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Neurodevelopmental Schizophrenia: The Rediscovery of Dementia Praecox

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Many people with severe schizophrenia have increased cerebral ventricular size and diffuse reduction in cortical volume; recent attention has focused on subtle malformations of the cytoarchitecture in the hippocampus and parahippocampal cortex. Sufferers also show an excess of dermatoglyphic and minor physical abnormalities, and a significant proportion had psychomotor deficits, cognitive or behavioural problems as children. Such findings suggest that the form of schizophrenia most akin to Kraepelin's original description of dementia praecox results from neurodevelopmental impairment. This may have its origin in genetic defects in the control of early brain growth, or in early environmental hazards such as prenatal exposure to maternal influenza or perinatal complications. How foetal or neonatal lesions produce hallucinations and delusions two or three decades later remains a mystery, but maturational changes in the brain may be important.

It is almost one hundred years since Emil Kraepelin (1896) delineated dementia praecox, or schizophrenia as it came to be known. Kraepelin considered that there was something wrong with the brain in schizophrenia but, sadly, psychiatrists gradually discounted this view. By the 1960s many psychiatrists, and almost all other mental health workers, regarded the idea that schizophrenic symptoms could be consequent upon brain dysfunction as a relict of the primitive thinking of a bygone era. However, it is now clear, as Ron & Harvey (1990) have pointed out, that "to have forgotten that schizophrenia is a brain disease will go down as one of the great aberrations of 20th century medicine".

The modern era of schizophrenia research began in 1976, when Johnstone *et al* showed that some chronic schizophrenics had enlarged cerebral ventricles on computerised tomography (CT). Many studies have now confirmed these findings. Furthermore, it now appears that the ventricular enlargement is present at the beginning of the illness and is not progressive but is instead related to the degree of premorbid impairment (Weinberger *et al*, 1980; Lewis, 1993).

Magnetic resonance imaging (MRI) has confirmed and extended the CT findings. For example, Harvey *et al* (1993), comparing 48 schizophrenics and 34 normal controls, found that total cerebral volume was slightly, but significantly, reduced in the schizophrenic subjects. This overall decrease was entirely accounted for by a more striking decrease in the volume of the cortical grey matter. These volume decrements were not found in a comparable series of bipolar patients (Harvey *et al*, 1994), indicating that they are not a feature of psychotic patients in general.

Even in the darkest days when psychiatrists were regularly accusing the parents of schizophrenics of having induced the illness in their children, some retained a more balanced view. In 1962, Eliot Slater presented a paper at the Royal Society of Medicine in which he suggested that the psychoses associated with temporal lobe epilepsy represent a model of schizophrenia (Slater & Beard, 1962). In the subsequent discussion, the distinguished neurologist Sir Charles Symonds stated, "The schizophrenia-like symptoms of temporal lobe epilepsy suggest that the temporal lobe includes within its boundary, circuits concerned with the physiological basis of the psychological disorder which we call schizophrenia."

Since that time, schizophrenia researchers have been particularly interested in the grey matter of the temporal lobe. Recent MRI studies have found that this is reduced in overall volume (Harvey *et al*, 1993, 1994), and much attention has focused on structures within the temporal lobe. For example, Bogerts *et al* (1990*a*) suggested that the volume of the hippocampus is decreased by about 20% in schizophrenia.

If neuroimaging studies can show these abnormalities in life, then one would expect that post-mortem studies would show similar findings. Indeed, neuropathological studies have reported slightly but significantly reduced brain weight and brain volume in schizophrenia (Brown *et al*, 1986; Pakkenberg, 1987; Bruton *et al*, 1990). The MRI findings of decreased cortical volume have been complemented by neuropathological evidence of thinning of the prefrontal cortex (Selemon *et al*, 1993), while Brown *et al* (1986) showed that,

compared with subjects with affective psychoses, schizophrenic subjects had larger lateral ventricles, especially temporal horns, as well as thinning of the parahippocampal cortex. Bogerts *et al* (1990*b*) also found a smaller hippocampus and hippocampal gyrus at post-mortem.

