

# The psychotic hinterlands or the fringes of lunacy

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The hinterlands of the major psychoses--schizophrenia and bipolar and unipolar affective disorders--are occupied by both unusual and quite ordinary individuals, only some of whom go on to a full-blown psychosis and some of whom get no worse. This essay deals with the nosological, methodological, and logical issues in trying to identify the relevant disorders or personality dimensions or trait configurations which may be useful to the clinician and to the aetiologist. Multifactorial, polygenic threshold models inform the discussion as do recent developments in the molecular genetic and brain imaging laboratories. So-called schizophrenia spectrum disorders are examined through family, twin, adoption, and prospective high risk strategies. Clinical-phenomenological approaches do not provide sufficient resolving power. Our hope lies with endophenotypes closer to the gene end of the gene-to-behaviour pathways involved in the major psychoses.

A growing literature and the continued lack of success in determining the aetiologies of the psychoses attest to the importance of mapping out and identifying those conditions which may either herald a future psychosis, or indicate (mark) a presumed genotype relevant to determining the mode of transmission of one of the psychoses.<sup>1-10</sup> Phenocopies,<sup>11</sup> genocopies,<sup>12</sup> and a too crude nosology all conspire to frustrate the would-be cartographers of major psychopathologies.<sup>13-15</sup> Disagreements and inconsistencies between the two major classificatory schemes on both sides of the Atlantic (ICD and DSM) are a further impediment to understanding the results of empirical investigations into the so-called

schizophrenia spectrum and affective spectrum disorders. The issues we shall grapple with in this essay are different from the problems broached by Crow<sup>16</sup> in his discussions about the continuum of psychosis, but not entirely so.

As the daylight changes to twilight, then dusk and then night followed again by dusk, twilight and day, we can observe an analog to the nosological problem faced by those who would attach names to those sets of behaviours alleged to be on the fringes of the psychoses proper. Almost everyone will agree on classifying night and day or psychosis and normalcy. Where could or should the rational taxonomist place the boundaries to demarcate on the one edge, a psychosis and on the other edge, normalcy? Is there some helpful 'point of rarity' to help,<sup>13</sup> some qualitative change, or is there indeed a phenotypic continuum from sanity to insanity? Alternatively, there may be a continuum with one or more threshold effects at a physiological (and possibly genetic) level leading to a qualitative change at the behavioural level.<sup>17-20</sup>

Gowers, concerned about the subtle indicators of epilepsy in 1908, introduced the notion of the 'borderlands' of epilepsy, a region which included migraine, syncope, bedwetting, and night terrors.<sup>21</sup> The lack of high sensitivity for predicting epilepsy from such symptoms was ignored and indicators associated with a so-called ictal personality were even added to the borderlands. Such inefficient indicators of an impending overt case of epilepsy have now been replaced by insights into the aetiological heterogeneity<sup>22</sup> of the disorder-which, in turn, have been aided by technological advances in neurochemistry, LEG, BEAM, MRJ, and regional cerebral blood flow. Absent such technology for the 'functional psychoses', how do we go about detecting the valid indicators or the candidate psychopathologies that belong on the fringes of such conditions as schizophrenia, unipolar affective disorder, and bipolar affective disorder?<sup>23-26</sup>

Strategies differ for identification of one of the following: (1) an incipient form of the disease; (2) a spectrum condition, which is necessary but not sufficient for developing the disease; (3) a spectrum condition that is simply a risk increasing factor for the disease and neither necessary nor sufficient. Further complications may be expected from the fact that the prediction problem in the general population appears to be different from prediction of affected status within the family of a proband.<sup>27</sup> Let us take Huntington's

disease (HD) as an exemplar for a simple dominant gene caused disease. If we observe that several children of Huntington probands (known a priori to have a 50% risk for the disease at some time in life) are 'fidgety' and therefore posited to be the real carriers of the abnormal gene on the short arm of chromosome 4, we have a refutable hypothesis and a prospective high risk research design. We predict that fidgety children in Huntington families will get the disease and that their non-fidgety siblings will not. Given our knowledge about the dominant gene aetiology of the condition as opposed to a multifactorial polygenic basis, we are not tempted to search for spectrum disorders, concentrating instead on detecting the early stages of the disease in carriers.<sup>28</sup> Note that we do not predict that fidgety children in the general population are at risk for HD; the lifetime risk for HD in the population is 5 per 100 000 and new mutations are rare, while overactivity characterises about 50% of boys at some time in their lives. Given the latter fact, fidgetiness is a very fallible predictor of HD, even in the families of HD probands where the children may well be fidgety for reasons other than carrying the HD gene. It makes sense then to look for candidate conditions or traits within the families of schizophrenic or affective probands without having to argue that they will work equally well in the general population.

