DIAGNOSTIC ASSESSMENT IN CHILD AND ADOLESCENT PSYCHOPATHOLOGY

Edited by

David Shaffer
Christopher P. Lucas
John E. Richters

Foreword by Professor Sir Michael Rutter

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Assessment of Family History of Psychiatric Disorder

RICHARD RENDE
MYRNA M. WEISSMAN

It is not an overstatement to suggest that most forms of psychopathology run in families. Indeed, it would be a challenge to document psychiatric disorders that are not in part familial. A recent review has suggested significant familial aggregation for essentially every childhood psychiatric disorder (Rutter, Silberg, O'Connor, & Simonoff, 1999b). Given the accumulating evidence for familial aggregation of most if not all psychiatric disorders, including those that arise in childhood or adolescence, the uninitiated reader might wonder why there is a need for further family studies. For example, an often-noted limitation of family studies is that they cannot disentangle genetic and environmental influences; more specialized methodologies, such as twin and adoption designs are necessary for that purpose. Furthermore, molecular genetic techniques are recognized as a critical component of psychiatric research (Rutter, Silberg, O'Connor, & Simonoff, 1999a). Such tides of interest might seem to diminish the need for future family studies of psychiatric disorders, including child and adolescent psychopathology.

We believe, however, that family studies may continue to have an important role in psychiatry. First, although many studies have provided evidence of familial aggregation of childhood and adolescent psychopathology, they have not adhered to the contemporary standards of methodological rigor (see Rutter et al., 1990, 1999b). Hence, firm conclusions cannot readily be drawn from these studies, and there is a need for more carefully designed studies (e.g., ones

that use appropriate control groups, take comorbidity into account, and ensure so-called "blindness" on the part of raters) to provide data on the precise risk and specificity involved in the familial transmission of disorders.

Second, family studies may provide information that will prove invaluable in defining diagnostic boundaries between disorders. To take a classic example, family studies have demonstrated that although affective illness and schizophrenia sometimes co-occur within individuals, these disorders do not cluster within families and hence appear to have different etiological bases (e.g., Guze, Cloninger, Martin, & Clayton, 1983; Kendler, Gruenberg, & Tsuang, 1985; Weissman et al., 1984). In addition, family studies may extend traditional diagnostic boundaries to include a broader range of problems. A notable example is that social and cognitive abnormalities are found in the relatives of autistic individuals, suggesting that genetic influence on autism may affect these areas of functioning (Folstein & Rutter, 1988). Hence family studies of psychopathology in childhood and adolescence not only may indicate the precise risk involved for specific disorders, but also may provide important data on the diagnostic specificity involved within and between different disorders.

Third, the heightened interest in molecular genetic approaches to adult psychiatric disorders has been tempered by the lack of replicated findings of linkage. Because molecular genetic approaches to adult disorders will involve more complexity than originally thought, clearly applications to childhood and adolescent disorders will not take place immediately. The identification of highly familial phenotypes may aid in the search for specific genes by highlighting potential subtypes of disorders that may have genetic causes (see Rutter et al., 1999a). Family studies will also provide valuable data on persons at increased risk, which will be useful for targeting secondary prevention. Furthermore, most psychiatric disorders involve the expression of environmental as well as genetic factors. Because of this, family studies should be viewed as a resource for studying environmental risk factors.

The primary purpose of this chapter is to describe the designs and methods used to conduct family studies, especially those designed to examine the familiarity of childhood and adolescent psychopathology. We discuss research designs, assessment of family members, issues of data analysis, and the role of family studies in disentangling genetic and environmental influences on psychopathology.

RESEARCH DESIGNS

Top-Down, Bottom-Up, and High-Risk Designs

A prototypical family study is the "family retrospective cohort design," in which subjects are asked to recall their lifetime course of psychiatric disor-

ders. As a first step, an "affected proband" (i.e., case with the disorder under investigation) is identified and matched to a "control proband," who is an individual not affected with the disorder but matched to the affected proband on other salient characteristics (e.g., age, sex, socioeconomic status) that may influence the rates of disorders in relatives. As a second step, all living and willing first-degree relatives (i.e., biological parents, siblings, and offspring) are assessed to determine their lifetime course of disorders, and family history information is obtained for deceased relatives or for relatives who cannot be interviewed directly. All assessments of relatives are conducted by evaluators who are unaware of ("blind" to) the probands' status (i.e., affected vs. control). The prevalence of the disorder under study in first-degree relatives of affected probands is then compared with its prevalence among relatives of control probands. If the prevalence is statistically greater in the relatives of affected probands, then the disorder under investigation is considered to aggregate within families. Second-degree (grandparents, aunts, uncles) and third-degree (cousins) relatives can also be studied, but the number of subjects in such a study will become very large, and cooperation will usually decrease. (However, see below.)

