain development is more characteristic of male subjects and that the neurobehavioral asymmetries correspond to the neuroanatomical structure.

A DYSPLASTIC NETWORK DISORDER

What does the brain look like?

It seems likely that in some cases at least, the process that characterises schizophrenia starts early in the life of the individual.

Some support for a neurodevelopmental disturbance starts from the suggestion of an abnormal migration of neurons in utero, with a greater number of neurones in the deep layers than in the more superficial ones in the cortex of schizophrenic subjects. At a more macroscopic level, the presence of subtle abnormalities in the brain structure of schizophrenic subjects — enlarged ventricular size, decrease in the volumes of cortex, temporal lobe and hippocampus, and abnormal hemispheric asymmetry — may also have a developmental origin (Suddath *et al.*, 1990).

A possible anomaly in the development of hemispheric asymmetry has also been studied. Normally, the cerebral hemispheres start growing asymmetrically in utero, and by the second trimester of intrauterine life the hemispheric asymmetry is already recognisable. The asymmetry consists of right > left prefrontal, premotor and temporal volumes, and left > than-right occipito-parietal and sensorimotor volumes. In patients with schizophrenia, this

hemispheric asymmetry has been described as reduced (hemispheres more symmetrical) or simply reversed (Luchins *et al.*, 1979; 1982; Bilder *et al.*, 1994). This lack or reversal provides further evidence of a neurodevelopmental aetiology of schizophrenia.

Given the disorders of speech observed in schizophrenia, much interest has focused on the shape and size of the Planum Temporale (PT). The PT is an area on the superior surface of the superior temporal gyrus (STG) of the temporal lobe and it is involved in language comprehension and, to a lesser extent, production. This area has been reported to show a natural leftward (i.e., left > right) asymmetry (Geschwind & Levitsky, 1968) in most right and left-handed subjects. Although it has been suggested that this asymmetry is lost or reversed in schizophrenic patients, other studies have not shown this. Barta *et al.* (1990) observed a reversed asymmetry of the surface of the PT (right > left), but this asymmetry did not correspond to a reversal of its volume. In a recent meta-analysis, Shaplenske *et al.* (1999) remarked that the PT gross anatomical boundaries remain in dispute and the methods of measurements of the PT in different studies lack comparability. They conclude that the PT shows a leftward asymmetry in normals, reduced in left handed and females, and that this asymmetry appears reduced in schizophrenic subjects due to a relatively larger right PT than normal controls.

Loss of connectivity?

Patients suffering from schizophrenia show a diffuse but subtle impairment of neuropsychological tasks, similar to that of mildly brain damaged patients. These deficits are already present in first-episode, never-medicated schizophrenic subjects (Saykin *et al.*, 1994). From an extensive review of the literature, Saykin *et al.* (1991) conclude that schizophrenia is associated with deficits in verbal memory, learning, attention, abstraction and visuo-motor processing.

Using modern imaging techniques, the pattern of cerebral blood flow (a proxy for neuronal activity) during the performance of a specific task or the occurrence of a specific symptom has been studied. Studies on task-activated blood flow in schizophrenic subjects show a reduced blood flow in the frontal lobes (*hypofrontality*) during tests of frontal lobe function as the Wisconsin Card Sorting Test. Studies of brain activation during the execution of ver-

bal fluency tasks (Frith *et al.*, 1995) have shown that in schizophrenic subjects the left dorsolateral prefrontal cortex is activated though perhaps to a lesser extent than in normal subjects. However, schizophrenic subjects show a failure of the normal suppression of activation of the left superior temporal cortex during this task. This is thought to reflect loss of the normal connectivity between the frontal and temporal cortex.

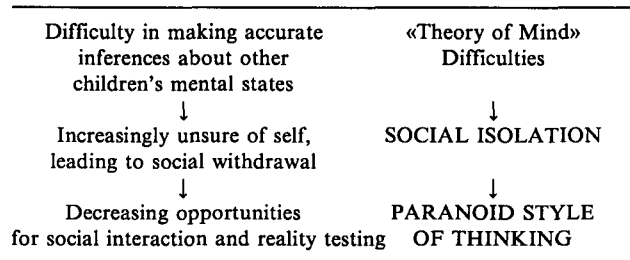


Figure 3. – Self-perpetuating cascade of abnormal function (Jones *et al.*, 1994).

Which hand?

