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Childhood precursors of psychosis as clues to its evolutionary origins

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Abstract Those who as adults will be admitted to a psychiatric ward with a psychotic illness can be distinguished (on the basis of group differences) from others by their behaviour and academic performance at the ages of 7 and 11 years. Pre-schizophrenic boys are anxious and hostile towards adults and peers at the age of 7 years and show poor concentration. By age 11 years these boys are also rated as depressed, and pre-schizophrenic girls as depressed and withdrawn. Pre-affective psychotic boys show minor changes (for example an increase in hostility and restlessness) at age 7 years, although these features are not obvious at age 11 years. Abnormalities that in some respects resemble those in pre-schizophrenic boys are present at age 11 years in a group of females who will be admitted to psychiatric units with non-psychotic diagnoses by the age of 28 years. Academic impairments (including speech and reading difficulties) at ages 7, 11 and 16 years are more severe in pre-schizophrenics than in the other groups. Schizophrenics-to-be are slow to develop continence and show poor coordination and vision at age 7 years, and are rated clumsy at age 16 years. Psychosis reflects a disturbance of aspects of central nervous system function that are time-dependent and in certain respects gender specific. It is argued that the psychoses represent extremes of variation in a gene (or genes) that differs between the sexes and controls the timing of development of the two cerebral hemispheres. The diversity associated with this gene(s) may be maintained by the selective pressures that have led to the neotenic process of encephalisation in humans and the evolution of language.

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Introduction

Psychotic illness is common and apparently universal in human society (Jablensky et al. 1992). What is its origin and why does it persist? These questions may be unanswerable if they are not recognised as related to more fundamental questions such as the characteristics that distinguish humans from other primate species and the nature of human individuality. It is arguable that the phenomena of psychotic illness provide important clues to the evolution of homo sapiens.

Since Kraepelin (1919) it is conventional to distinguish between schizophrenic and manic-depressive psychoses. However, although the association between form of illness and outcome is undoubted, and prototypical affective and schizophrenic illnesses are observed, great diversity in clinical manifestations and outcome is commonplace, and there is serious question whether a fundamental distinction between categories of psychotic illnesses can be drawn. For these reasons it is more realistic to regard the variations in psychosis as part of a continuum, rather than discrete illnesses (Crow 1990b).

This conclusion influences the set we should adopt in considering the problem of causation. The diversity of human personality and intellectual ability is relevant. In some way variation within the normal population is related to the abnormalities that present themselves as disease. One must assume either that the manifestations of illness depend on an interaction between an extrinsic pathogen and the individual's pre-existing psychological structure, or perhaps more parsimoniously, that personality ad illness are part of a single developmental process.

The epidemiology of psychosis emphasises the singularity of the problem. The WHO Ten Country study shows that when schizophrenia is defined restrictively and when steps are taken to identify all presenting cases, incidence rates are remarkably similar in populations in widely varying climatic, industrial and social environments (Jablensky et al. 1992). In this respect psychotic illness differs from most, if not all, other common illnesses. It ap-

pears invariant with regard to the environment; it may be intrinsic to human nature.

Onsets are rare before puberty, but then rise steeply, and remain high throughout the reproductive period of life (Penrose 1991). This is paradoxical if the disease is genetic, because it significantly impairs procreativity (MacSorley 1964). Onset itself requires an explanation, because it cannot be attributed to an environmental precipitant. When illness occurs in two siblings it occurs at the same age, and not the same time (Crow and Done 1986).

Kraepelin (1919) drew attention to what is perhaps the most puzzling aspect of onset, the sex difference, which is perhaps the best established, but least explained, epidemiological fact about schizophrenia. Onsets are earlier in males than females by 3–4 years, and this difference cannot be accounted for by differences in the facility with which early symptoms are detected or patients admitted to the hospital (Häfner et al. 1992; Lewine 1991).

New light has been cast upon onset by a cross-cultural comparison of case registers (Eaton et al. 1992). Early onset predicts likelihood of relapse, as do male gender and single status. When onset is taken into account, however, neither gender nor marital status add significantly to prediction. A single variable concerned with timing an aspect of central nervous system (CNS) development is a major determinant of the course of the disease.

What is the significance of onset itself? Onset is conveniently defined as the point of hospital admission which reflects that a threshold of distress or behavioural disturbance has been passed. It may or may not correspond to the onset of psychotic symptoms, but it is well recognised that this event is often preceded by dysfunction that has lasted for months and sometimes years. In two recent studies duration of symptoms before onset was found to be a predictor of outcome following a first episode of illness (Crow et al. 1986; Loebel et al. 1992). Of more fundamental significance are precursors in childhood that are related in a systematic way to the form of psychosis in adult life. That there are such precursors has been suggested by a number of retrospective studies of the childhoods of individuals who later developed schizophrenia. Lane and Albee (1964) found that the intelligence scores in the second, sixth and eighth grades at school of children who became schizophrenic were significantly reduced compared with their siblings. Offord and Cross (1971) found low intelligence quotient (IQ) in childhood to be a predictor of early age of onset and longer duration of hospitalisation, and Offord (1974) reported that the deficit in IQ and poor school performance relative to siblings applied particularly to males. Gittelman-Klein and Klein (1969) had previously identified a group of schizophrenic patients with "premorbid asociality" who also had academic problems and were likely to have a poor outcome. In a study of school records Watt (1978) described pre-schizophrenic girls in their early school years as emotionally unstable, introverted and passive, and the boys as emotionally unstable and disagreeable, becoming more so in later school years.