There are a few variants of this approach, which are especially relevant to the study of psychopathology in childhood and adolescence. An important distinction is made between "top-down" and "bottom-up" designs when children and adolescents are included in family studies (Puig-Antich, 1984; Strober, 1984; Strober & Carlson, 1982). Family studies that begin with adult probands and study psychopathology among their offspring as well as other relatives are known as "top-down" studies, which is the design just described. In contrast, "bottom-up" studies identify children or adolescents as the probands, and their relatives are then examined for lifetime rates of psychiatric disorders.

Top-down and bottom-up designs are different because the rates of disorders are calculated for relatives of different ages, and these designs thus require different types of controls. In a bottom-up design, the parents are the ones who bring affected child probands for treatment and who grant permission for the children to be included in the study. This creates a potential bias in the family design, because parents who have psychiatric disorders themselves may be more likely than unaffected parents whose children have a disorder to bring their children to treatment and to consent to the children's inclusion in a study. This sampling bias can artificially produce high rates of disorders in the child's adult relatives. One method used to control for this referral bias is to include a control proband group of children with another psychiatric disorder where the same bias of selection for psychopathology may exist. That is, the rates of psychiatric disorders will also tend to be higher in the adult relatives of this comparison group. Hence differences in either the types or rates of disorders between the adult relatives of the cases and the

relatives of the psychiatric control group may provide useful information on the familial nature of the disorder under study.

The "high-risk" design is a variant of the family study; specifically, it is a modification of the top-down design. In the high-risk design, the focus is usually limited to the young offspring of affected probands, and strong efforts are made to interview both biological parents and offspring (and, as discussed in detail later, other adults in the children's lives, such as nonbiological rearing parents). Ideally, the offspring are identified before the age of onset of the disorder in question and studied longitudinally, so that the early signs and first episodes of the disorder may be examined. In addition, a focus on offspring at high risk for a disorder also permits potential investigation of salient risk and protective factors, which may be more obvious in younger individuals through childhood and adolescence. In general, high-risk studies have been developed after the familial nature of a disorder has been established by means of the family case–control and top-down designs.

One additional design should be mentioned. A few family studies of psychiatric disorders have widened their focus from first-degree relatives (i.e., parents, siblings, offspring) to include second- and third-degree relatives (i.e., aunts, uncles, grandparents, grandchildren). In general, the assessment of extended pedigrees is used in order to develop statistical genetic models of the way in which a disorder is transmitted across generations. For example, inclusion of second- and third-degree relatives may be useful for developing genetic models of psychiatric disorders, because their resemblance would not be due to common family experiences shared by first-degree relatives. Although this method has not been used very frequently in the study of child and adolescent psychopathology, there is increasing interest in this approach (Todd, Neuman, Geller, Fox, & Hickok, 1993).

Family History versus Family Study

A traditional method for collecting family data in clinical psychiatry has been to ask a patient about psychiatric illness in the family. This approach has been standardized, so that the questions and relatives included are precise, and it is referred to as the "family history method" (Andreasen, Endicott, Spitzer, & Winokur, 1977). Here the goal is to gather systematic information on the psychiatric history of family members (the specific methods used are discussed in the next section of this chapter), whether the design is top-down, bottom-up, or high-risk. One difficulty with the family history method is that it underreports rates of disorders in family members. One way to correct this problem is to obtain family history from multiple informants and piece together a picture on each noninterviewed relative. Using more than two informants can produce results approaching those obtained through a direct interview (Thompson, Kidd, & Weissman, 1979).

Although the family history method represents an important approach to assessing family history of psychiatric disorders, a more powerful and preferable approach is to interview the family members directly. This approach, referred to as the "family study method," attempts to use direct interviews with all available family members under study, in order to gather sufficient diagnostic information from each individual. This approach is preferred because direct interviews have been found to provide more complete diagnostic information on individuals within a family (see Weissman et al., 1986). Again, the family study method can be used within top-down, bottom-up, or high-risk paradigms. The one difficulty with this approach, however, is the pragmatic problem of being able to conduct direct interviews with all family members, for reasons including refusal to participate in the study, unavailability due to geographic distance, or death. It is for these reasons that the family history method has a place along with the family study method in the assessment of family history of psychiatric disorders.

