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Developmental precursors and biological markers for schizophrenia and affective disorders: Specificity and public health implications

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Abstract Schizophrenia's developmental dimension includes causes being active early in life. Precursors are manifest before psychosis begins, and there is an emerging public health agenda including prediction and prevention. We discuss the specificity of some developmental precursors to schizophrenia as an outcome, with particular reference to longitudinal birth cohort studies. Underlying structural brain abnormalities are considered. Differences from controls are found in schizophrenia and, to a lesser extent, before affective disorder on many measures. This apparent lack of specificity may not be the case in neurobiological terms, as underlying mechanisms may be different; parsimony suggests not. This same lack of specificity may be an advantage in public health terms, raising the possibility of strategies to predict and prevent a range of psychiatric disorders, not just schizophrenia.

Key words Schizophrenia · Bipolar affective disorder · Psychosis · Development · Causation · Specificity · Prediction · Public health · Prevention · Early intervention · Evidence-based practice

Introduction

There is no doubt that schizophrenia is linked to the life-course. It is very rare before puberty, incidence climbs through early adult life before tapering in later years (Hafner et al. 1993; Hambrecht et al. 1992). Developmental aspects to schizophrenia have been proposed (Weinberger 1987; Murray & Lewis 1987) with causal factors active in early life. Their physical and psychological effects are apparent before the psychotic syndrome that we call schizophrenia. Whether these manifestations are themselves part of a causal pathway to psychosis or merely indicate risk and vulnerability is not certain; it probably varies for different factors. However, their specificity for schizophrenia versus affective disorder and other mental illness is important.

Classification on the basis of causes is important in medicine. Lack of specificity for early factors weakens the case for affective psychosis and schizophrenia being distinct disorders. Furthermore, studying precursors may also be useful for the prediction of illness. Where prevention is feasible, specificity is important if an intervention is itself specific in terms of benefiting only one outcome, particularly where it may also do harm. Here, we consider developmental and psychological precursors in general population samples, minor physical anomalies and, briefly, structural brain abnormalities. We have considered other examples elsewhere (Tarrant & Jones 1999 a, b & c).

Some precursors are "risk modifiers", intimately associated with causation; remove them and there will be less disease. Others are "risk indicators", not intimately related to causation, but merely markers of a causal process. Both may be considered as a longitudinal aspect of the disease itself. The dimension of time before psychosis allows a third class of precursor to be identified, the abnormal developmental mechanism that precedes and leads to the adverse outcome. This is not a genetic or environmental risk factor, but a biological process upon which either or both of these types of factor may impinge.

These latter manifestations, perhaps abnormal behaviour or cognitive processes, may *themselves* impinge upon the developmental process. This abnormal behaviour will, itself, tend to alter the environment in which a child functions, leading to altered experience and *further* abnormality in the developmental process. This increases the complexity of a developmental model and allows one way for

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lack of specificity in precursors to be included. The model is dynamic, and allows inclusion of what we have referred to as a "self-perpetuating cascade of abnormal function" and development prior to schizophrenia (8).

Specificity of precursors in general population birth cohort studies

Studies of birth cohorts provide prospective data that are relatively unbiased by recall and blind to outcome. Several have collected relevant data on child development, have followed subjects into or through the period of risk for schizophrenia, and have been large enough to yield sufficient cases for analysis. Numbers of subjects with affective disorder are greater, but less representative of the disorder if hospital contact is required for case ascertainment. First, we consider results for schizophrenia, together with a description of some of the cohorts themselves. Next, we consider affective disorder before comparing and contrasting the findings. We do not include results from the remarkable North Finland 1966 birth cohort because this is considered in detail elsewhere in this volume (Isohanni et al. 2000). Neither do we review studies of early environmental risk factors as possible causes, such as viral infection or famine (see Jones 1999, for review).