Some follow-up studies have yielded comparable findings. Thus Hartmann et al. (1984) identified 24 individuals in the cohort of 500 delinquent and 500 non-delinquent boys that Glueck and Glueck (1950) had studied between the ages of 10 and 17 years 40 years earlier, who had been diagnosed as suffering from schizophrenia in adult life. The 24 pre-schizophrenics were matched for IQ, ethnicity, original grouping and age at testing with 48 non-schizophrenic controls. Five psychosocial indicators were identified as significant predictors of a schizophrenic outcome: lack of historicity (lack of sense of self continuing over time, poor goal direction), anxiety, difficulty in interpersonal relationships, lack of competency (developmental delays, poor schoolwork) and permeable boundaries (easily distracted, daydreaming, tangential thinking).

Amongst child-guidance attenders Ambelas (1992) matched 18 boys who subsequently met DSM-III criteria for a diagnosis of schizophrenia for age, sex and time and reason of referral with 18 control attenders. The index group were more likely to have been diagnosed as suffering from a mixed emotional and conduct disorder and less likely to have an adjustment reaction, were more likely to have had developmental (including speech, language and reading) and relationship problems, and had lower IQs.

Across studies the picture that emerges is that individuals who are later destined to suffer from schizophrenic illnesses are distinguishable (at least on the basis of group means) from individuals not so predisposed 10 or 15 years before the onset of psychosis. The distinguishing features include academic performance and difficulties in establishing interpersonal relationships. There is at least a suggestion that deficits in IQ are a predictor of poor outcome. Questions that are unanswered are the time course of emergence of these impairments, the relationship between them and the meaning of the sex difference.

United Kingdom perinatal mortality survey and national child development study

The Perinatal Mortality Survey included 98% of all births in England, Scotland and Wales registered during the week 3–9 March 1958. Four subsequent attempts to trace all members of the cohort to monitor physical, educational and social development (in 1965, 1969, 1974 and 1981) became known as the National Child Development Study (NCDS). There were 16,980 individuals in the Perinatal Mortality Survey and 15,398, 15,303, 14,761 and 12,537 in the subsequent follow-ups, at ages 7, 11, 16 and 23 years, respectively. Using the Mental Health Enquiry (a register of admissions to psychiatric hospitals and units that continued until 1986) we were able to identify all cases recorded in the NCDS who had been treated as inpatients for psychiatric reasons between 1974 and 1986, i.e. until the cohort members were aged 28 years. From the case histories PSE CATEGO diagnoses (Wing et al. 1974) were derived to give groups of patients suffering from schizophrenia by broad (n = 57) or by narrow criteria (the presence of nuclear symptoms; n = 40), affective psychosis (n = 35) and neurosis (n = 79; Done et al.

1991). These groups were compared either with the total sample (Done et al. 1991) or with a randomly selected 10% sample (Done et al. 1994a) of individuals within the NCDS population who had never been admitted to a hospital for psychiatric reasons.

Behavioural assessments at the ages of 7 and 11 years

At the ages of 7 and 11 years the teacher of each subject in the NCDS cohort was asked to complete the Bristol Social Adjustment Guide (BSAG), a standardised psychometric test of social adjustment and maladjustment in which the teacher underlines which of approximately 200 descriptions of school behaviour are relevant to the child. From these assessments a number of core syndromes are identified, and these can be placed into two groups of over- and under-reaction. In over-reaction are included the syndromes hostility towards adults, hostility towards children, anxiety for acceptance by adults and children, inconsequential behaviour and restlessness; in under-reaction are included unresponsiveness, withdrawal and depression, as well as dismissing adult values. Two further categories comprise miscellaneous symptoms and miscellaneous nervous symptoms. The major descriptors of the items that make up these syndromes are listed in Table 1. Comparisons were made between a group of patients with schizophrenia (narrow criteria, $n = 40$). With affective psychosis ($n = 35$), neurosis ($n = 79$) and a 10% random sample of the NCDS populations assessed in the follow-ups at 7 and 11 years never admitted to a psychiatric facility. Reports on clinically recognised emotional maladjustment were made by the medical officer who interviewed cohort members and had access to information obtained in an interview with the parents. There was no significant increase in emotional maladjustment in any of the patient groups. On the BSAG ratings differences are present at the ages of 7 and 11 years that cast light on the nature and development of the psychotic disease process.