GENERAL PROCEDURES

Selection of Affected Probands

Family studies begin with the identification of affected probands, or index cases with the disorder under investigation. The criteria for including or excluding these probands should be well defined, as they form the sampling frame for a study; such criteria include demographic variables (e.g., including/excluding probands of certain ages or one gender) or diagnostic considerations (e.g., including/excluding probands with comorbid conditions). Probands should be selected without knowledge of family history, and probands without family members should be omitted from a study.

With rare exceptions, affected probands in family studies of psychiatric disorders are patients receiving psychiatric treatment. This situation represents a potential bias in family studies, as a majority of individuals with psychiatric disorders never receive treatment (e.g., Shapiro et al., 1984). Hence questions may be raised about the generalizability of findings to the population as a whole. For example, such a bias may influence results in regard to severity, as treated individuals are generally among the more severely affected. If severity is related to familial aggregation, then the findings based on treated samples of affected probands may not extend readily to the full range of the disorder in the population. Moreover, patients with ill family members may be more likely to come to treatment—a bias that could result in increased rates of illness in relatives. However, it should be noted that in one family study of panic disorder and major depression, patterns of familial aggregation were not affected by whether affected probands came from treatment clinics or a community sample (Weissman et al., 1993).

Selection of Control Groups

The reason for inclusion of control groups is to permit comparison of the rates of the disorder among relatives, in order to obtain data on relative risk. Although earlier studies have compared rates of disorders in relatives of affected probands to population rates (see Weissman et al., 1986), the use of a control group allows a more stringent testing of the hypothesis of no familial aggregation: Data on relatives of affected and control probands are collected in an identical manner, reducing possible sources of bias introduced by using different diagnostic instruments. In addition, affected and control probands may be matched on likely confounding factors, which may affect the rates of disorders in relatives. Such basic confounding factors include age, sex, socioeconomic status, race, and ethnicity.

The types of control groups used in family studies of psychopathology vary according to the purpose of the study. Many family studies have used a "normal" control group, consisting of individuals who have never had a psychiatric disorder. Such a control group can be randomly sampled from the community (e.g., Weissman et al., 1984). Another approach is the "acquaintanceship" procedure, in which relatives of probands are asked to name acquaintances who of are the same gender and of about the same age and socioeconomic status as themselves; then their relatives are interviewed. In this method, it is important to screen for mental illness in the acquaintances, in order to create a control group without lifetime histories of psychiatric disorders (Mannuzza et al., 1992).

There have been suggestions that the use of a normal control group may lead to inflated rates of familial aggregation, and that a population control group would be more informative (Kendler, 1990). Such a bias could theoretically occur if affected probands in a family study have a secondary disorder that is also associated with the primary disorder in relatives (see Weissman et al., 1993). However, relying on population control groups could also result in overestimating the degree of familial aggregation; thus multiple control groups offer the best alternative. Normal controls may be used to study the aggregation of the primary disorder in the absence of a secondary disorder, and comorbid groups may serve as appropriate controls for studying the effects of a secondary disorder on the aggregation of the primary disorder in affected probands and relatives (Weissman et al., 1993).

Other control groups may serve more specialized purposes in family studies. A control group of individuals who have a disorder other than that of interest, and who have sought treatment for this disorder, provides a test of the hypothesis that the rate of the primary disorder in relatives of affected probands "breeds true" (i.e., is specific to that particular type of disorder). In addition, an inclusion of a medically, but not psychiatrically, ill control group allows a test of the hypothesis that high rates of psychopathology reflect dysfunction due to major psychosocial stressors result-

ing from having any form of illness. One example of a study involving children using multiple control groups was conducted by Hammen, Burge, Burney, and Adrian (1990); the controls included psychiatric, medical, and normal controls.

Identification of Relatives

Relatives can be first-, second-, or third-degree, depending on the study design. The ascertainment of relatives should be systematic, and methods for eliciting and recording the pertinent information on relatives (or "pedigree") have been developed to ensure complete and unambiguous data, which can be transferred directly to a computer file (Thompson et al., 1979; see Weissman et al., 1986). Such a process is essential to the proper conduct of family studies: The database for such studies may be quite large, and it is crucial to identify all family members, living or deceased, by sex, current age (or age at death), and precise biological relationship (e.g., "grandfather" rather than "second-degree relative"). As will be discussed below, the various types of family structures observed in contemporary society also require that systematic methods be used for identifying all members of non-nuclear families, and especially for defining the precise relationship of each family member to each proband. Several data management systems that monitor the collection of pedigree data, check for errors, and track persons as they progress through data collection are now available (Adams, 1994).

