Family-Genetic Studies and Identification of Valid Diagnostic Categories in Adult and Child Psychiatry

JAMES F. LECKMAN, MYRNA M. WEISSMAN, DAVID L. PAULS and KENNETH K. KIDD

Family-genetic studies of child and adult psychiatric disorders have become increasingly fashionable over the past decade. The development of structured diagnostic interview schedules, the emergence of uniform diagnostic criteria such as DSM–III, and the use of refined design and analytic techniques from the field of chronic disease epidemiology have made substantial contributions to the methodology of such studies. Advances in molecular genetics, particularly our emerging capacity to perform chromosomal linkage studies throughout the human genome, have renewed hope that the constitutional underpinnings of some psychiatric disorders can be identified and that the pathophysiology of these disorders can be elucidated. Family-genetic techniques in child and adult psychiatry are discussed with a particular focus on their potential value in validating diagnostic categories spanning developmental epochs.

A variety of ‘family-genetic’ strategies have been developed over the past century (Kidd & Matthysee, 1978). Classically, four types of evidence are suggestive of genetic or familial factors being aetiologically important in behavioural disorders: (a) an increased frequency of the disorder observed in at-risk family members; (b) an increased frequency of the disorder in the adopted-away biological offspring of affected individuals; (c) a higher concordance for the disorder among monozygotic than among dizygotic twins; and (d) evidence for a specific genetic factor transmitted in an area adjacent to a known chromosomal locus. Although this paper will focus primarily on the first and last of these, many of the comments regarding assessment methodologies apply equally to twin and adoption studies.

Recent methodological advances

Each of these family-genetic strategies requires the ability to assess reliably the psychiatric status of large numbers of individuals, many of whom have never been in treatment. Over the past decade, family-genetic studies in the USA have increasingly been influenced by putative advances in psychiatric nosology and by corresponding changes in assessment procedures. Historically, the search for reliable diagnostic criteria and the development of standardised methods to elicit the needed information can be traced to work at Washington University in St Louis. Feighner et al (1972) published criteria for 15 major psychiatric disorders and developed a structured interview instrument, the Renard Diagnostic Interview, to collect systematically information relevant to the application of these criteria (Robins et al, 1977). These criteria were subsequently modified and elaborated, and specific 'Research Diagnostic Criteria' (RDC) were proposed (Spitzer et al, 1978a; Endicott & Spitzer, 1979). The RDC focused on past and present episodes of illness and provided inclusion and exclusion criteria by which clinically homogeneous groups of patients may be diagnosed and studied. The Schedule for Affective Disorders and Schizophrenia (SADS), a structured interview, was developed at the same time to ensure that the information on signs and symptoms were collected systematically (Spitzer & Endicott, 1978). A 'lifetime' version of the SADS was also developed to record information concerning past as well as present episodes of illness for use in family studies. Use of the RDC and the SADS greatly improved inter-rater agreement (Endicott & Spitzer, 1979). DSM–III (American Psychiatric Association, 1980) is a direct descendant of these earlier diagnostic schemata.

Similar developments in the standardisation of diagnoses have taken place in the United Kingdom – particularly the work of Wing et al (1967, 1974) on the Present State Examination (PSE), which incorporates standard methods of defining, eliciting, and recording information about 140 symptoms and signs in an interview format. The PSE is reliable, and modified versions have been widely used in large-scale international studies (Wing et al, 1977). Only recently, however, have attempts been made to modify the PSE to include information on 'lifetime' symptoms (Torgersen, 1983).
The movement to define reliable categories has also led in the USA to a proliferation of diagnostic categories in both the adult and childhood areas of DSM–III. Whether this is a real advance or merely legerdemain is debatable (Rutter & Shaffer, 1980; Tyrer, 1985); our ability to construct reliable diagnostic categories may have outstripped our ability to validate such categories. The hierarchical organisation of diagnoses in DSM–III has also proved to be problematic. Although the exclusion of some diagnoses, such as anxiety disorders, during episodes of depression or schizophrenia is parsimonious, it may be misleading when the validity of the hierarchical scheme is unproven (Leckman et al., 1983a). The revision of DSM–III currently under way largely does away with these exclusionary criteria.