Table 1 Bristol Social Adjustment Guide

Over-reaction
Anxiety for acceptance by adults:
Overly friendly or talks excessively to teacher
Seeks to engage excessively/monopolise teacher
Anxiety for acceptance by children:
Buffoonery, overly brave, shows off, brags
Hostility towards adults:
Variability of mood and perfomance when asked to do something
Damages property, lies, uses bad language
Steals, aggressive
Hostility towards other children:
A variety of criteria for being unpleasant towards other children
Inconsequential behaviour:
Poor concentration, undisciplined
Careless und untidy, lazy, mischievous
Restlessness:
Too restless in indiviual games or when working alone, lacks persistence
Under-reaction
Unforthcomingness (unresponsiveness):
Timid and shy, e.g. does not initiate conversations, reluctant to approach teacher
Withdrawal:
Distant, cut off from people, avoids communication
Depression:
Mood variation, sometimes alert, sometimes lethargic and lacks interest
Usually apathetic, lifeless or miserable and depressed
Writing off (dismissing) adult values:
Unwilling to work except when compelled to do so
Suspicious, selfish, untrustworthy
Miscellaneous
Miscellaneous symptoms:
Immature and babyish, plays with younger children, gets bullied
Truant
Miscellaneous nervous symptoms:
Stutters, twitches, bites nails badly

At the age of 7 years pre-schizophrenic subjects are rated as more anxious and hostile towards adults and children and more likely to engage in inconsequential behaviours (Fig. 1), each of these differences being significant at the 1% level of less. These differences are largely confined to males. Moreover, with the exception of the category of miscellaneous symptoms, the differences between patients and controls are confined to the component of over-reaction; there are no differences with regard to unresponsiveness and withdrawal, and the difference for depression is significant (for males) only at the 10% level. The changes are therefore gender-specific and relate to those components of behaviour that one might be inclined to relate to positive rather than negative symptoms.

At the age of 11 years the picture has changed (Fig. 1). Pre-schizophrenic females, as a group, are now rated as more withdrawn and depressed than controls, and as more likely to dismiss adult values, each of these differences being significant at the 1% level or less (see legend to Fig. 1 for note regarding significance levels). Males are rated as significantly more likely to be depressed, although not withdrawn, and there is a trend with regard to dismissing adult values. Even at this age the female group shows no evidence of the over-reaction that was present in the male group 4 years earlier, with the exception of a trend in relation to hostility towards adults.

One may ask what proportion of the male group is rated as abnormal at the age of 7 years. On an aggregate of over-reaction ratings 50% of the pre-schizophrenic group were rated 13 or above, whereas only 10% of the comparison group achieved such a rating. Fifty percent of the boys (and presumably nearly all the females) are being