DIRECT INTERVIEW OF FAMILY MEMBERS

As discussed previously, the preferred method for collecting information on the lifetime psychiatric status of relatives is the family study method, in which all relatives of interest are assessed through direct interview. A few specific guidelines should be followed in choosing the most appropriate diagnostic assessment procedure for a family study. One essential feature is to use a structured or semistructured interview that assesses the lifetime history of a variety of diagnoses, such as the instruments discussed below. An important feature is that widely used methods should be chosen in order to facilitate comparability with other studies. No matter what instrument is used, it is essential that all interviewers of family members be unaware of probands' clinical status, so that bias does not influence the interviews.

Assessment of Adults

It is important to note that as yet no methodological studies have compared the utility of different instruments for diagnosing disorders in adults within

family studies. Rather, the emphasis in family studies has been on choosing a method that meets the fundamental requirements indicated above—primarily the capacity to indicate *lifetime history* of psychiatric disorders. Many studies utilize criteria that fit either with a given diagnostic system (e.g., the *Diagnostic and Statistical Manual of Mental Disorders* [DSM] or the *International Classification of Diseases* [ICD]) or with the well-established Research Diagnostic Criteria (RDC). In general, studies also usually rely on structured diagnostic interviews that systematically elicit signs and symptoms of disorders, such as the Schedule for Affective Disorders and Schizophrenia—Lifetime (SADS-L; Mannuzza, Fyer, Klein, & Endicott, 1986) and the Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, Gibbon, & First, 1992). Other measures include the Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, & Ratcliff, 1981), which was designed as a diagnostic interview to be used by lay interviewers.

A fairly recent methodological development has been the introduction of the Diagnostic Interview for Genetic Studies (DIGS), which was designed specifically for psychiatric genetic studies (Nurnberger et al., 1994). The DIGS, which focuses on the assessment of major mood and psychotic disorders, was developed (1) to ensure a broad sampling of possible diagnoses, with maximum comparability across data sets; (2) to provide detailed information on the phenomenology of mood and psychotic disorders (not typically assessed with other instruments); (3) to allow for quantitative assessments of the relevant phenotypes, in addition to diagnoses; and (4) to incorporate an algorithmic scoring capability. An initial study using the DIGS reports satisfactory reliabilities for most disorders of interest, and in fact reports that the algorithmic approach produced test–retest coefficients superior to those obtained with more traditional measures such as the SCID and SADS (Nurnberger et al., 1994).

Assessment of Children and Adolescents

Family studies assessing psychopathology in children and adolescents have also used structured and semi-structured diagnostic instruments. These instruments have been designed for assessing children's and adolescents' presentation of psychopathological symptoms in a systematic fashion. Three instruments that may be put to such use in family studies are the Diagnostic Interview Schedule for Children (DISC-2.3; Schwab-Stone et al., 1996), the Child and Adolescent Psychiatric Assessment (CAPA: Angold et al., 1995), and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL; Kaufman et al., 1997). These instruments are of interest because they all have a standard set of questions as well as specific criteria for each question, include a wide range of syndromes and disorders, and include both child and parent versions. The CAPA and K-SADS-PL are

designed to be administered by clinicians, whereas the DISC was developed for use by lay interviewers. Hence, in choosing an interview for a family study involving children and adolescents, researchers must keep in mind the time demands of the various interviews available. Again, it is essential to note that there are no studies which compare the utility of different instruments in the assessment of children and adolescents in family studies.

Choice of Informants

One issue that arises when assessing children and adolescents is the choice of informants. To date, most family studies have collected diagnostic information on a child directly from the child and from at least one parent, given the considerable discrepancy found between parent and child reports (e.g., Andrews, Garrison, Jackson, Addy, & McKeown, 1993; Ivens & Rehm, 1988; Orvaschel, Puig-Antich, Chambers, Tabrizi, & Johnson, 1986; Weissman et al., 1987). Children have been found to be better informants about their own internal feelings, whereas parents underreport affective disorders in their children (Weissman et al., 1987). Parents are essential as informants, however, for very young children. Parental reports are necessary for externalizing disorders such as attention-deficit/hyperactivity disorder, and teacher reports are also useful in making diagnoses (Biederman, Faraone, Milberger, & Doyle, 1993). Hence a general principle is to acquire information from as many relevant sources as possible (e.g., Rutter, 1988). Various strategies for combining the information from different informants are available (e.g., Bird, Gould, & Staghezza, 1992).