## SEMANTIC AND NOSOLOGICAL CONFUSION AND LOGIC

We are interested in indicators, whether they be traits or syndromes, that herald either a future schizophrenic or an affective psychosis, or identify a specific contributor to the liability for developing one of these presumably multifactorially caused disorders-specific contributors may be categorical or dimensional. These psychoses are best conceptualised within a diathesis-stressor framework, which provides for the epigenetic interaction of major genetic, neurobiological, and psychosocial factors.<sup>20</sup> We shall concentrate on the schizophrenia problem and its borderlands, with citations permitting *entrée* to the literature on the same problem for the affective psychoses.<sup>24,25</sup>

Schizoidia is a noun invented from the adjective schizoid. Clinical observations of the premorbid statuses of schizophrenics resulted in about half of them acquiring the descriptor schizoid, but only half. Observations of the first degree relatives who were not

clinically schizophrenic resulted in varying proportions being described as schizoid. Luxenburger observed more schizophrenia than schizoidia in the siblings of probands (11.5% vs 3.6%), while Kallmann reported the opposite weighting (31.5% schizoidia, 14.3% schizophrenia)--of necessity both relied on their clinical impressions.<sup>3</sup>

Kahn, an assistant to Kraepelin, posited two separate, genetic, necessary components for the development of schizophrenia- schizoidia and psychosis. Such notions still continue to be of interest. Various commonsense elements of schizoidia or schizoid personality are so common as to be misleading as useful predictors. Observations of normal children over time show that excessive reserve characterises 59% of 10-year-old girls and 52% of 11-year-old boys; excessive shyness is seen in 37% of 11-year-old girls; and oversensitiveness is, like the common cold, present in 53% of 6-year-old girls and in 59% of 10-year-old boys. Cycloid personality suffers similar measurement problems-e.g., 40% of 11-year-old girls and boys are characterised as having mood swings.<sup>29</sup> The clinician taking a lifespan view of personality would generate many false positives for the putative indicators of the psychoses.

Indicators of schizoidia would have to be reliably measured with convergent and discriminative validity. The water has been muddy on one side of the Atlantic by the invention of schizotypal personality as a construct which competes with schizoid personality in this area of research. The former has a curious history<sup>23,27</sup> and combines disorders which are likely to be diagnosed as borderline or latent schizophrenia (295.5), residual schizophrenia (295.6), paranoid personality, or schizoid personality in Europe (ICD). Despite the aids to diagnosis provided in DSM III, it is extremely difficult to separate American personality disorders from one another.<sup>14,30</sup> However, a DSM III diagnosis of schizotypal personality leads to the prediction that 60% will also meet criteria for borderline personality and 56% for passive-aggressive personality. Using DSM III criteria schizoid personality leads to the prediction that 29% will also meet criteria for schizotypal personality; the reverse prediction-i.e., given schizotypal, what is the frequency of meeting criteria for schizoid-results in the low figure of 4%.<sup>31</sup> Caution is required in generalising from such experiments, as the results depend greatly on the base rates of the conditions in inpatient vs outpatient settings and the manner in which the clinicians apply the 'rules'. The fact that only 8% of non-psychotic inpatients received

a DSM ITT diagnosis of schizoid compared with 57% meeting criteria for schizotypal suggests that the category of schizoid may be much more relevant to the task of specifying the borderlands of schizophrenia.<sup>31</sup> The difficulties in teasing apart the relevant personality orders from each other would be even more confusing (or perhaps less so) if DSM III allowed for ICD 301.1, affective personality disorder. Chronic depressive or hypomanic personalities have no official role in either nosology. It is very difficult to aggregate knowledge from an international data base as terms or categories found useful in the USA are not used in Europe—schizotypal, bipolar II, borderline—and vice versa—a simple or latent (borderline) schizophrenia, affective personality. Worse, the same term—schizoid personality—is defined ad hoc in DSM III so as to differ from schizotypal personality and this differs from the ICD definition with the very same code number, 301.20.

## A LOGICAL LOOK AT SCHIZOID

One of the most difficult aspects of the term schizoid has been the extent to which it implies merely a phenotypic resemblance to schizophrenia, or a genetic connection with it, or both. Figure 1 is a Venn diagram to illustrate three of the four uses the term schizoid can take on, all three of them having no necessary aetiological implications.