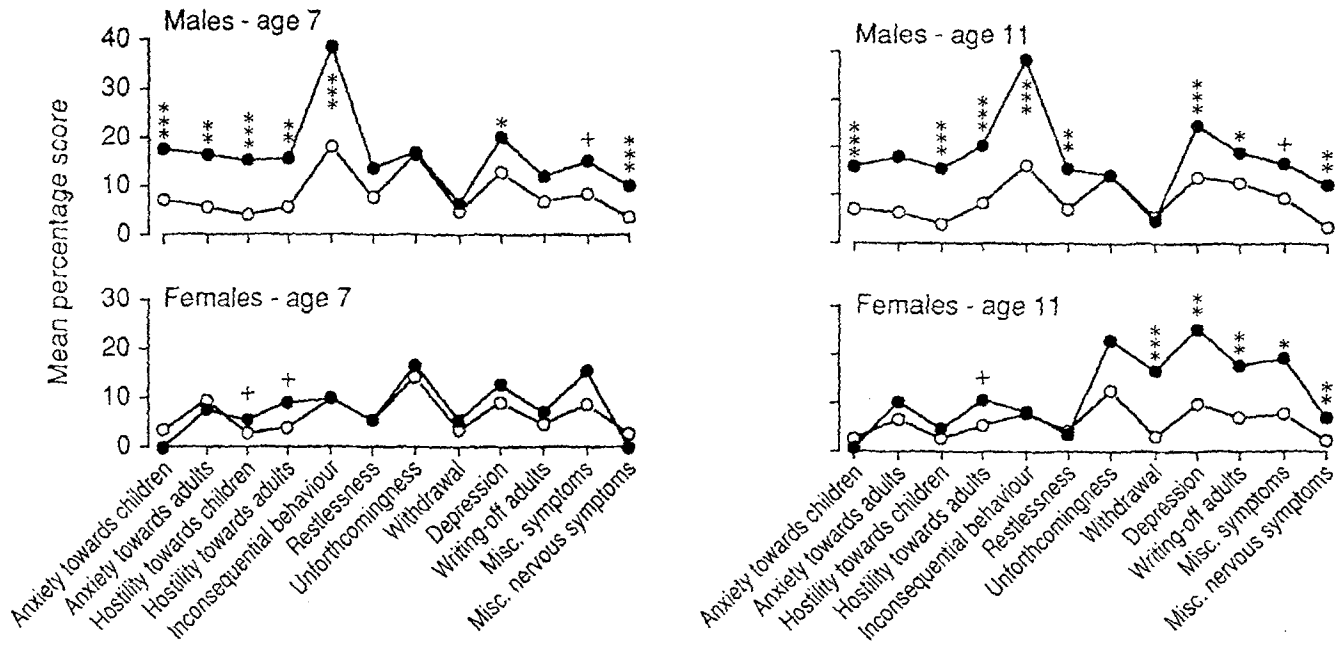

Fig. 1 Bristol Social Adjustment Guide (BSAG) profile in pre-schizophrenics: $^{+}P < 0.1$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.005$. Note that P values based on Mann-Whitney U-tests for each syndrome are uncorrected for multiple testing. We have previously (Done et al. 1994a) examined profile differences across core syndromes, the significance values for those comparisons incorporating a correction for multiple testing

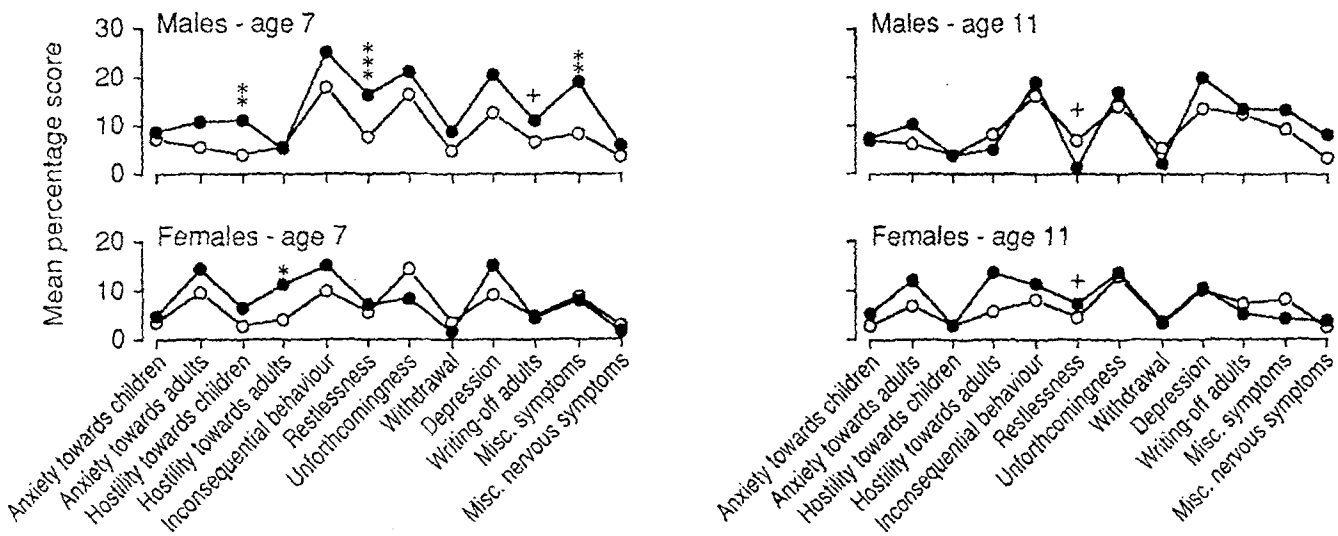

Fig. 2 BSAG profile in pre-affectives aged 7 and 11 years (for significance values see legend to Fig. 1)

rated well within the normal range. It should be recollected also that very few of these children are being assessed as emotionally disturbed, although they have been seen by a medical officer who has available parents' (and teachers') ratings and has been asked to address this question.

The profile of behaviour for the pre-affective psychotic boys at age 7 years is notably different (Fig. 2). Although the overall profile does not significantly differ from controls, examination of core syndromes reveals that they were rated more hostile to other children and more restless. Both features have disappeared by the age of 11 years. Females are rated as slightly more restless ($P < 0.1$) than controls at age 11 years, but are otherwise unremarkable in their profiles.