Telephone Interviews

Another method that aids in the collection of direct interview data from relatives is to conduct interviews by telephone. Since family members often live at great distances from one another, it is not feasible to conduct in-person interviews with everyone. Even when probands are able and ready to be interviewed in person, their family members may be less invested in or less available for research. Telephone interviewing is a practical solution to these problems and may reduce the costs of a study, and information is becoming available on how information derived from telephone interviewing compares to that acquired through face-to-face interviews. One study compared the diagnostic results obtained from relatives of probands who were interviewed in a family genetics study either via telephone or face to face (Sobin et al., 1993). No significant differences in the rates of disorders or in the patterns of familial aggregation were found between the two interview methods, suggesting that telephone interviewing may represent a valid way of conducting direct interviews with relatives in family studies.

Brief Assessments

A direct and extensive interview with each relative is the ideal method for assessing lifetime psychiatric status in a family study. However, in large-scale investigations (such as epidemiological studies), the time constraints and costs of conducting direct interviews may prohibit the use of a family study component. Hence there is a need for instruments that can serve as screens for psychopathology in large studies. One such instrument that has potential is the Family History Screen for Epidemiologic Studies (FHE), which was developed as a brief, structured, computer-scorable instrument to screen for 15 DSM-III diagnoses. In one study, the FHE was administered to one informant in each of 77 families in which pedigrees had been collected by clinically trained interviewers, and in which 316 relatives had been interviewed with the SADS and diagnosed "blindly" and independently by doctoral-level clinicians (Lish, Weissman, Adams, Hoven, & Bird, 1995). For adults reporting on themselves, the FHE showed excellent specificity and fair to excellent sensitivity. Hence the FHE is a potentially useful method as a screen for psychiatric disorders in a subject's adult relatives. For studies of children and adolescents, it has potential utility for obtaining family psychiatric history of parents and/or relatives if each relative is directly screened.

Locating Relatives

A difficulty often encountered in using the family study method is locating family members, especially when populations with unstable living patterns are under investigation. There are now several strategies that may be used to help locate family members. A first strategy is to mail recruitment letters both to the subjects' last known addresses and to contacts identified in a thorough review of case records (if any such contacts are available). A powerful method is to gain low-cost access to electronic nationwide databases that provide address information on the basis of last known address, Social Security number, surname, and/or phone number. Such databases also provide the names of the current residents of a given address and neighbors in close proximity to an address. Other potential strategies include developing contacts with departments of motor vehicles, as well as state agencies such as departments of criminal justice and departments of income maintenance, all of which have guidelines concerning record searches for address information (Denny, n.d.).

Training Interviewers

Whichever instrument is used in a family study, certain standard procedures should be followed to ensure the integrity of the data collected. All interviewers should undergo a period of training sufficient for the instrument of

choice. Formal training manuals are available that explain methods for contacting subjects, scheduling appointments, conducting interviews, and checking errors; such manuals also provide instructions for completing diagnostic assessment, obtaining family history and pedigree, assessing social functioning, and writing narratives. Training can include lectures, small-group workshops, viewing of videotaped interviews, role-playing practice, assigned homework, and supervised interviews (see Weissman et al., 1993). Formal interrater reliability studies should also be conducted, as different interviewers will be assessing different families. Interviewers should also be monitored periodically for reliability (e.g., by having two interviewers assess the same individual) to avoid rater drift, which can skew the results of a family study.

FAMILY HISTORY METHOD

As discussed earlier, although the family study method is the preferred methodology for determining familial aggregation, pragmatic issues often require the use of the family history method. The basic procedures that have been used to date are described in Weissman et al. (1986) and are summarized here. The best-known procedure is the Family History Research Diagnostic Criteria (FH-RDC) method, in which structured family history interview methods are used systematically to obtain the data necessary to make RDC diagnoses in family members (Andreasen et al., 1977). The FH-RDC approach has been updated in a new format—the Family Informant Schedule and Criteria (FISC; Mannuzza, Fyer, Endicott, & Klein, 1985). The basic procedure is as follows. First, basic information on first- and second-degree relatives is listed on a pedigree collection form, as described previously. Second, the proband completes a direct diagnostic interview about himself/herself. Third, the proband then serves as an informant about his/her first-degree relatives (and possibly second-degree relatives as well, depending on the design of the study), as the interviewer asks the informant whether each relative (one by one and by name) has had any of the problems that were just mentioned in the interview about himself/herself. This approach ensures that the informant is well acquainted with the symptoms that he/she is asked to identify in his or her family members. When the informant indicates that a relative has had a problem, the interviewer is instructed to probe for the information necessary to generate diagnoses by using the diagnostic interview as a guide and by completing symptom checklists for relevant disorders. It should be noted that this overall procedure may also be carried out with relatives who have completed direct diagnostic interviews, so that multiple sources of information are collected about relatives unavailable for direct interview.

