The right answer for the wrong reasons?

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The Kraepelinian dichotomy has been challenged by evidence from many fields of psychiatric research (1-3). Following on from the pioneering critique by Tim Crow (4) fifteen years ago, Craddock and Owen now examine the dichotomous approach from a molecular genetics perspective. They introduce the beguiling prospect of certain candidate genes such as neuregulin 1 having phenotypic specificity for psychopathological features, in this case mixed "mood" and "schizophrenia" features. However, as Kendler, one of the leading American psychiatric geneticists, has so eloquently reviewed recently (5), the effect of individual genes on susceptibility to different psychiatric disorders is likely to be too small to be useful in drawing up a novel classificatory system.

Furthermore, while it is certainly true that evidence against the validity of the Kraepelinian dichotomy is mounting, it is premature to argue the case using molecular genetic data, because of their inconsistency. Different methods of meta-analysing whole-genome linkage scans of bipolar disorder and schizophrenia have yielded different results. For example, using the technique of multiple scan probability, Badner and Gershon (6) found common loci for both disorders on chromosome 22q, as well as two distinct susceptibility loci. On the other hand, Craddock and Owen were co-authors of a rank-based meta-analysis of schizophrenia and bipolar disorder, which showed significant evidence for linkage to several chromosome regions in schizophrenia (7), whereas no region achieved genome-wide statistical significance in bipolar disorder (8).

Maziade et al (9) undertook a genome scan of schizophrenia and bipolar disorder in multigenerational families affected by schizophrenia, bipolar disorder or both. Their work was based on the hypothesis that susceptibility genes may be shared by the two major psychoses (the common locus phenotype). Their results showed convergence in some regions, but suggested that other susceptibility genes may be specific to each disorder.

Our group's previous twin study also supports the idea that schizophrenia and bipolar disorder may share some common genes, while others may be specific to each condition (10). We have used these data to argue elsewhere that developmental and dimensional perspectives are likely to throw the greatest light on the relationship between schizophrenia and bipolar disorder (3,11). Thus, neuropsychological and grey matter deficits are much more noticeable in schizophrenia than bipolar disorder (12,13), as are neurological soft signs. Indeed, children who later develop bipolar disorder do not share the excess of subtle neuromotor and cognitive impairments of their pre-schizophrenic counterparts and often appear superior to the normal population in motor development and school examinations (14).

Furthermore, the risk-increasing effect of obstetric complications appears to be confined to schizophrenia (15). Exposure to perinatal hypoxia is known to result in smaller volume of the amygdala and hippocampus, which are reduced in schizophrenia but not in bipolar disorder. These findings suggest that one distinction between schizophrenia and bipolar disorder is that there exists a gradient of neurodevelopmental impairment which is much more important in the former than the latter.

We accept that the neo-Kraepelinian view that schizophrenia and bipolar disorder are totally discrete entities is not supported by the available scientific evidence. However, in our opinion, what is needed is not a rush from one invalid system to another. Rather, we require careful and systemic enquiry and large scale empirical studies. Already, such studies have shown that the symptom dimension model as proposed by van Os (16) adds substantial information to Kraepelin's system. Dikeos et al (17) suggest that the categorical and dimensional approaches

are complementary, and that the use of both maximizes the potential of available information. We now need to carry out comparable studies using external validators, such as neuroimaging, neuropsychology and developmental epidemiology, as well as molecular genetics (11), to establish the extent to which incorporating these measures adds value to our ways of describing patients.

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