The pre-neurotic group (patients admitted to a psychiatric hospital with a non-psychotic diagnosis by the age of 28 years) are noteworthy in that at age 11 years they show changes that are generally greater than those present in pre-affective psychotics and, by contrast with pre-schizophrenics, these deviations are more marked in females than in males (Fig. 3). At age 7 years the differences are small, but the pre-neurotic females are more anxious and hostile to other children, and the males show more anxiety towards adults, these differences being significant at the

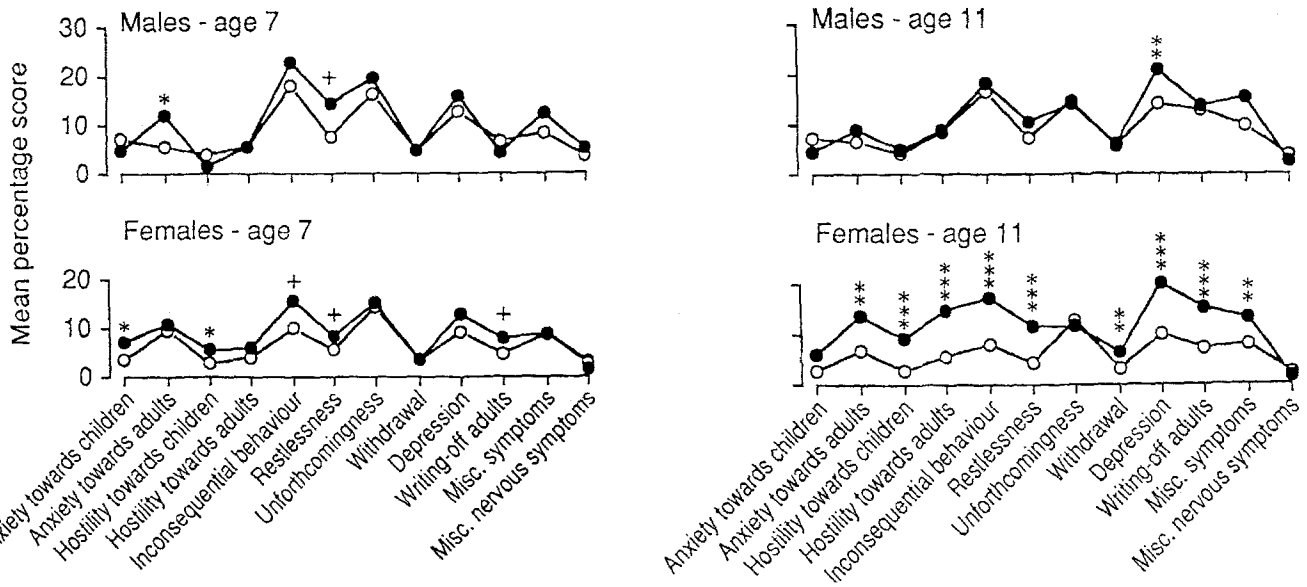

Fig. 3 BSAG profile in pre-neurotics aged 7 and 11 years (for significance values see legend to Fig. 1)

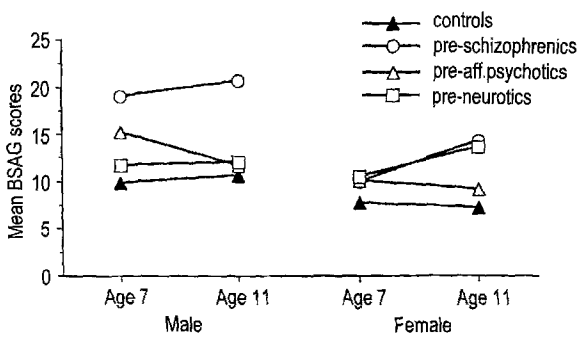

Fig. 4 Changes in BSAG profiles between ages 7 and 11 years

5% level. There is a trend ($P < 0.1$) towards more inconsequential behaviour in females, and restlessness in both sexes. At age 11 years a large number of significant ($P <$ 0.01 or less) differences between female pre-neurotics and controls have emerged. For over-reaction these differences encompass all features, with the exception of anxiety towards other children. The females are also more depressed and withdrawn (less so than pre-schizophrenics), but not less forthcoming than controls. The males differ from controls only in being more depressed. Therefore, in several respects these individuals, who will be admitted with a non-psychotic illness to a psychiatric unit before they are aged 28 years, resemble those who will be admitted with a diagnosis of schizophrenia, but the changes are present (and have emerged at a slightly later stage of development) in females rather than in males. Most of these patients acquire a diagnosis of depression. Whether they will suffer from a psychotic illness, either affective or paraphrenic, at a later age cannot be determined from our database, because the Mental Health Enquiry did not continue beyond 1986.

The major changes over time and their relationships between the groups are summarised in terms of total BSAG ratings in Fig. 4. Here it can be seen that for males the pre-schizophrenic group is well separated from the controls at ages 7 and 11 years whereas the pre-affective psychotics apparently become more normal and the pre-neurotics are not distinguished from the controls at either age. For the females the pre-affective psychotics show no gross abnormality at either age, but the pre-schizophrenic and pre-neurotic groups become more abnormal between these ages.