Studies have converged on the finding that the family history method leads to underestimation of the frequencies of disorders in both adult and

child relatives (Andreasen et al., 1977; Weissman et al., 1986). A few suggestions have been made for increasing the sensitivity of the family history method, such as using multiple informants, which increases the sensitivity of the method (Orvaschel, Thompson, Belanger, Prusoff, & Kidd, 1982). A new twist in this area, however, is the suggestion that the family history method may add unique information not discerned through personal interviews (Kendler & Roy, 1995). For example, these authors report that family history diagnoses of major depression, though agreeing poorly with personal interview diagnoses, nonetheless are predictive of risk for subsequent episodes of major depression (even after personal interview diagnoses are statistically controlled for). Hence Kendler and Roy (1995) suggest that a multimethod approach—one that incorporates both family history methods and direct interview—may yield a more accurate measure of psychopathology than either method used alone.

In some instances, the psychiatric history of relatives may be derived from case records when a family member has received psychiatric treatment. In such cases, the information available from case records should be combined with all other available data in constructing lifetime histories of psychiatric disorders that meet either DSM or ICD criteria or the RDC. However, in general this approach rarely provides sufficient information for making lifetime diagnoses in the absence of either direct or informant report.

Another issue that has received attention in the last decade is the impact of informants' psychiatric status on their reports of psychiatric disorders in family members. Kendler et al. (1991) examined this issue in a study of twin pairs discordant for psychiatric diagnoses, derived from an epidemiological sample of adult female twin pairs. In this study, the affected twin with a history of either major depression or generalized anxiety disorder was significantly more likely to endorse the same disorder in a parent than was the unaffected cotwin. These data, however, did not allow for an inference of which report was "correct," because direct interviews with parents were not possible. That is, it was not known whether the affected twins were more accurate informants because of their familiarity with the disorder from their own experience, or whether they were biased informants who distorted family history. Along these lines, Tarullo, Richardson, Radke-Yarrow, and Martinez (1995) report that both parental agreement and mother–child agreement on childhood disorders is greater in families with an affectively ill mother than in control families, and they argue that maternal psychopathology should not be assumed to be a distorting factor in the assessment of child psychopathology.

THE BEST-ESTIMATE PROCEDURE

Once all the diagnostic data on each family member are obtained, a standard procedure is to use the best-estimate procedure to integrate the infor-

mation collected on each individual (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982). This procedure is critical, since multiple sources of data may be used (e.g., different informants, records, direct interviews), and discrepancies that require resolution will inevitably occur. The procedure is based on all available information, and the estimate is made by at least one clinician who is unaware of the diagnostic status of the proband and who has not been involved in direct interviews of any of the probands or relatives. An independent assessment is frequently obtained from a second clinician. Substantial disagreements between the two diagnosticians may be reviewed on a case-by-case basis until agreement is reached, but "blindness" with regard to the clinical status of the proband should always be maintained.

The best-estimate procedure is especially relevant for semistructured instruments such as the SADS and K-SADS, which yield clinically relevant diagnoses from different individual respondents (e.g., parent and child reports on the child). It should be noted that other instruments that may be used in family studies may have explicit algorithms for combining information from different informants, and such algorithms should be used if these instruments are employed in future family studies.

OTHER ISSUES IN ASSESSMENT

Assortative Mating

"Assortative mating," which is nonrandom mating for the disorder under study or for related disorders, is an important topic in family studies that involve children and adolescents. Several studies have documented assortative mating based on psychopathology, in which individuals with psychiatric disorders are more likely than controls to have spouses with psychiatric disorders (e.g., Colombo, Cox, & Dunner, 1990; Merikangas, Weissman, Prusoff, & John, 1988; Parnas, 1988). Assortative mating may increase the risk for psychopathology in offspring via both genetic (i.e., higher genetic loading) and environmental (i.e., increased exposure to environmental risks associated with psychopathology) mechanisms. For example, parental concordance for psychiatric illness in general poses an increased risk for offspring at risk for depression (Merikangas et al., 1988).

Family studies involving children, especially high-risk and top-down studies, should thus attempt to assess lifetime psychiatric status of both biological parents, even though only one parent is typically identified as a proband in a study. In addition, rates of disorders in offspring should be examined as a function of assortative mating, in order to compare the risks involved in having two affected parents (as opposed to one).

