Hierarchy and Heritability: The Role of Diagnosis and Modeling in Psychiatric Genetics

In seeking to make sense of the bewildering array of psychiatric nosologies proposed in the 19th century, Kraepelin decided that course of illness was the most important and etiologically relevant defining feature. On the basis of this principle, and using his famous system of patient cards (1), he proposed in 1896 the fundamental distinction between dementia praecox and manic-depressive insanity or, as we will call them, schizophrenia and affective illness (2, 3).

Kraepelin argued that symptoms were less critical than the course of illness in defining diseases. His extensive clinical descriptions commonly note disturbances of mood in patients with schizophrenia and psychotic symptoms in individuals with severe affective illness (4, 5).

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In the years since then, the validity of Kraepelin's proposal has been debated many times. Findings of family, twin, and adoption studies have been used in arguments by both detractors and defenders of Kraepelin's position. The large majority of such studies, including studies of patients with schizophrenia (6–12) (and two studies of offspring of mothers with schizophrenia) (13, 14) and of patients with affective illness (15–17), suggests little if any familial/genetic link between the two syndromes. The results are particularly clear for schizophrenia and bipolar illness. For example, in the Roscommon Family Study, the risk for bipolar illness was 1.2±0.7% in interviewed relatives of probands with schizophrenia, compared with 1.4±0.7% in relatives of comparison subjects from the general population (12), although several family studies have found increased rates of depressive illness in relatives of schizophrenic probands (18–20).

In their article in this issue, Cardno and colleagues reach a quite different conclusion—that schizophrenia and mania share substantial common genetic risk factors. How can we understand and interpret their findings? (I will focus here on their results for schizophrenia and mania. Space constraints preclude a detailed discussion of the more complex interrelationship between schizophrenia, mania, and schizoaffective disorder.)

Let's begin by reviewing their methods and findings. Cardno and colleagues worked with the famous Maudsley twin series. To be included in the study, subjects had to be from same-sex twin pairs in which one twin had been treated at the Maudsley Hospital complex for a psychotic or manic syndrome between 1948 and 1993. Clinical information was derived from a variety of sources, including interviews, case records, and informant material. In 1999, Cardno and colleagues, using the Research Diagnostic Criteria (RDC) (21), examined several diagnostic categories including schizophrenia, schizoaffective disorder, and affective psychoses (22). Using typical hierarchical rules that assign one lifetime diagnosis to each subject, they found strong evidence for heritability of each of the disorders.

In the research reported in the current paper, Cardno and colleagues worked with the same group of subjects but took a very different diagnostic approach. Using the RDC and

focusing on the three syndromes of schizophrenia, schizoaffective disorder, and mania, they assigned these diagnoses *nonhierarchically*, i.e., a subject who met the criteria for one of the disorders at some point in his or her lifetime would be assigned that diagnosis regardless of other aspects of the subject's longitudinal course. This is a critical methodologic point. In the RDC, the minimum duration for these syndromes is only 2 weeks for schizophrenia and 1 week for schizoaffective disorder and mania. Longitudinal studies have indicated that the specificity of psychotic and manic symptoms when examined cross-sectionally is relatively poor (23–25). For example, several key symptoms of mania (i.e., irritability, grandiosity, distractability, and hyperactivity) are commonly seen in otherwise classic schizophrenic syndromes. What other authors have referred to as diagnostic unreliability or instability, Cardno et al. are calling comorbidity.

The difference between hierarchical and nonhierarchical diagnostic approaches can be illustrated by a vignette:

> Mr. X, a 46-year-old single male, demonstrated substantial negative symptoms and poor psychosocial functioning at interview. On his first admission at age 24, he demonstrated a classic manic syndrome with mood-congruent delusions and hallucinations, although some silliness and mild thought disorder were noted. Four months later, however, he was admitted with bizarre delusions and hallucinations, a flat rather than euphoric affect, and significant negative symptoms. He had six further admissions in the next 18 years, all with typical schizophrenic features and no recurrence of the manic symptoms.