Because in various respects the pre-schizophrenic group differs from the NCDS population as a whole – for example, they show academic impairments (see below) and were more likely to have been in care, experienced parental separation or loss, or to have been referred to a specialist for emotional problems – the question of whether the behavioural anomalies could be secondary to these differences arises. However, in a covariance analysis (Done et al. 1994a) that took these variables into account and also included social class the difference between pre-schizophrenics and controls remained significant ($F_{1,1470} = 6.3$; $P = 0.01$) after these adjustments. Therefore, the group differences in behaviour do not appear to be a consequence of adverse social or educational experience.

Academic performance

Assessments of reading and mathematical ability were made in the NCDS cohort at the ages of 7, 11 and 16 years, and a test of general ability (GAT) that includes an assessment of verbal and non-verbal intelligence was administered at the age of 11 years. The tests used differed at the different ages, e.g. at age 7 years a word-recognition test (the Southgate group reading test) was used to assess reading skill, whereas at the later ages this was assessed by a reading comprehension test. Mathematical skill was assessed by tests appropriate to each age. Test perfor-

Table 2 Performance on tests of reading and mathematical skills at the ages of 7, 11 and 16 years in psychiatric in-patient groups compared with controls

	Controls	Preschizo-phrenic	Pre-affective	Pre-neurotic
Age 7 years n	1520	33	31	67
Reading	23.3	18.4***	20.3*	22.3
Mathematics	5.2	3.9**	4.4*	4.6*
Age 11 years n	1446	29	29	70
Reading	16.0	12.6**	14.4	13.6***
Mathematics	16.8	11.6**	13.4*	12.4***
Verbal GAT	22.4	16.9**	19.5*	17.5***
Non-verbal GAT	20.9	16.3***	17.5*	17.5***
Total GAT	43.2	33.2***	37.0*	35.0***
Age 16 years n	1217	22	21	56
Reading	25.3	21.2**	23.8	23.2*
Mathematics	12.6	10.2	11.6	9.8**

*$P < 0.05$
**$P < 0.01$
***$P < 0.001$

NOTE: *t*-tests were used for between-group contrasts
GAT general ability test

mance was correlated between ages with coefficients of between 0.64 and 0.79 for reading and between 0.48 and 0.76 for mathematical skill, the lower coefficient being for the relationship between ages 7 and 16 years and the higher between ages 11 and 16 years in each case. The comparisons between the groups at the three ages are summarised in Table 2. The striking feature of the findings is the widespread nature of the impairments. The deficits are greatest in the pre-schizophrenic group followed by the pre-neurotics, and least in the pre-affectives, although the greater significance of the differences between pre-neurotics and controls may in part be attributable to the greater sample size in this group.

Of potential interest are gender differences and trends over time. Although there was a trend towards a greater impairment in performance on the GAT in male pre-schizophrenics, and the impairment was greater in verbal than non-verbal ability, the ANOVA group-by-gender-by-ability interaction did not reach the 5% level of significance. Scores on reading and mathematics attainments were standardised with regard to normal controls at each age. Deficits at age 7 years (with the schizophrenic group 1.1 SD below the mean for controls) were as great as at later ages, suggesting that the impairments reflect a constitutional limitation, rather than the emergence of a disease process. For the reading-test performance there were no significant age-by-gender interactions for the pre-schizophrenic and pre-affective groups (although there was a trend for the schizophrenic males to perform worse at younger ages), but for the pre-neurotic group there was a significant age-by-gender interaction, the males improving and the females deteriorating with time. On the mathematics tests the deficits were greatest in the pre-schizophrenic group, somewhat less in the pre-neurotics and least (0.2 SD) in the pre-affectives. There were no significant age-by-gender interactions.

The deficits on objective tests can be matched against ratings made by parents, teachers and individuals themselves at the various ages. Thus, when questioned when the probands were aged 7 years parents did not rate their pre-schizophrenic children as significantly abnormal with regard to their acquisition of speech by the age of 2 years, as ever having stammered or stuttered, or as having had unintelligible speech, but according to the teachers' assessments at this age these children were poor on oral and reading ability and mispronounced words. At age 11 years the pre-schizophrenic children were rated (at the 2% level of significance or less) by teachers as having speech difficulties, an imperfect grasp of English, mispronouncing words and having difficulties with number work and the use of books. At the age of 16 years the pre-schizophrenics were rated ($P < 0.001$) as poor in English ability, as having problems with reading and spelling, and again as mispronouncing words, and these individuals rated themselves as having problems with reading.

The picture that emerges overall is of a group of individuals who are significantly impaired across a range of intellectual abilities from an early age, these impairments having a particular impact on their ability to communicate either in written or oral format. The gender differences in academic ability are less striking than in the case of the disturbances of behaviour.

Physical and neurological development

No significant differences were observed between patients and controls with regard to height or weight at the ages of 7, 11 or 16 years, or with regard to head circumference assessed at the age of 7 years. The timing of puberty was assessed with ratings of pubic hair and genital and breast development at the age of 11, and pubic hair, the onset of menstruation and age of the voice changing made at the age of 16 years. These assessments did not distinguish psychiatric patients from controls.