Assessment of Non-Nuclear Family Structures

Family studies of psychopathology involving children have usually assumed, and assessed, a conventional nuclear family structure involving a stable two-parent unit biologically related to a child, as well as full biological siblings. In general, families that have not conformed to this structure have been considered outliers in a family study and have not been included in analyses. However, fewer than 40% of children born in the 1980s in the United States will spend their entire childhood with both biological parents (Hofferth, 1985; Kazdin, 1992; National Center for Children in Poverty, 1990). Because the nuclear family structure may no longer represent the prototypical living arrangement for children (e.g., Scott, 1993), the assumptions underlying future family studies involving children and adolescents may need to be recast.

The preponderance of non-nuclear family structures presents two methodological goals for family studies of psychopathology involving children. A first goal is to develop methods for assessing such family structures in ongoing studies involving children that can be incorporated into the typical procedures used to identify pedigrees reviewed earlier in this chapter. We have developed a Rearing Parent Form (Rende, Sobin, & Weissman, 1993) to collect systematic information necessary for creating a family structure typology for each child within a family (see Haurin, 1992; Hunter & Ensminger, 1992)—namely, the child's biological parents; any adult who has lived with the child over the past 3 years and his/her precise relationship to the child (e.g., first-degree relative, spouse or partner of biological parent); and the various types of siblings (full, half-, or unrelated siblings). Preliminary data from an ongoing study of the offspring of opiate addicts revealed that only about a third of the offspring assessed had lived in a conventional nuclear family over the past 3 years, and that over a third of the siblings were half-siblings (Rende et al., 1993). Although such data need to be collected from family study designs for other forms of psychopathology, such a finding is consistent with the estimations of population trends cited earlier.

A second goal is to determine whether there are adults other than the biological parents who play a significant role in a child's life. One consideration is whether there are other adults who should be assessed when potential environmental influences on the child are being documented. Exposure to psychopathology in nonrelatives who are functioning as parents can clearly have an effect on children; therefore, in family studies such "rearing parents" should be assessed in the same manner as biological parents. In our preliminary study, we have found that over 90% of the rearing parents of offspring of opiate addicts suffer from at least one psychiatric disorder, with a majority of these individuals meeting criteria for alcohol and/or other substance abuse. The assessment of rearing parents may thus, as in this example, identify potentially salient social influences on offspring in family studies, especially in samples at high risk (Rende et al., 1998).

A related consideration involves determining who is the best informant (or source of information) about a child. Although it is common in family studies to collect information on children by interviewing one of the biological parents, the existence of non-nuclear family structures implies that the best informant on a child may not necessarily be a biological parent. This topic should receive more attention in future studies.

Proximal versus Distal Risk Factors

Research on risk and protective factors in the development of psychopathology has led to a distinction between "distal" and "proximal" risk factors, which carries implications for family studies. "Distal" factors are variables that are labeled or grouped to subsume specific environmental influences; a notable example is socioeconomic status, which is a labeled environmental factor that may reflect many specific environmental influences (Wachs & Gruen, 1982). "Proximal" factors are the actual environmental experiences nested within distal factors. With respect to psychopathology, family history of psychopathology has been classified as a distal variable, in that it is not what is experienced by individuals at risk (Baldwin, Baldwin, & Cole, 1990; Richters & Weintraub, 1990; Luthar, 1993). It has been suggested that the risk posed by such distal variables is mediated by proximal variables, such as ineffective parenting or family discord (Luthar, 1993; Richters & Weintraub, 1990).

Future studies should directly assess potential environmental risk factors and take them into account in analyses. For example, numerous studies have documented that children of depressed parents are exposed to many proximal risk factors, such as hostile, negative patterns of interactions with parents and family discord (e.g., Rutter, 1990). An explicit focus on environmental risk factors in family studies is necessary in order to reveal the specific processes by which parental psychopathology leads to negative outcomes in offspring (e.g., Rende & Plomin, 1993; Richters & Weintraub, 1990).

Phenotypic and Biological Markers

In family studies involving children and adolescents, it has been typical to assess such social and psychological traits as temperament and self-esteem in addition to psychopathology, in order to provide a more complete picture on developmental course and outcome. However, a primary advantage of assessing children at high risk for disorders is that both early manifestations of a disorder ("phenotypic markers") and biological indices of risk for a disorder ("biological markers") may be examined (Weissman et al., 1986). Hence a crucial topic for family studies involving children and adolescents is to identify such markers. They may help isolate the earliest signs of a disorder, and

they may permit investigations into how these predispositions may lead, in conjunction with other risk factors, to the development of disorders.