*Sd 1:* This would be using schizoid in the literal mode of a diluted form of schizophrenia. The term is used this way on both sides of the Atlantic in schizoid personality but requires somewhat different criteria; however, wherein the DSM III version is more dilute than ICD, the category schizotypal personality overlaps with ICD schizoid as well as ICD latent (borderline) schizophrenia. Cases of Sd 1 are marked by shyness, sensitive, aloof, incapacity to express feelings, slightly eccentric, and introspective reserve. Sd 1 does not imply a genetic connection or a necessary component to schizophrenia. It is on a continuum with normalcy and also overlaps with paranoid personality. In principle it could be extended to persons obtaining schizophrenic-like MMPJ profiles, or Rorschach protocols, or attention and information processing patterns. It excludes other pathologies not usually described as schizophrenic-like—e.g., depressives or criminals.

*Sd 2:* This circle encompasses those psychiatric disorders occurring

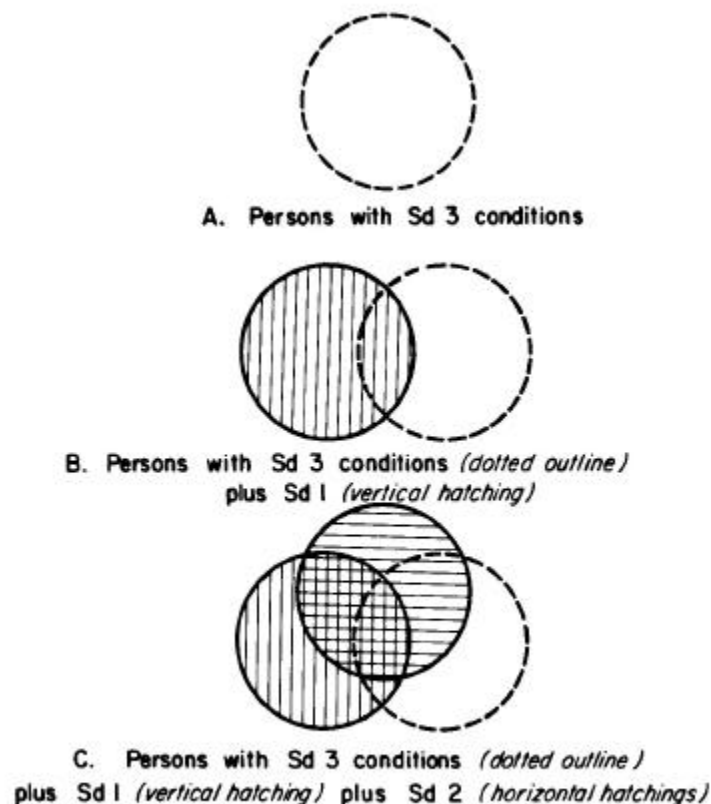


Fig. 1 Schematic diagram of the relationship between Sd 1, 2 and 3

in the twins or first degree relatives of schizophrenics, even when they do not patently resemble schizophrenia and even when they are not more frequent than in control families (cf. fidgety in the HD example above). Again, a genetic connection to schizophrenia is not necessary. The conditions in Sd 2 comprise the eligible candidates for Heston's 'schizoid disease'<sup>4</sup> and could be clues to pleiotropic effects or to closely linked genes.<sup>32</sup>

*Sd 3:* This circle encompasses those disorders observed more often in the families of schizophrenics than in their controls. They are expected to occur in non-relatives of schizophrenics and would be clues to their risk status for schizophrenia. Examples of Sd 3 would include all the positive findings from the Danish adoption studies on spectrum disorders, including the extended spectrum<sup>3,33,34</sup>

*Sd 4*: We reserve this concept for a diagnosis or behavioural trait or complex of traits, either within the normal range or not, which one's theory implicates as either a probable carrier of the hypothesised single major locus gene or of a high risk genotype on a multifactorial polygenic model.<sup>2,4,18,20</sup>