A number of aspects of neurological function were recorded (by medical officers) at each age, and some of these separated the pre-schizophrenics from controls. For example, at age 7 years patients were more likely to have been recollected by parents as having been wet by day at age 3 years and by night at age 5 years. At 7 years they were also recorded ($P < 0.01$) as showing poor coordination, and were rated as poor on a simple test of vision for both the left and right eyes. By age 11 years vision is recorded as normal and on indices of motor coordination (walking backwards, heel-to-toe standing) they were not now impaired. At this age they were still more likely than controls to be recorded as incontinent. At age 16 years, although coordinated in heel-to-toe standing and hopping on either foot, they were rated as significantly ($P < 0.01$) clumsy.

Summary of salient findings

The findings in this cohort with regard to birth complications (Done et al. 1991) and the 1957 influenza epidemic (Crow and Done 1992) give no support to claims that these factors contribute significantly to the aetiology of psychosis. The absence of abnormalities of physical development fail to support theories, e.g. of Kretschmer (1921), that psychosis is associated with significant anomalies of somatic growth, and the relative normality of indices of puberty adds no empirical support to hypotheses, e.g. that of Saugstad (1989), that there are substantial deviations in the timing of endocrine changes.

The changes in behaviour suggest that psychosis reflects a disturbance of selected aspects of CNS function that are time-dependent and in certain respects gender-specific. Thus, the schizophrenics-to-be are hostile and anxious towards other children and adults, and show inconsequential behaviours at ages 7 and 11 years. But the differences at age 7 years are more marked in males (50% of whom are rated as deviant as the most deviant 10% of the school population), and there is little evidence of the social withdrawal that has sometimes been regarded as characteristic of pre-schizophrenic children. By the age of 11 years the changes in the pre-schizophrenics are more striking and include (particularly in females) those items of under-reaction, e.g. withdrawal, that might be thought to correspond to the asociality that is often a precursor as well as a sequel to a first episode of schizophrenic psychosis.

The affective-psychotics-to-be (but not the schizophrenics) are rated restless at age 7 (but not 11) years, and the schizophrenics-to-be (but not the depressives) are rated depressed at age 11 years. A surprising finding is the emergence of a range of abnormalities (more striking and, with the sole exception of depression, confined to females) in the neurotic group. Uncertainty concerning the nature of the disorder in these patients who have required admission for non-psychotic illness by the age of 28 years makes these changes difficult to interpret: Some patients, it may be suspected, will go on to develop affective or other psychoses at a later age.

Academic impairments are present in each of the psychiatric groups, but are uniformly more severe in the pre-schizophrenics. In this group language and reading difficulties are present in both genders from the age of 7 years. Although not abnormal on a number of indices of coordination at ages 11 and 16 years, and vision tested at 11 years, schizophrenics-to-be are slow to develop continence and show poor coordination and vision at age 7 years, and are rated clumsy at 16 years.

Discussion

In several respects our findings are in agreement with those of Watt's (1978) school-record study of schizophrenic patients and normal controls: marked gender differences were present, the boys showing a pattern of irritability, disagreeableness and defiance of authority, whereas the girls were insecure, shy and participated less in groups. As in the present study the changes were more striking in males. Our study supports Watt's conclusion that "over-inhibition" is characteristic of female, rather than male, pre-schizophrenics. But the two studies suggest differences in the time sequence of development of changes in the two genders. Watt found that schizophrenic girls were rated lower on an "extraversion" factor in the kindergarten years through to grade 6 (12 years), and this difference remained through grades 7 to 12 (13–18 years), whereas boys increased their separation from controls on the factor of "disagreeableness" between these two sets of ratings. Watt concluded that there was greater evidence of progression of deviance in males than in females. Our findings, resting on measures at two specific ages, suggest that deviation is certainly present (mainly as over-reaction) in males as a group as early as 7 years; and is more widespread (and includes depression) at age 11 years, whereas the changes in females (that include withdrawal and depression) present at age 11 years are of borderline significance at age 7 years. "Progressive deviance" could be used as a term to describe the changes in both males and females, but the sequence in either case is different.

The range of deviations in behaviour and intellectual function that are present many years before onset casts light on the nature of psychotic illness. It is unlikely, although further work is required, that the disturbances in behaviour can be accounted for in terms of the intellectual deficits, or vice versa. In some sense it seems that psychosis is a disorder of both intellect and social ability, and in this respect our findings resemble those of Watt (1978), Hartmann et al. (1984) and Ambelas (1992). That anomalies of personality or social ability are present, and differ between the psychoses, long before psychotic symptoms adds credence to the concept of Kretschmer (1921) that there is a relationship between personality variation in the general population and the varieties of psychosis. According to Kretschmer there is an association between schizophrenia and the schizothymic or introverted personality on the one hand, and between manic-depressive illness and the cyclothymic or extraverted personality on the other.