Schizophrenia in the British 1946 birth cohort – the National Survey of Health and Development

This study of 5362 subjects born in March 1946 (Jones et al. 1994; Jones & Done 1997) has yielded 30 cases of narrowly defined (DSM-III-R) schizophrenia up to age 43 years. Compared with the rest of the cohort, those who went on to develop schizophrenia had later attainment of motor milestones of sitting, standing and walking alone. They talked later, and speech problems were more frequent between the ages of 2 and 15 years. The differences in mean ages of milestones were small, they walked and talked 1.2 months later, but are evidence of developmental differences in the schizophrenia group (Weinberger 1995). By adolescence, these differences appeared to have disappeared. There was evidence of increased twitches and grimaces in the classroom but the lack of gross problems suggests that motor development had in some way caught up. The unique "home movie" studies by Walker and colleagues (Walker et al. 1994) indicate a similar phenomenon.

Educational test scores at ages 8, 11 and 15, adjusted for sex and social class, were consistently lower for the pre-schizophrenia group; the gap between potential cases and peers appeared to increase with age. Deficits were particularly noted in verbal, non-verbal and mathematical skills and were independent of behaviour ratings. Adults with schizophrenia had preferred to play alone at 4 and 6 years of age, and at age 13 had reported themselves as more anxious in social situations compared with their peers. Teachers also rated them as being more anxious at age 15. Thus, there appears to be some continuity in these rather "schizoid" characteristics throughout childhood and adolescence. No association was found with antisocial behaviour and later schizophrenia.

Schizophrenia in the 1958 National Child Development Study (Jones & Done 1997; Done et al. 1994)

This sample originally comprised 15 398 subjects, with from birth and ages 7, 11, 16 and 23. Cases were identified using a case register and CATEGO diagnoses made using medical notes. Twenty-nine subjects were diagnosed with "narrow" schizophrenia, 29 with affective psychosis and 71 with neurotic illness. The control group was a random 10 % sample of cohort subjects who never had psychiatric treatment. At ages 7 and 11 significant differences were found in motor and neurological signs between cases and controls. Poorer balance, co-ordination and clumsiness, more tics and twitches, different hand preference, poorer hand skill and other miscellaneous neurological deficits were associated with those who went on to develop schizophrenia.

Stable deficits were apparent in the pre-schizophrenia cases through ages 7, 11 and 16 in a broad range of cognitive tests measuring verbal and performance IQ, reading, mathematics, general knowledge and speech. Social disadvantage did not account for these differences, but abnormal social functioning and personality, as described below, were found to account for about half of the cognitive deficit.

Boys who went on to develop schizophrenia showed characteristics of "over-reactive" behaviour at age 7 and 11, being anxious for acceptance towards teachers and hostile towards their peers. Girls, however, showed a different pattern of social maladjustment. At age 11 they were shown to be more "unreactive" with the characteristics of being more withdrawn and "unforthcoming".

Schizophrenia in the 1949–1950 Swedish Conscript Study

This comprised some 50 000 Swedish male conscripts in 1969–1970 (David et al. 1997; Malmberg et al. 1998). Baseline assessment of verbal and visuospatial abilities, general and mechanical knowledge were collected at conscription age of 18. Thirty-three were diagnosed as psychotic at baseline and excluded. Cases were identified over 13 years from the Swedish national register of psychiatric care. Diagnoses were made according to ICD–8 from case notes. One hundred and ninety-five cases of schizophrenia and 192 cases of other psychoses were identified.

Psychometric testing at age 18 showed a significant relationship between low IQ scores and later schizophrenia. The premorbid personality and social adjustment of cases showed a constellation of variables reflecting difficulties in social interaction. They were more likely to have fewer than two close friends, preferred to socialise in small

groups, felt more sensitive than their peers and were less likely to have a steady girlfriend.

Schizophrenia in the Israeli Conscript Study

This study involves a case-control study nested within a cohort of male conscripts into the Israeli army between 1985 and 1991 (Davidson et al. 1999). Data from psychometric tests at conscription were linked to a national case register up to 1995, resulting in a comparison between 509 men healthy at conscription but who later developed schizophrenia, and 9215 men who did not appear on the register, matched on age and school attended. Deficits in social functioning, organisational ability and intellectual functioning assessed at conscription strongly predicted later schizophrenia. This is a remarkable study that may lead to realistic prospects for practical prediction. To date, schizophrenia is the only outcome on which work has been published.