Let us begin to explicate the necessary logic with persons in the population who have *Sd 3* conditions, within the dashed circle (Fig. 1A). Such persons have disorders of a kind found more often in the relatives of schizophrenics than normal controls—ideally such research requires other psychiatric controls in order to determine specificity for schizophrenia.<sup>35</sup> The fact that much of the literature has used the adoption strategies rules out the possibility that the implicated pathologies are simply reactive to the presence of a schizophrenic relative. According to Kety et al,<sup>3,34</sup> early on in their program, *Sd 3* could include suicide and inadequate personalities; but according to Kendler et al,<sup>36</sup> it could include conduct disorder, childhood social withdrawal, schizotypal and paranoid personalities; and according to Heston, *Sd 3* includes mental retardation.<sup>4</sup> *Sd 3* conditions will differ from study to study as a function of base rates in the control populations and as a function of the index population's manner of ascertainment (adoption, state hospital, Harley Street practice). It is even possible to control too much, e.g., for social class, and thereby lose sight of correlated or causal contributors. The degree to which *Sd 3* conditions are related to schizophrenia causally or genetically—the true *Sd 4* distal causes—is still an open question.

We can now add the *Sd 1* circle (vertical hatching in Fig. 1B) to make the point that conditions which resemble schizophrenia clinically by being a diluted version thereof almost certainly belong within *Sd 3* as well, e.g., ICD borderline schizophrenia. Other *Sd 1* conditions may not necessarily distinguish the relatives of schizophrenics from those of either other psychiatric or normal controls. Overinclusive thinking and other forms of thought disorder are examples.<sup>37,38</sup> It is unlikely that 'never having married' (an accurate descriptor of about 50% of schizophrenics) would be found to be an *Sd 3* trait, even if it deserves to be an *Sd 1* trait. The possible overlap of *Sd 1* and *3* is clear in the Venn diagram as is the uniqueness of each concept. Each deserves consideration in its own right.

Lastly we can add a circle (horizontal hatching in Fig. 1 C)

to reveal the overlap among *Sd 2* conditions and those described above. Some of the *Sd 2* relatives of schizophrenics will also share a common space with *Sd 1* and *Sd 3* conditions. However, others may have reactive psychopathology or other high base rate psychopathologies, such as anxiety disorder, which do not show up in *Sd 1* or in *Sd 3*. It is also clear that many *Sd 1* and *Sd 3* persons are 'out there' and are not relatives of schizophrenics.

Classifying people according to each of the three ways of defining schizoidia may well provide a better phenotype for genetic analyses than the full blown schizophrenic psychosis itself and clues to events closer to the gene end of the gene-to-behaviour pathway.<sup>39</sup> However, given the inevitable heterogeneity within each of the circles, what proportion of each are predicted to be *Sd 4*—accurate indicators of schizoidia in the genetic sense, a preview of the genotype? It is difficult to find consensus on this question; and, if we are constrained to using clinical but not biological information, the question may be premature. An identifiable characteristic, either categorical or dimensional with thresholds, which is the best currently attainable indicator of *Sd 4* in the general population or in relatives of schizophrenics, should be sought in the space occupied in the Venn diagram by all three circles simultaneously—i.e., setting all three definitions as necessary. Note that schizophrenic genotypes do not reveal themselves easily. A minority, about 10%, of schizophrenics have a schizophrenic mother or father; a somewhat larger proportion have an affected parent or sibling (19%); and the majority of schizophrenics are not premorbidly *Sd 1* or *Sd 3*.<sup>17</sup>

Despite these words of caution, some would say dirge, the relatives of psychotics remain a strategic population for both phenomenological and molecular biological exploration. One such group, the monozygotic cotwins of schizophrenics, highlights the reasons for exercising considerable caution before claiming that one has detected a phenotype linked with a genotype for psychosis. The newcomer to the field might expect that the cotwins of identical twins who suffer from schizophrenia (or affective psychoses) would provide direct information about what constitutes the range of *Sd 4* phenotypes indicating the unexpressed or partially expressed genotype for schizophrenia. Note that the cotwins' statuses could delimit the disorders found (*Sd 2*), could delimit which disorders are diluted forms of schizophrenia (*Sd 1*), and specify disorders which occur more frequently than in control groups (*Sd 3*). Such an expectation reveals an innocence about the dynamics of molecular