Why should it matter if an individual has decreased cortical volume, or smaller hippocampi? The diminished volume may be important because it indicates likely abnormalities of the cellular architecture (Harvey *et al*, 1993). Kovelman & Scheibel (1984) were the first to report that there were abnormalities of the cellular organisation of the hippocampus in schizophrenia. They claimed that some of the pyramidal cells in the CA1 and CA2 regions were misplaced and disorientated. In addition, several studies (e.g. Jakob & Beckman, 1986) have now shown that a group of cells – the pre-alpha cells – have not migrated into their normal position in the parahippocampal gyrus in some schizophrenic people. Akbarian *et al* (1993) have reported frontal and temporal alterations in cell distribution consistent with a disturbance of the cortical subplate during brain development.

It seems unlikely that the above cytoarchitectonic abnormalities could have arisen other than through some failure of cerebral development in foetal or, at latest, neonatal life. The evidence implicating abnormal early development has been strengthened by the finding of increased frequency in schizophrenia of normally rare congenital brain abnormalities, such as cavum septum pellucidum and agenesis of the corpus callosum (Lewis & Mezey, 1985; Lewis *et al*, 1988). Schizophrenic subjects are also more likely to show an excess of minor physical anomalies, particularly craniofacial, and dermatoglyphic abnormalities (Green *et al*, 1988; Mellor, 1992); once again, these suggest abnormal foetal development.

What causes the structural brain abnormalities?

Genes

A genetic contribution to schizophrenia is widely accepted (Murray *et al*, 1986; McGuffin *et al*, 1987), although two recent reviews of twin studies suggest that it has been overestimated (Walker *et al*, 1991; Torrey, 1992). Similarly, a recent (unpublished) follow-up and reassessment of the famous Maudsley twin series of Gottesman & Shields (1972) has produced considerably lower heritability estimates for DSM–III schizophrenia than those previously calculated. Molecular genetic studies are attempting to identify the predisposing genes but as yet there have been no replicated positive reports (Murray & Gill, 1990; Gill *et al*, 1993). Since schizophrenia is associated with faulty brain development, then perhaps particular attention should be paid towards genes which are involved in the control of neurodevelopmental processes (Jones & Murray, 1991).

In 1982, Reveley *et al* published a CT study which compared ventricular size in a series of identical twins who were discordant for schizophrenia; the schizophrenic twins had larger ventricles than their well co-twin. This finding has been confirmed and extended by Suddath *et al* (1990), who carried out MRI scans on 15 pairs of identical twins discordant for schizophrenia. The schizophrenic twins had larger ventricles and less temporal lobe grey matter than their identical co-twins. As identical twins have identical genes, these findings suggest that the structural changes which predispose to later schizophrenia are, at least in part, environmental in origin.

Obstetric complications

Since neuropathological studies suggest that the abnormalities are present either at or before birth, any environmental insult must operate very early in life. What could it be? Many studies have shown that obstetric complications are commoner in early onset (e.g. O'Callaghan *et al*, 1992), male (Owen *et al*, 1988; O'Callaghan *et al*, 1992), and in chronic schizophrenic subjects than in controls (Murray *et al*, 1988; Lewis *et al*, 1989). Particularly convincing are those studies which have gone back to the original birth records and thus exclude the possibility of retrospective bias (Eagles *et al*, 1990; O'Callaghan *et al*, 1992).

Acute, late-onset and female schizophrenic subjects do not seem to share the excess of obstetric complications. This may be one reason why not all studies show an association with obstetric complications (Done *et al*, 1991). In addition, we must remember that perinatal complications themselves may sometimes be a consequence of some earlier anomaly. This fact was first pointed out by Sigmund Freud (1887), who studied the relationship between birth trauma and cerebral palsy and suggested that "the difficult birth in itself is merely a symptom of deeper effects that influenced the foetus".

Maternal influenza

One of the most consistent epidemiological findings in psychiatry has been that people with schizophrenia

are more likely to be born in the late winter and spring months (Hare, 1988). The most obvious explanation is exposure to viral infection *in utero*, for many viral infections are commoner in winter. Mednick *et al* (1988) examined the effect of the pandemic of 'Asian flu' which occurred in Helsinki in the autumn of 1957. They claimed that several months after the influenza epidemic (i.e. in spring 1958), there was a doubling of the number of births of people who subsequently were diagnosed as schizophrenic.