Similarities and differences between the cohorts for schizophrenia

There were differences in the measures and ages at data collection in these samples. Similarities and differences have to be interpreted with caution; a broad view is the safest (Jones & Done 1997).

Both the 1946 and 1958 birth cohorts indicate abnormal neurodevelopment. The 1946 cohort reported delayed early developmental milestones, but indicated that those who go on to develop schizophrenia did not have gross problems by adolescence. The 1958 birth cohort found ongoing abnormalities of neuromotor functioning at ages 7 and 11. This indicates that the developmental differences occur early in schizophrenia and, although effects are subtle, can be detected through childhood. It has been suggested that those functions that are developing most quickly at any particular age are those where differences are apparent. One problem with this is that these functions are just those most likely to be measured in studies such as these. It is possible though that these motor and speech differences are the precursors of the motor (Gervin et al. 1998); language (Crow 1998) aspects to the abnormalities in schizophrenia.

All the cohorts discussed have found a general lowering of cognitive ability in children who develop schizophrenia as adults. This is evident throughout childhood and adolescence, and at the age of 18. In the 1958 cohort abnormal previous behaviour was found to account for some of the difference in cognitive deficit. In the 1946 cohort these two parameters were independent of each other. Whether or not the cognitive deficit is stable over time remains uncertain (Russell et al. 1997); it was in the British 1958 cohort that the premorbid deficit appeared stable, but this was not so clear in the 1946 cohort.

The 1946 cohort and both the Israeli and Swedish conscript studies indicate more socially anxious characteristics in cases' premorbid personality and adjustment. The 1958 cohort indicated a sex difference with girl cases being more withdrawn in the premorbid period, while boys had earlier evident antisocial behaviour. The conscript studies are restricted to men.

As in the British 1946 cohort (Jones et al. 1994), the effects for behaviour and IQ in the Swedish and Israeli conscript studies were not the result of dramatic differences in a small group of individuals. Rather, there was a more general shift in the distribution of all those affected such that the more abnormal or "less optimal" the score, the greater the risk of subsequent schizophrenia. Such dose-response relationships are common in chronic physical disease epidemiology, and are increasingly recognised in psychosis.

Affective disorder in the 1946 National Survey of Health and Development (van Os et al. 1997)

Childhood affective disorder (CAD) was defined on the basis of teachers' ratings of behaviour and mood at ages 13 and/or 15. Adult affective disorder (AD) was defined on the basis of Present State Examination (PSE) and Psychiatric Symptom Frequency (PSF) interviews at ages 36 and 43. Female sex and lower scores on childhood cognitive tests were associated with depression at any age. CAD was associated with later milestone development, the presence of twitches, lower cognitive test scores at ages 11–15 and behavioural apathy at ages 6–11 years. CAD strongly predicted later AD. This group, who had both CAD and then AD, could be discriminated from AD only by childhood abnormalities in neuromotor and speech development.

Affective disorder in the 1958 National Child Development Study (Jones & Done 1997; Done et al. 1994)

Affective psychotic disorder was associated with clumsiness and poor co-ordination at ages 7 and 11, and with tics and grimaces at 11. Neurotics (non-psychotic depression and anxiety) had no abnormal neuromotor signs at age 7 but had poorer co-ordination at age 11. Small differences on all educational tests were found in pre-affective psychosis cases compared with their controls. More marked deficits were found in children who later developed "neuroses" but this difference was accounted for by social disadvantage. Social maladjustment at age 11 in terms of over- and under-reaction were marked in girls who later developed neurosis. Pre-affective psychosis cases were less clearly abnormal than either the pre-schizophrenic or the pre-neuroses group on all the measures of social adjustment.

The cohorts compared

Both cohorts discovered premorbid abnormalities in neuromotor functioning. The 1946 cohort found that these variables discriminated between childhood onset and adult affective disorder. The 1958 cohort found a wider range of

deficit in those who would develop an affective psychosis compared with those who developed non-psychotic affective disorder or anxiety. Lower cognitive scores predicted both CAD and AD independently in the 1946 cohort. Minor cognitive deficits were found in pre-affective psychosis cases in the 1958 cohort. The deficits in those who developed non-psychotic affective disorder or anxiety were attributed the difference in social disadvantage. The 1946 cohort showed that behavioural apathy at ages 6–11 was associated with a persistence of illness in both CAD and AD groups. While premorbid social maladjustment did not appear important in pre-affective psychosis cases in the 1958 cohort, girls who would later develop non-psychotic depression or anxiety had a generalised disturbance in social functioning at the age of 11.