and developmental genetics. Setting aside, for the moment, phenocopies and genocopies, we must contend with the fact that the 'effective genotypes' of identical twins are not identical owing, in part, to the differential effects of the environment affecting the turning on and off of relevant genes. A salient example of our dilemma is provided by the finding that an Sd 2 condition in MZ cotwins is *normality*. The United Kingdom studies by Slater<sup>40</sup> and by Gottesman & Shields<sup>17</sup> each found about 1 in 5 MZ cotwins of schizophrenics to be clinically normal, despite close scrutiny and lengthy follow up times since the probands' onsets of hospitalisation. Fischer's Danish study reported 43% of cotwins to be normal in an aged cohort well through most of the risk period.<sup>41</sup> In the latter twin cohort it is clear that the normal cotwins did indeed carry the unrevealed genotype for schizophrenia as they were able to transmit the disease to their offspring at the same high rate usually observed in the offspring of schizophrenic parents. Gottesman & Bertelsen (unpublished observations) confirmed and extended Fischer's<sup>41</sup> findings to fraternal twins discordant for schizophrenia; the DZ probands transmitted the disorder to their offspring at the same rate as the MZ probands and their normal cotwins, while the normal DZ cotwins transmitted at a rate observed in the second degree relatives of probands.

In conclusion, it cannot be claimed that 100½ of MZ cotwins are Sd 1 or Sd 2. It is also relevant that matings between two schizophrenics result in many schizoid and normal offspring in addition to the expected yield of schizophrenics proper.<sup>17</sup>

## PROSPECTIVE HIGH RISK STUDIES OF OFFSPRING

Retrospective accounts of the origins of the psychoses and their premorbid pictures contained too many opportunities for distortion. For any familial disorder with a low population lifetime risk it should be cost-effective to study the offspring born to schizophrenics or manic-depressives and wait for them to fall ill—Pearson & Kley<sup>42</sup> formalised the strategy for HD and schizophrenia in 1957 and many instances of it now fill the literature. It is the hope of such work that prospective methods will permit the early detection of the psychosis, as well as uncover potentiating or protective factors (extrinsic and intrinsic). Many of the difficulties described above also apply here. In only a few of the studies have enough of the children reached an age when they might reasonably be expected to show their potential

for illness. Early 'hits', given that we are not dealing with adoptees, may turn out to have been transient adjustment reactions to their parents' psychoses. The 'proof of the pudding' Will always be in the follow-up, until the expected yield of 10 to 15% of genuine schizophrenia is realised. Promising biobehavioural indicators and risk factors include various aspects of attention and information processing as well as neuromotor development and cognitive event-related brain potentials.<sup>43,44</sup>

One major goal of prospective high risk research according to Hanson et al<sup>45</sup> is to validate childhood predictors of adult schizophrenia as indicators of the Sd 4 roots. At least three scenarios can be sketched. The predictor variables might be indicators of Sd 4. Such childhood variables would inform the processes whereby specific neurobiological or neurointegrative deficits participated in the epigenesis of schizophrenia. They would identify the individuals with the predisposition, even when that predisposition might never be exposed (cf. the MZ cotwins above). Further, valid childhood predictors of adult psychoses might identify potentiators or correlates of potentiators that 'catalyse' breakdowns. Such potentiators might be part of the genetic or environmental background on a multifactorial polygenic model. For example, followback and prospective high risk studies report school failure as a significant factor in schizophrenic-like decompensations. Such a school failure sign might be due to family pathology (or low IQ) and the family pathology (or low IQ) might be a potentiator of schizophrenia in Sd 4 individuals. However, the school failure is neither a consequence of Sd 4, nor a specific indicator of schizophrenia. Finally, predictors detected in the high risk design might represent the earliest stages or the effects of already potentiated schizophrenias. Such predictors would be useful as clues to the need to start treatment but would not reveal the hoped for genetic or environmental contributors to schizophrenia.

## CONCLUSIONS

Despite the gloomy picture we have drawn with its unreplicated findings and barriers to international consistency in the use of concepts relevant to studying the psychoses, there is some light. The most promising clinical pointers towards Sd 4 remain in the area of our Venn diagram (Fig. 1) where Sd 1, 2, and 3 overlap. New facts from dual mating, twin, and family strategies using Sd 1, 2, and 3 as probands would be welcome,<sup>46,47</sup> similar remarks pertain to the

affective psychoses.<sup>48</sup> Reliably schizophrenic-like disorders, such as ICD schizoid and paranoid personality and ICD borderline schizophrenia, appear to inhabit the fringes of lunacy Drug responses in personality disorders give useful clues.<sup>49</sup> Beyond all this, little can be said until new technologies-including brain imaging of neurotransmitters or subcortical neuronal changes, restriction length polymorphisms and the new genetics, and tomorrow's inventions-are applied in thoughtful designs to the problems of defining the psychoses and their hinterlands.<sup>39,50-53</sup>

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