O'Callaghan *et al* (1991) examined similar but much larger data for most of England and Wales, and compared births of schizophrenics in the months August 1957 to July 1958 with similar births in the two years before and two years after the index 12 months. The epidemic was in September/October 1957, and then, five months later, there was an 88% increase in the births of schizophrenics over that expected. Similar replications have now come from Kinugi *et al* (1992) and Adams *et al* (1993). Barr *et al* (1990) and Sham *et al* (1992) have studied the relationship between the prevalence of influenza and the number of schizophrenic births in Denmark and England over four and two decades, respectively. Both studies showed that influenza epidemics had a small but consistent 'schizophrenogenic effect' in increasing the births of people who later became schizophrenic. Thus, in spite of some dissent (e.g. Kendell & Kemp, 1989; Crow *et al*, 1991), it seems that maternal influenza may contribute to the aetiology of a minority of schizophrenics.

The mechanism whereby maternal influenza increases the risk of schizophrenia in the unborn baby is not established. Any theory must explain why only a minority of mothers infected with influenza during pregnancy have a child who becomes schizophrenic. Knight (1991) pointed out that rabbits inoculated with influenza produced an antibody that cross-reacted with a neuronal protein, and suggested that a maternal antibody to influenza might cause auto-immune damage to the brain of the foetus. Wright *et al* (1993), therefore, proposed that certain mothers may be genetically predisposed to produce the harmful immune response.

Varying incidence?

If perinatal hypoxic ischaemic damage or maternal influenza can increase the risk of schizophrenia, then the incidence should vary according to the prevalence of these and other early environmental hazards. This is a view which goes directly against accepted dogma, for most psychiatrists believe that schizophrenia shows the same incidence over time and place (Sartorius *et al*, 1986). If the latter were the case, it would be a unique phenomenon among common medical disorders, which usually vary both geographically and temporally (Barker, 1989).

Hare (1988) has long maintained that schizophrenia became much more common during industrialisation in the 19th century, and that throughout the 20th century schizophrenia has been becoming milder. In addition, studies from Scotland, England, Ireland, Denmark, New Zealand and Australia have suggested that the incidence of schizophrenia may have been declining over the last 20 years (Der *et al*, 1990). Gupta & Murray (1991) claim that this decline cannot be explained away in terms of a change in diagnostic habits or in terms of more schizophrenic individuals being treated in the community. It is certainly clear that any decline is far from uniform. Schizophrenia is still disturbingly common in inner cities. Indeed, Castle *et al* (1991) have shown that rates of schizophrenia in the deprived area of Camberwell in south London have, if anything, increased.

The high rates in south London are largely due to the influx into the area of Afro–Caribbeans who do not have a high incidence of schizophrenia in the West Indies but undoubtedly do in the UK (Castle *et al*, 1991). Is it possible that this now predominantly inner-city population is encountering similar 'schizophrenogenic' environmental factors as affected migrant whites, when the native British population became urbanised in the 19th century? There is much evidence that there are higher rates of schizophrenia in inner cities. Many authorities believe that this can be explained by social drift, but a brief look at the evidence leads one to conclude that this is not a sufficient explanation (Castle *et al*, 1993*a*). Furthermore, in discussing aetiological factors, Kety (1980) has suggested that:

> "Certain biological hazards associated with lower social class should also be considered. To the extent that perinatal injuries, malnutrition and pre-natal infection may play roles in the environmental aetiologies of schizophrenia their impact would be exaggerated in the lower social classes in large cities."

Takei *et al* (1992) have examined the relationship between place of birth and risk of schizophrenia in England and Wales. Birth in cities and towns with more than 100 000 inhabitants was associated with an 18% increase in risk of later schizophrenia. The increased risk was not present among those born in summer, but reached 25% in those born in winter. Two other studies have also shown that urban-born schizophrenics are particularly likely to show a

winter-birth excess. These findings are compatible with the view that density of population promotes transmission of some pathogenic winter-born infection(s).

Structure and function

What other predictions can one make from the neurodevelopmental hypothesis? If the anomaly is present at or before birth, then it seems unlikely that an affected individual would be entirely normal throughout childhood until delusions and hallucinations develop in adolescence or early adult life. Indeed, many studies have shown that some schizophrenic adults were deviant as children. Premorbid IQ scores of schizophrenics obtained during childhood are lower than the scores of their siblings, and some studies suggest that approximately 40% of schizophrenics show abnormalities of personality and social adjustment in childhood (Foerster *et al*, 1991*a*,*b*).