Validation of diagnostic categories and distinctions

How can we ‘validate’ a diagnostic category? In the absence of specific neuropathological evidence, how can we establish that any two individuals are suffering or have suffered from the same disorder? This fundamental question has yet to be answered for most, if not all, psychiatric disorders. The identification of clinically homogenous groups of patients is insufficient (Rutter & Shaffer, 1980). DSM–III offers many examples of such a priori groupings. While they may be acceptable first approximations, they incautiously assume that cross-sectional clinical homogeneity accurately reflects an underlying aetiological homogeneity. Indeed, some medical disorders with similar pathophysiological and clinical expressions, have been found to be aetologically heterogeneous, e.g. anemias, coagulation disorders, and congenital deafness. Historically, most psychiatric researchers have emphasised the use and importance of natural history data regarding the onset, course, and outcome to establish valid diagnostic categories. Differential response to treatment and the presence of a ‘biological-marker’ have more recently been proposed as alternate means to validate categories of psychiatric disease. Although a thorough review of these strategies is beyond the scope of this paper, it is clear that none of them is wholly adequate. Each is vulnerable to the presence of factors which are unrelated to the underlying disease process but which may dramatically influence its onset, course, or treatment outcome.

The use of family history and family study data to help define nosological categories more precisely is well-known (Robins & Guze, 1970; Spitzer et al., 1978b). For example, more than a score of family studies of schizophrenic probands have found that the risk of schizophrenia and related conditions significantly exceeds the risk observed in the general population, thus confirming Kraepelin’s (1904) original view that familial factors are aetologically important in this disorder. Although the familial nature of schizophrenia has recently been challenged, the most rigorous family studies of schizophrenia using DSM–III criteria and structured interviews continue to provide strong support for the view that schizophrenia is a familial disorder (Tsuang et al., 1980; Kendler et al., 1985). The Iowa studies have also helped to clarify the possible connections between schizophrenia and a variety of other disorders. While the relationship between schizophrenia, psychotic major depression, and schizoaffective disorders remain obscure, the evidence is persuasive that alcoholism, unipolar depression, non-psychotic depression, major depression, and some anxiety disorders are aetologically unrelated to schizophrenia (Tsuang et al., 1980; Kendler et al., 1985).

In providing an independent source of data, family-genetic studies also allow investigators to assess directly the importance of various clinical features of a putative disorder. By stratifying groups of at-risk relatives on the basis of the presence or absence of a particular symptom or pattern of symptoms in the index cases, it has been possible to assess the predictive value of such symptoms or symptom constellations by their effect on the rates of illness and the types of illness among the relatives. Recent examples of such work have focused on the importance of primary social role impairment (Gershon et al., 1986), age of onset (Weissman et al., 1984a), sex of proband (Merikangas et al., 1985a), and ‘endogenous’ symptom patterns in discriminating familial from non-familial forms of major affective disorder (Leckman et al., 1984a,b; Andreasen et al., 1986).

Family study data have provided valuable information by tentatively identifying alternate manifestations of the same underlying diathesis. The relationship of obsessive-compulsive disorder to Gilles de la Tourette’s syndrome (TS) is one such example, where high rates of obsessive-compulsive disorder were found among the first-degree relatives of probands with TS (Pauls et al., 1986b; Pauls & Leckman, 1986). Better known is the apparent association of schizophrenia with a ‘spectrum’ of related disorders (Kety et al., 1968; Kendler & Gruenberg, 1984).

Restratification techniques have also proved useful in studying the relationship of co-morbid conditions, such as panic disorder and alcoholism, with major affective disorder (Leckman et al., 1983b; Merikangas et al., 1985b). In the case of panic disorder, we have investigated the relationship between
FAMILY-GENETIC STUDIES AND IDENTIFICATION OF VALID DIAGNOSTIC CATEGORIES

symptoms of depression and recurrent panic attacks as part of a large scale family-genetic study of major affective disorders (Weissman et al., 1984a,b). As noted above, the prevailing diagnostic conventions in the United States assert that prominent anxiety symptoms (including recurrent panic attacks) that occur solely during depressive episodes do not have any nosological significance. Our family study data, on the contrary, have indicated that the association of depression and recurrent panic attacks in index cases was associated with increased rates of depression and anxiety in the adult at-risk relatives, compared with the adult at-risk relatives of depressed probands without prominent anxiety symptoms (Leckman et al., 1983a,b). This increased risk was observed regardless of whether or not the recurrent panic attacks occurred concurrently with the depressive episodes. Similar findings were also observed in the offspring under the age of 18 years in these families (Weissman et al., 1984c).