Most clinicians, faced with this case, would implicitly use a hierarchical approach and assign a single diagnosis of schizophrenia. A nonhierarchical system, however, would require diagnoses of both mania and schizophrenia. The two systems differ in the diagnostic significance accorded to Mr. X's first "mania-like" psychotic episode.

Using this nonhierarchical approach, Cardno et al. began by looking at the correlations between schizophrenic, schizoaffective, and manic syndromes within individuals in their study group. The correlations were quite high, with a correlation of approximately 0.60 between schizophrenia and mania. Next, they examined the resemblance for the nonhierarchical diagnoses across twin pairs. For example, if Mr. X was a monozygotic twin and his co-twin had schizophrenia, the pair would contribute to a positive "cross-twin cross-trait" correlation (between schizophrenia in one twin and mania in the co-twin). Indeed, using nonhierarchical diagnoses, Cardno et al. found just this correlation to be much higher in monozygotic twin pairs (r=0.51) than in dizygotic pairs (r=0.12). These results would be expected if mania and schizophrenia had a strong genetic relationship.

The investigators then applied standard multivariate twin modeling to the data for the three diagnoses. The results suggest that one common set of genetic risk factors contribute strongly to nonhierarchically diagnosed schizophrenia, mania, and schizoaffective disorder. It would be easy to conclude from these analyses that schizophrenia, mania, and schizoaffective disorder are, from a genetic perspective, closely related syndromes.

How are we to understand these results in light of the substantial prior data suggesting that, when hierarchical diagnoses are used, schizophrenia and mania have little if any overlap in familial/genetic risk factors? To answer this question, we must understand 1) the assumptions of the analytic model used by Cardno et al. and 2) the relationship between hierarchically and nonhierarchically diagnosed syndromes.

The model used by Cardno and colleagues to analyze the relationship between schizophrenia and mania makes the critical assumption that *the factors that influence the risk for mania in a person who has schizophrenia are the same as those that influence the risk for mania in a person who does not have schizophrenia.* Is this assumption justified?

One set of results, consistent with results from three prior reports (26–28), suggests perhaps not. In a study of a large set of carefully diagnosed Irish sibling pairs concordant for schizophrenia, the siblings substantially resembled one another in the level of manic and depressive symptoms demonstrated during their course of illness (29). This study group did not have any appreciable admixture of mania or schizoaffective disorder because no increased risk for bipolar illness in relatives was observed (30). This pattern of results is consistent with the hypothesis that there are familial factors that influence the probability of demonstrating mania-like symptoms in individuals with schizophrenia but that these factors do not increase the risk for mania in individuals without schizophrenia.

The data of Cardno et al. contain a critical test of this hypothesis. Is the increased rate of mania observed in co-twins with schizophrenia largely or entirely confined to co-twins with a diagnosis of schizophrenia? This is a distinct possibility, given that the study group included no pairs in which one twin had a hierarchical diagnosis of schizophrenia and the other had a hierarchical diagnosis of mania.

So, what is the take-home message? Although provocative, it is not, on the basis of the report of Cardno et al., time to bury Kraepelin. Given how differently Cardno et al. approached the diagnosis of psychotic syndromes, it is not surprising that their results differ so widely from those obtained by using more standard approaches. Because they departed substantially from prior practice in the diagnosis of psychotic illness, I would argue that the burden should be on them to demonstrate that their modeling assumptions hold. The critical question again is whether schizophrenia in one twin significantly increases the risk for mania in a nonschizophrenic co-twin and whether this pattern is seen more commonly in monozygotic than in dizygotic pairs. The creative work of Cardno and colleagues demonstrates the close interrelationship between diagnosis and modeling in psychiatric genetics. We will need valid diagnoses, incisive statistical modeling, and careful coordination between them to make the necessary critical advances in our understanding of the etiology of psychiatric illnesses.

Acknowledgments

The author thanks Carol Prescott, Ph.D., Michael Neale, Ph.D., and Patrick Sullivan, M.D., for their comments on an earlier version of this essay.

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