This view can be contrasted with the categorical or disease entity view of psychotic illness according to which disease onset represents the intrusion into psychic life of a pathological process that is independent of the existing personality structure. Such a concept is sometimes ascribed to Kraepelin (1919); but it is interesting that towards the end of his life Kraepelin came to a view of psychotic illness not far from that of Kretschmer. Thus, Kraepelin (1920) wrote "...we must seriously consider how far the phenomena on which we normally base our diagnoses really do afford insight into the basic pathological process. While it may be admitted that this procedure is generally valuable there is a fairly extensive area in which such criteria are lacking.... This is understandable if we

assume that the affective and schizophrenic forms of mental disorder do not represent the expression of particular pathological processes, but rather indicate the areas of our personality in which these processes unfold." Such a concept raises the question of the nature of personality variation within the normal population. Kraepelin went on: "...if we try to relate the syndromes of insanity to particular stages of personality, we have few hypotheses on which to base our arguments. If these attempts are to be more than tentative gropings we must trace the phenomena of our inner life back to their roots in the psyche of the child, of primitive man, and of animals." The relationship between personality and psychosis suggested by our findings is perhaps more compatible with the disorder being seen in terms of a lifetime perspective, as Kraepelin appears to be suggesting, rather than in relation to a static personality type, as Kretschmer's concept is often interpreted.

A clue to the roots of psychosis in personality structure is the gender difference in age of onset, perhaps the best established, but least explained, fact about the illness. Onsets are earlier in males, a difference that applies to the first symptom as well as to the time of admission. The gender difference in the personality deviations that precede psychosis indicates the areas of psychological function in which the origins of psychosis may be found, and these include particularly the ability to interact with others, whether parents or contemporaries. Of potential relevance is the finding that the personality dimension of cooperativeness is one for which a substantial gender difference has been identified (Cloninger et al. 1991).

One can envisage that there are trajectories of development that are determined by genetic factors acting early in ontogeny. Such genes must be variable between individuals and the range of variation presumably differs between the genders. The male brain shows a greater mean asymmetry than the female brain, and it is plausible that this accounts for the small mean discrepancy in the pattern of intellectual abilities between the genders: females performing better on tests of verbal fluency and males on tests of spatial ability. This asymmetry is determined presumably by a gene(s) that acts early in development, and it is conceivable that this action could also account for gender differences in personality traits (for example sociability), and perhaps in the age of onset of psychosis (Crow 1993).

Characteristics of the human species are a long period of maturation and a complex social life. These phenomena may well be related, the complexities of social interaction being a selective factor in the delay of sexual maturity. Humans, as Bolk (1926) first suggested, are a neotenic species, the prolongation of fetal characteristics into adult life endowing them with a brain that is enlarged relative to other primates and retains its plasticity for a greater proportion of the life span. Such a brain confers an increased capacity to deal with conspecifics (e.g. through the evolution of language), and for this purpose the ability to take account of the dispositions and intentions of other individuals – or, as it has been labelled, to develop a "theory of mind" – is an adaptive advantage. Deficits in this ability are at the heart of a number of psychiatric syndromes including some that are related to psychosis (Brothers 1990; Frith 1992). Complex social behaviour requires a well-developed concept of the self and its relation to others. Increasing hostility towards others culminating in paranoid delusions can be seen as one type of abnormality in this relation, and first-rank symptoms with loss of the psychological boundary between the self and the external world can be seen as another.

However, if there is variation in the several aspects – intelligence, language and social ability – of psychological function, and particularly if the variation is genetic in origin, one must ask how does this variation arise, and how is it maintained in the population? Only when this more general question has been answered will it be possible to explain the persistence of the genes that predispose to psychosis in the face of a fertility disadvantage, the problem addressed by evolutionary theories of the origin of psychosis (Crow 1993).

Timing is central to a number of these related problems. Within the spectrum of psychotic illness early onset is a predictor of poor outcome. Males generally have an earlier onset and worse outcome, but as Eaton et al. (1992) have shown, when age of onset is taken into account gender no longer has an influence. A single genetic factor that has a range (overlapping, but with a small mean difference in males and females) of influence on the development of an aspect of CNS function could account both for the premorbid deviations in behaviour and the gender difference in onset of psychosis.

But what is the critical rate-determining factor? A number of findings in morphological studies are compatible with the concept that in schizophrenia there is an arrest of development of cerebral asymmetry (Crow 1990 a). There may also be a reduction in total cortical mass. Perhaps these two findings are related and there is a trade-off between brain size and asymmetry. Perhaps various combinations of size and asymmetry are associated with different cognitive and personality structures, and this diversity is maintained by the selective factors that have increased brain size and retarded its maturation. The extremes of this variation may be expressed as the cognitive and behavioural deviations that we recognise as psychosis.

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