These data call into question the validity of the prevailing diagnostic convention and suggest that additional studies are needed to clarify the aetiological relationship between recurrent panic attacks and depression; they have also led to the hypothesis that some forms of depression and some forms of 'panic disorder' partially or wholly share a common underlying diathesis. If this can be established and the critical clinical features identified, more precise studies in other areas of clinical investigation will follow. Specific differences in natural history, treatment response, and biological measures may be expected. Even our capacity to apply sophisticated mathematical models and to perform state-of-the-art genetic linkage studies in high-density families using newer recombinant DNA techniques will be enhanced through our ability to identify aetiologically more homogenous patient groups.

Another example of assessing the relationship of a co-morbid condition involves an effort to sort out the nosological significance of frequent symptoms of hyperactivity, attentional impairment, and impulsivity in children with TS. In a family study of TS we found that the at-risk relatives of probands with TS and attentional impairment had an increased rate of attentional impairment, but no increase in the rate of TS or chronic multiple tics compared with the at-risk relatives of probands with TS only (Pauls et al., 1986a). These data, together with the observation that the attentional impairment and the tics or TS did not co-segregate within these families, have led us to conclude that the TS diathesis is largely independent of the aetiological factors which underlie the attentional problems observed in a sizeable proportion of TS patients (over 50% in most clinic samples). The increased frequency of attentional problems among TS patients, which has been observed in clinic patients, may be due to a referral bias (Berkson's bias). Children with two disorders may be more likely to come to the attention of health care professionals, particularly if both adversely affect school performance and behaviour.

Limitations

The use of family study data to establish valid diagnostic criteria is largely limited to those disorders in which transmission within families is known to occur. As such, efforts to refine and validate criteria logically follow studies in which familial or genetic factors have been demonstrated to be aetiologically important. Even with this constraint, the list of disorders for which such a determination has been made is substantial and includes schizophrenic disorders, affective psychoses, paranoid states, some forms of alcoholism, panic disorder, agoraphobia, and antisocial personality disorder in adulthood; in children it includes infantile autism, attention deficit disorder, tic disorders, stuttering, and some learning disorders. In other instances, suitable studies have not yet been performed on which to judge the aetiological importance of familial or genetic factors. Conversely, hypotheses invoking environmental factors transmitted within families cannot be rejected for most psychiatric disorders. However, the potential importance of genetic factors in creating unique environments should not be discounted (Scarr & McCartney, 1983).

On a more practical level, the need to establish 'lifetime' diagnostic estimates is associated with important methodological problems involved with the recall of symptoms for remote episodes of illness. These problems are compounded when the individual is dead or otherwise unavailable for direct interview. In such cases the diagnostic estimates must be made on the basis of indirect reports from other relatives or from medical records. The under-reporting of psychiatric disorders associated with indirect 'family history' methods has been well documented (Andreasen et al., 1977). Not surprisingly, individuals living in the closest proximity, such as spouses, are generally the best informants (Thompson et al., 1982). Nor is it surprising that severe disorders can be more consistently identified by family members (Orvaschel et al., 1982). These methodological difficulties culminate in making final 'best estimate' diagnoses on the basis of all available information. Inevitably, the quantity and quality of data available for this procedure are often quite variable. However, good inter-rater agreement using the best estimate method was
found for major depression, depressive personality, alcoholism, drug abuse, panic disorder, phobia, and antisocial personality among interviewed individuals (Leckman et al., 1982).

The diagnostic procedures become even more problematic in dealing with childhood disorders. Although structured and semi-structured instruments have been developed for school-aged children (Herjanic et al., 1975; Puig-Antich & Chambers, 1978), the test-retest reliability of these instruments is marginal for many diagnoses (Chambers et al., 1985). Similarly, the level of parent-child agreement is often low. A related problem has to do with attempts to make childhood diagnoses, such as separation anxiety, retrospectively, in adult subjects who no longer display the symptoms. Many of these difficulties are substantive and may not yield to refinements in assessment methodology. Examination of these issues raises fundamental questions concerning the developmental continuities or discontinuities of psychopathological states. They also highlight the limitations in perception and recognition over time by individual children, parents, and investigators of mental disorders as opposed to states that are perceived as being within the range of 'normal' experience.

Another major limitation involves the potential effects of assortative mating – the tendency for couples with similar phenotypic traits to select one another more frequently than would be expected by chance alone. Assortative mating for psychiatric disorders in general, as well as for specific psychiatric disorders, has been consistently reported (Merikangas, 1982). This non-random mating can influence the distribution of disorders in a population, by increasing the population variance and the proportion of homozygous individuals, and so mislead the unwary investigator. The Danish Adoption Study and the American-Danish High Risk Project provide examples of the potentially confounding effects of this phenomenon in studies of schizophrenia (Rosenthal, 1975; Parnas, 1985).