Studies on symptoms have focused on auditory hallucinations. The presence of auditory hallucinations is associated with increased cerebral blood flow in the left frontal and temporal lobes (Gur & Pearlson, 1993). In a study by McGuire *et al.* (1993), patients experiencing auditory hallucinations showed increased blood flow in Broca's area, an area involved in the production of words. It was therefore suggested that hallucinations could represent the patient's misinterpretation of his own inner speech, and that this could arise because of loss of the normal fronto-temporal connectivity, i.e. between the areas concerned with the «inner voice» and those concerned with the «inner ear».

PSYCHOSOCIAL PRECIPITATING FACTORS

Living in the city

The prevalence of schizophrenia is higher in urban than in rural areas (Torrey & Bowler, 1990). It used to be thought that this was explained by selective migration of preschizophrenic subjects from rural to urban areas before the onset of the illness. However, it has been recently observed in several studies (Lewis *et al.*, 1992; Mortensen *et al.*, 1999)

that the risk appears higher in people born or brought up in urban areas, independently from their place of residence. This is not a universal finding and it is not clear what the causes of this are. Possible candidates include overcrowding which could facilitate the spread of infections, and increased exposure to drug abuse or paradoxically to social isolation.

Abusing drugs

Comorbidity between schizophrenia and substance abuse is common, and in particular, cannabis is commonly used, by schizophrenic subjects. The reason for this association is not totally clear. However, there is some evidence that the heavy consumption of Cannabis is associated with an increased risk of psychosis (Andreason *et al.*, 1987), and that cannabis could actually precipitate a psychotic illness in subjects genetically predisposed to the illness (McGuire *et al.*, 1994).

Being an immigrant

The incidence of schizophrenia has been historically reported as increased in groups of immigrants. An initial explanation was the misdiagnosis by local psychiatrists or the cultural intolerance of the host country. Other possible explanations have included the selective migration of predisposed individuals, the role played by the stress of leaving one's own country, and the difficulties in adapting to a different culture (McKenzie & Murray, submitted for publication). Much interest has focused on the high rates of schizophrenia observed in the African-Caribbean population in the United Kingdom (Wessely *et al.*, 1991). This is in contrast with the rates in the Caribbean, which are comparable to those in the white UK population (Bhugra *et al.*, 1997). Most interestingly, the rates are especially increased in the siblings of the second generation suggesting the operation of some environmental factor(s) not present in the Caribbean.

And suffering life events

An excess of life events has been observed in schizophrenic subjects in the 3 weeks preceding the onset or a relapse of the illness, when compared to controls subjects (Bebbington *et al.*, 1993). Some suggest that

the excess of life events could constitute an effect of the illness rather than a cause of it (i.e., the event could be the consequence of the abnormal behavior exhibited in a prodromal phase of the illness or in the initial phase of an incoming relapse. Alternatively, and more probably in our view, social adversity might precipitate psychosis in those already predisposed individuals.

CONCLUSION

There is increasing dissatisfaction with the concept of schizophrenia but little agreement on how to replace it. One historical alternative to the traditional Kraepelinian concept is to apply the «Bonhoeffer paradigm» to schizophrenia. This postulates that identical or similar clinical pictures do not necessarily share the same aetiology and that their course and outcome may be completely different from each other.

In schizophrenia, the presence of similarity in the core Schneiderian symptoms is inevitable, given that such symptoms are necessary for the diagnosis to be made. But such symptoms do not describe the whole picture. A number of recent studies have suggested that a number of other features tend to occur together in two major constellations. On one side, we find male sex, obstetric complications, childhood cognitive and behavioral abnormalities, early onset, neuroanatomical abnormalities and worse outcome. On the other side, we see a different constellation: female sex, later onset of illness, good premorbid and interepisodic functioning, and almost unremarkable brain structure. The first constellation has been said to reflect neurodevelopmental impairment (Castle *et al.*, 1994) and a possible association with language deficits and a less asymmetric brain is currently investigated. The second constellation certainly appear to be similar to the clinical picture of the affective psychosis.

Do these differences reflect different illnesses or do they represent different dimensions of psychosis? They certainly appear to reflect the operation of different aetiological factors, i.e. a) neurodevelopmental and b) affective-socially reactive respectively. Murray *et al* (1992) suggested the existence of two discrete illnesses, both exhibiting Schneiderian first rank symptoms but such a classification was found no better than the traditional Kraepelinian dichotomy, since there appeared to exist many cases in which both factors were operating. Therefore, more

recently, Murray and colleagues (Van Os *et al.*, 1998; submitted for publication) have postulated a dimensional model in which neurodevelopmental impairment is most prominent at the severe «chronic schizophrenic» pole and the affective-reactive factor at the other, «manic-depressive» pole. Such an interpretation allows for many mixed cases.

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