Comparing precursors for schizophrenia and affective disorder

Some of the apparent lack of specificity is going to be due to what is, effectively, measurement error. Definitions of schizophrenia and affective disorder vary between cohorts, and even between these two diagnoses; different sets of operational definitions may be used for each outcome. Similarly, different cohorts use different measures of childhood behaviour and educational/cognitive ability, as well as for other risk factors. Symptoms of adult depression may be present in childhood and affect behaviour in a way that features of the adult schizophrenia syndrome very rarely do.

However, some general conclusions can be drawn. The studies described provide evidence for widespread attenuation and disturbance in development in those with both schizophrenia and affective disorder. Later developmental milestones and neuromotor abnormalities are present in schizophrenia and in those who develop CAD. This disorder is strongly predictive of AD, suggesting that earlier onset of depressive symptoms may presage a more severe form of the disease with more obvious neurodevelopmental precursors. Pre-affective psychosis cases also show greater abnormalities than pre-neurotic cases.

Lower scores on tests assessing many different cognitive functions at different ages similarly predict both schizophrenia and affective disorder. However, the extent of this deficit appears smaller in pre-psychotic affective disorder cases compared with those with schizophrenia.

Behavioural differences in children later to develop schizophrenia are shown in all three of these cohort studies. Those described by Done et al. involved more externalised, "naughty" behaviour compared with the more commonly demonstrated shy and schizoid traits indicated in the NSHD and the Israeli and Swedish conscripts. The possible reasons for these differences are explored by Jones and Done (9). Social maladjustment and behavioural differences are not so apparent in those who later develop affective disorder.

Although these precursors are not completely specific to schizophrenia, the effects are most dramatic in this group. This lack of specificity and the overlap with normal variation in developmental attainment and CNS integration cannot, as yet, allow us to viably predict future illness on an individual basis from childhood. As mentioned above, the symptoms of the adult syndrome itself may be present in depression making prediction a much more secure exercise. Studies of children at genetic high risk for schizophrenia indicate remarkable concordance with the birth cohort studies in the types of abnormalities that may predate schizophrenia. The scope for prediction may be greater in such samples where the risk of eventual disorder is so much higher than in the general population. The possible advantage of lack of specificity of precursors in terms of prevention is discussed below.

Are structural brain abnormalities that may underlie these developmental precursors specific to one disorder?

Structural brain abnormalities at the resolution of contemporary MRI are not specific to schizophrenia or affective disorder. However, Elkis et al. (1995) concluded that the magnitude of the difference between cases and controls in measures such as ventricular enlargement was smaller in affective disorder than in schizophrenia. Differences in more specific regions of interest have been found in and around temporal lobe structures in schizophrenia. This has not been consistently shown in affective disorder, where the focus has been on the cerebellum and brainstem structures, together with the frontal lobes.

Thus, while structural differences are apparent in the brain of both diseases, the areas where abnormalities are found are not the same. Stability of the structural abnormalities in schizophrenia and the apparent lack of acute or chronic gliosis at post mortem (Benes et al. 1991) are consistent with a developmental hypothesis but, as described above, such a view does not exclude further change later in life. Definition of affective disorder is perhaps even more difficult than schizophrenia (Jones et al. 1994). Just as important is the problem of defining the population at risk for these cases, and the controls with which they are compared. Closer links between epidemiology and structural neuroimaging, ideally in a birth cohort study, will enable us to further define structural abnormalities associated with each disorder and their specificity.

Summary and practical implications

The findings we have considered suggest a variety of behavioural and biological precursors to schizophrenia, with none being specific to this disorder. Most differences and abnormalities also occur in people with other mental illnesses, particularly affective or bipolar patients, but, as with structural brain abnormalities (Elkis et al. 1995), not to the degree of those with schizophrenia. We have noted the methodological problems concerning differences between studies in terms of case definitions, controls and the

exact exposures or precursors that were collected. We have noted elsewhere (Tarrant & Jones 1999 a, b & c) that our concepts of the disorders themselves inhibit direct comparison. Depressive symptoms in childhood might be considered a *precursor* of adult affective disorder, but delusions or hallucinations would be considered to *be* schizophrenia. Thus, it may not be surprising that conclusions are not clear.