Improvements in the statistical methods for handling these large data sets from family-genetic studies have included: the development of methods for quantifying lifetime prevalence which handle the age correction of the data without ancillary information on population age-specific incidence rates and are independent of mortality (Thompson & Weissman, 1981); the successful application of log-linear models to deal with potentially confounding variables which may be related to outcome (Kidd et al., 1981; Weissman et al., 1982); and the use of survival time models with non-proportional hazard functions (Weissman et al., 1984d; Wickramaratne et al., 1986).

Prospects for the future: genetic linkage studies

Genetic linkage has long been recognised as a way of demonstrating that a specific genetic factor is etiologically important in the transmission of a particular disorder. If linkage can be demonstrated it may be possible, given the current revolution in human genetics, to isolate a specific genetic factor and gain insight into the basic constitutional events that may predispose an individual to the expression of a particular psychiatric disorder (Cloninger et al., 1983; Kidd, 1982, 1985). Equally exciting is the possibility that by ascertaining which individuals are at risk it will be possible through the use of appropriate longitudinal research designs to identify those risk and protective environmental factors which mediate the expression of the disorder. Important and rational strategies for treatment and possible prevention would also be anticipated.

Until a few years ago this method had limited applicability to human disorders, because of the small number of polymorphic genetic markers that were available. Over the past few years the field of human molecular genetics has changed dramatically. Using recombinant DNA techniques, investigators are identifying a growing number of highly polymorphic markers. As of mid-1985 over 800 new polymorphisms had been identified (Willard et al., 1985), and that number has significantly increased during the last two years. Since new polymorphisms are being discovered at an ever-increasing rate, it should be possible to construct a genetic linkage map of the entire human genome in the next few years. This development may have major consequences in the field of psychiatry. For example, the recent reports of Gerhard et al. (1984) and Egeland et al. (in press) detailing the possibility of linkage of manic-depressive disorder in large Amish pedigrees to markers on chromosome 11, if confirmed, may clarify the relationship of unipolar to bipolar affective disorders in at least some cases, as well as herald other dramatic advances in our understanding of this disorder.

Although the number of psychiatric disorders which may be amenable to this technique (i.e. for which a single major locus accounts for a sizeable portion of the total phenotypic variance) is unknown and may well be small, the potential power of these recombinant DNA techniques argues against any premature judgement that complex behavioural traits with non-Mendelian patterns of inheritance are necessarily polygenic in origin.

Finally, genetic linkage strategies may provide an elegant means of 'validating' some diagnostic
categories in psychiatry. The outcome of such a validation might be the delineation of 'families' of related disorders that have the same underlying vulnerability but differing phenotypic expression. Tracing the range of phenotypic expression for specific disorders from childhood on will be a particularly important undertaking for investigators interested in the possible continuities between adult and child psychopathology. Pathognomonic symptoms may be identified that may have relatively little clinical significance but which are highly associated with the underlying vulnerability. It will also permit the identification of phenotypically similar but aetiologically distinct disorders which can confound empirical psychiatric research.

Acknowledgements

This research was supported in part by NIMH grants No. MH28274 and No. MH36197 from the Center for Epidemiologic Studies (Dr Weissman), Yale Mental Health Clinical Research grant No. MH130929, NIH grant No. RR00125 and NINCDS grant No. NS16648 (Dr Pauls), and by The John D. and Catherine T. MacArthur Foundation and the John Merck Fund (Dr Leckman). The authors thank Dr Kathleen R. Merikangas for her comments.

References


& LECKMAN, J. F., PRUSSOFF, B. A., PAULS, D. L. &


*James F. Leckman, MD, Coordinator of Research, Child Study Center and Associate Professor of Psychiatry and Pediatrics, Yale University School of Medicine; Myrna M. Weissman, PhD, Director of Depression Research Unit, Connecticut Mental Health Center and Professor of Psychiatry and Epidemiology, Yale University School of Medicine; David L. Pauls, PhD, Assistant Professor of Psychiatry and Human Genetics, Child Study Center, Yale University School of Medicine; and Kenneth K. Kidd, PhD, Associate Professor of Human Genetics and Psychiatry, Yale University School of Medicine

*Correspondence: Yale University School of Medicine, P.O. Box 3333, New Haven, Connecticut 06510, USA*