Several investigators have followed up large cohorts of infants and compared the few who became schizophrenic with the vast majority who did not. Thus, Jones *et al* (1994) examined the childhood characteristics of 4746 children born during one week in 1946. Those who later became schizophrenic were slower to pass their developmental milestones (e.g. walking) than normal, were more likely to play alone at the age of four years, and showed poorer performance on verbal and non-verbal tests at the age of eight.

Using a novel approach to address the same issue of premorbid deficits, Walker (1993) examined home movies of preschizophrenic children, taken by their parents. Compared with movies of normal children, the preschizophrenics showed more postural and movement abnormalities of the upper limbs, particularly during the first two years of life.

Several studies have linked deficits in childhood function (e.g. Weinberger *et al*, 1980; Lewis, 1993; Harvey *et al*, 1994) with structural brain abnormalities, and these in turn have been shown to be associated with negative symptoms and neuropsychological impairment (Lewis, 1993). Furthermore, Rifkin *et al* (1994) have shown that low birth weight predicts childhood social dysfunction, poor scholastic performance, and cognitive impairment in adulthood among schizophrenic men (but not women).

It is easy to see how the neuronal abnormalities in the frontal and temporal lobes could result in an abnormal pattern of cortical connections, thus causing the premorbid abnormalities shown by many preschizophrenic children, and indeed the social and cognitive deficits shown by schizophrenic adults. But could a pre- or perinatal lesion produce the positive symptoms of schizophrenia two decades later? The evidence of animal studies is that early brain lesions can be largely silent until the animals reach adult life. This is the case for lesions of the dorsolateral prefrontal cortex in prenatal monkeys (Goldman-Rakic *et al*, 1983). Furthermore, Lipska *et al* (1993) have shown that lesions made in the hippocampus of one-week-old rats remain behaviourally silent until early adult life, when hyper-responsiveness to stress and amphetamine challenge develop.

Is it possible that a similar process explains why preschizophrenic children do not show the positive Schneiderian symptoms of schizophrenia until adolescence or early adult life (Pilowsky & Murray, 1991)? Perhaps the lesions lie dormant until the normal processes of brain maturation in adolescence lead to the use of neuronal circuits that are not greatly developed in children. Benes (1989) has pointed out that the perforant pathway which provides one of the most extensive inputs to the hippocampal formation does not normally myelinate until adolescence. Her suggestion is that the myelination of this pathway signals the much greater importance of the prefrontal–hippocampal circuitry in the adult, and allows a previously latent defect in the parahippocampal cortex (e.g. misplaced pre-alpha cells) to become manifest.

An alternative hypothesis points out that the normal process of pruning of cortical synapses continues throughout adolescence, and suggests that an abnormality of the pruning of dopamine synapses may be critical to the development of psychotic symptoms (Feinberg, 1983). The dopamine hypothesis has a long history, but it has proved difficult to demonstrate unequivocal dopaminergic abnormalities in living schizophrenic patients. However, Pilowsky *et al* (1994) used single-photon emission tomography in 20 drug-free schizophrenic patients to show relatively increased D_2 receptor density in the left basal ganglia. This finding parallels that in two ligand studies using positron emission tomography, and is reminiscent of Reynolds' (1983) earlier post mortem evidence of increased dopamine in the left amygdala of schizophrenics.

There is indeed growing evidence that schizophrenia is particularly associated with left-sided pathology. Flor-Henry (1969) originally suggested that temporal lobe epilepsy was more commonly associated with schizophrenia-like symptoms when the focus was left-sided. Several recent studies have suggested left-sided volume deficits of structures, such as the planum temporale, which are thought to play a role in language.

McGuire *et al* (1993) carried out a study of 12 schizophrenic men at the precise moment when they indicated they were hearing voices, and then repeated the examination at a later time when the patients were free of hallucinations. A comparison of cerebral blood flow at the two points showed that the auditory hallucinations were associated with increased blood flow to Broca's area and other left-sided regions thought to be involved in speech. This is particularly intriguing since psychological theorists have suggested that auditory hallucinations may be 'inner speech' which schizophrenics falsely label as alien.

Sex differences

The neurodevelopmental hypothesis proposes that a proportion, but only a proportion, of schizophrenics appear to have a disorder which results from either the inheritance of abnormal genes which impair brain development, or from some form of foetal or neonatal adversity (Murray *et al*, 1988, 1992). The resultant cortical abnormalities produce the precursors of the negative syndrome in childhood with cognitive impairment, abnormal personality, and poor social adjustment (Foerster *et al*, 1991*a*,*b*). Then brain maturational changes in adolescence facilitate the development of delusions and hallucinations in early adult life.