We suggested before (Tarrant & Jones 1999 a, b & c) that a search for specific precursors, present in one case group whilst absent from controls and other disorders, is fruitless. The enthusiasm with which we have pursued this idea may have obscured another way of interpreting the data that we have referred to above. Considering a wide variety of factors such as childhood IQ (Jones et al. 1994; David et al. 1997), childhood behaviour (Jones et al. 1994; Malmberg et al. 1998), minor physical anomalies (Lane et al. 1997) or cerebral ventricle size (Jones et al. 1994), an abnormal sub-group specific to one disorder amongst many, and distinct from the general population is not apparent. Instead, there is a consistent, non-specific shift in the distribution of these factors. The further towards the "abnormal" end of a population distribution, the greater the risk of disorder. Thus, case groups have deviant mean or median values of the relevant measures, but few individuals will themselves be "abnormal" as defined by some absolute, usually arbitrary value. Suggestions for specificity to sub-types within disorders – for example, a neurodevelopmental subtype of schizophrenia (Murray & Lewis 1987) – are not generally supported in terms of risk indicators (Jones et al. 1994). However, there may still be specific underlying causes all leading to non-specific abnormalities that are apparent in childhood.

The case-control overlap underlies the low power that any single precursor has in terms of prediction of later disorder (Malmberg et al. 1998) in the general population where illnesses such as schizophrenia and affective psychosis are, thankfully, comparatively rare. The Israeli conscript study does the best in terms of prediction, but there would be many falsely classified individuals if there were a clinical programme based upon the results. Prediction in high-risk samples may be more feasible than in the general population but still many will be disappointed by this lack of an immediate, practical application in terms of identifying those who will become ill on the basis of markers of abnormal development.

Although it is rather unsatisfying that there are not clear and specific relationships between precursors and outcomes, but if an intervention were available to decrease the risk of later disorder then lack of specificity might be an advantage. Consider a set of childhood precursors that indicated high risk of later schizophrenia. If we had an intervention that modified this risk, then it would be helpful if the risk of other bad outcomes were also reduced. This benefit of lack of specificity does not exclude specificity of causes. A good example would be smoking and lung cancer. We advise patients to stop or cut down their tobacco consumption so as to reduce the risk of a variety or illnesses ranging from cancer at several sites to cardiovascular disease. This does not undermine the causal link between inhalation of tobacco smoke and lung cancer.

The background to interventions needs consideration. Medical interventions are rarely entirely benign. Interventions at the population level are not either but here small changes for individuals can have widespread benefits. Benefits to individuals may be very small. There may even be a price to pay (the prevention paradox; Rose 1989; Rose 1992). The shifted population interpretation of the associations between some precursors gives scope for intervention, and may move prevention beyond the individual to the whole population where a shift in the population mean in the direction opposite from that associated with risk of a disorder will may have widespread benefits. If these benefits are seen in terms of many disorders because the risk reduction is not specific then the advantages increase exponentially.

Jones & Tarrant (1999) gave an example where the prevention paradox is low. If lower educational achievement in childhood is a risk modifier not just for schizophrenia and affective disorder, but also for conduct disorder and, feasibly, for criminality, drug misuse and general low quality of adult life, an intervention to improve educational attainment would have huge benefits. The prevention paradox is low (seen only in opportunity costs) and lack of specificity an advantage. We are a long way from such interventions for schizophrenia but the general concept is being adopted for childhood psychiatric disorders and social problems (Sorensen et al. 1998; Kellerman et al. 1998).

In terms of what we can now measure we must conclude that there is little, if any, specificity for precursors of schizophrenia and affective disorder but this may not be the case at the more microscopic and underlying neurobiological level. However, whether one looks towards a public health perspective or a causal and mechanistic one, this only adds to the fascination and challenge of investigating the origins of these disorders.

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