Table 1 shows the number of incident cases of schizophrenia in Camberwell, south London, meeting various criteria for the disorder. It can be seen that only about one-third of those who were regarded as schizophrenic by clinicians using ICD rules met DSM-III criteria for the disorder. Furthermore, while the number of ICD cases in the two sexes was roughly equal, the narrower the criteria the greater became the male predominance (Castle *et al*, 1993*b*). In the above sample, as in almost all others, the onset of the disorder was later in women than in men.

There are two main explanations proposed for the greater severity and earlier onset of schizophrenia in males. The first suggests that during their reproductive years, females are partially protected by their production of oestrogen, which is thought to have some antidopaminergic actions. There is a simple way of testing this theory: to compare age at onset of schizophrenia in male and female cases with the same aetiology (i.e. genetic). Thus, Walsh *et al* (1993) have examined 168 cases of schizophrenia from families multiply affected with the disorder. Age at onset was early compared with the Camberwell epidemiological sample, and age at onset in the familial males and females was no different – oestrogen had no protective value.

Table 1
Numbers of first-contact patients in Camberwell 1965–84, fulfilling different criteria for schizophrenia

Criteria	Male	Female	M:F ratio
ICD	239	231	1:1
RDC	164	157	1:1
DSM-III-R	108	88	1.2:1
DSM-III	108	50	2.2:1
Feighner	96	39	2.4:1

Modified from Castle *et al* (1993*b*).

An alternative explanation arises from the evidence that the brains of schizophrenic men are significantly more abnormal than the brains of schizophrenic women (Castle & Murray, 1991). Why should this be? If we believe that obstetric complications are important in determining cerebral abnormalities, we should examine their sex distribution. Schizophrenic men have a higher rate of obstetric complications than schizophrenic women. The reason why the brains of schizophrenic men are more abnormal may be that more males have suffered neurodevelopmental insult.

If that is the case, then one would expect that a higher proportion of male preschizophrenic children would be abnormal, and that is exactly what has been found. Premorbid IQ deficit is uncommon in preschizophrenic girls, but appears to be a more pronounced characteristic of preschizophrenic boys. Foerster *et al* (1991*a*,*b*) examined premorbid personality and social adjustment in male and female psychotics. There were no significant differences in personality or in social adjustment between girls who went on to become schizophrenic and girls who went on to develop affective psychosis. However, preschizophrenic boys showed more abnormalities of personality and poorer social adjustment than pre-affective boys.

Those preschizophrenic children who had abnormalities of personality or cognition also had an early onset of psychosis. As more preschizophrenic boys show these abnormalities in childhood, it is not surprising that male schizophrenia presents, on average, five years earlier than female schizophrenia. Neurodevelopmental disorders – autism, dyslexia, conduct disorder, hyperactivity – are commoner in males. Thus early-onset schizophrenia shows the sex distribution characteristic of neurodevelopmental disorders. It seems likely that this excess of early-onset schizophrenia in males is a consequence of the greater frequency of neurodevelopmental schizophrenia in males (Castle & Murray, 1991). An analysis by Kirov *et al* (1994)

has shown that once patients with schizophrenia who have a history of obstetric complications are removed, then the gender differences of age of onset of schizophrenia disappear. This raises the question of whether the earlier age of onset for schizophrenic men is simply a reflection of their greater frequency of obstetric complications.

Conclusions

Neurodevelopmental schizophrenia has a great deal in common with dementia praecox as described by Kraepelin in 1896. Kraepelin originally believed that dementia praecox had its maximum incidence in young men, and stated (1896):

> "Men appear to be three times more likely than women to suffer from the forms of illness described here, a fact which seems strange when one considers the reverse ratio in catatonia".

Catatonia was not originally included in dementia praecox but Kraepelin subsequently broadened his concept to include catatonia and many paranoid psychoses, so that more female and later-onset cases were included. Bleuler and Schneider continued to expand the boundaries of schizophrenia. Consequently, I believe that we now confuse dementia praecox with relapsing and remitting conditions which present with positive Schneiderian symptoms but which differ in epidemiology, brain morphology, and clinical course. It is time to return to the original narrow concept of dementia praecox which, it is now clear, has a neurodevelopmental origin.

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