There are a few examples of how the search for phenotypic and/or biological markers may provide some insight into the etiology of disorders in childhood. One example comes from the New York High-Risk Project, a longitudinal study of children at risk for schizophrenia or mood disorders and low-risk controls (e.g., Erlenmeyer-Kimling et al., 1993). Findings from this study indicate that childhood attentional dysfunction may be a salient index of risk for schizophrenia. Identification of phenotypic markers such as attentional dysfunction may help map out the developmental course of schizophrenia from risk in childhood to expression of symptoms in adulthood; it may also help focus the search for genetic factors involved in schizophrenia, by defining specific markers that may represent the heritable predisposition to the disorder (e.g., Gottesman, 1991).

A second example involves research on behavioral inhibition to the unfamiliar, which is a temperamental construct characterized by shy and fearful behavior. Recent studies have indicated that this temperamental construct may be an early risk factor for the development of anxiety disorders. For example, children of parents who have panic disorder with agoraphobia are at increased risk for behavioral inhibition, and children with behavioral inhibition have high rates of anxiety disorders with onsets in childhood (see Rosenbaum et al., 1993). Such work suggests that behavioral inhibition is an identifiable predictor of anxiety disorders—a predictor that may be observed in early childhood and perhaps infancy. Hence, this work demonstrates the potential of identifying specific phenotypic profiles (in the form of temperamental constructs) that may have strong associations with the development of specific forms of psychopathology.

The studies on attentional dysfunction and schizophrenia, and on behavioral inhibition and anxiety disorders, illustrate the potential utility of defining early-emerging phenotypic markers of risk for psychopathology that have a familial basis. More work of this nature may help tremendously in defining more precisely phenotypic characteristics that reflect genetic predispositions to psychopathology, and such work would undoubtedly inform research on the genetic contributions to psychiatric disorders (e.g., Rende & Plomin, 1994).

ISSUES OF DATA ANALYSIS

Issues of data analysis are crucial in the assessment of psychopathology in family studies. Several methodological concerns make the analysis of family data a complicated proposition, and proper attention to these issues is essential in drawing appropriate conclusions from family studies. In this section, analytic issues that are especially relevant to the study of childhood and adolescent psychopathology are reviewed.

Confounding Factors

Ideally, family studies match affected and control probands on potential confounding factors such as age and gender. However, such confounding factors may vary across relatives of affected and control probands (e.g., by chance, there may be more females among the relatives of affected probands than among relatives of control probands). For this reason, these potential confounding factors must be controlled for statistically while the effect of proband status on rates of disorder in relatives is estimated. A standard method is to use multivariate-regression models for survival data, such as Cox's (1972) proportional-hazards model, with the potential confounding factors included as independent variables.

Lack of Independence in Family Data

Statistical methods used to assess familial aggregation of psychiatric disorders generally make comparisons across aggregate rates of disorders based on proband status (i.e., affected vs. control). Such methods carry the assumption that the observations are independent of one another. However, this assumption is usually violated in family studies, as more than one observation per family is often made (i.e., numerous members of a given family are assessed). In general, violations of this assumption produce biased results, in that dependent data may inflate patterns of association. Although the adverse consequences of the violation of the independence assumption in family studies have not been examined empirically, this issue deserves attention because of the potential for results from family studies to be misleading. For example, one potential problem is that a small number of "highly loaded" families could suggest significant familial association in a family study, when in fact the pattern of aggregation for the remaining families in the sample may not suggest familiarity. This point is especially important because family studies often assess variable numbers of family members, thus creating the potential for methodological problems of this nature.

To date, there are no completely satisfactory methods for controlling for the dependence inherent in family data. Attempts have been made to control for such dependence by using correlated binary regression with covariates specific to each binary observation (Liang & Zeger, 1986). Another method is to include family size as a potential confounding factor in regression models such as the proportional-hazards model mentioned above; if there are highly loaded families skewing the results, then family size may make a significant contribution in the model. Similarly, an examination of the data by family may indicate whether there are a few atypical families that severely affect the pattern of familial aggregation; another approach is to calculate the number of families in which at least one relative is affected (Biederman et al., 1992).

However, these methods do not entirely handle the more general problem of dependence.

Although the dependence of family data is a fundamental problem in the calculation of familial aggregation, statistical methods geared toward the assessment of dependent data may provide clues to etiology. For example, although family studies have suggested that most psychiatric disorders in childhood and adolescence have in part a familial basis, the extent to which children within a high-risk family have similar outcomes has not been examined (Rutter et al., 1990). Although it might be thought that familial risk factors would be shared equally by all children in a family, there is much evidence documenting the extent to which siblings have very different outcomes in development (Hetherington, Reiss, & Plomin, 1994). Hence there is much interest in capitalizing on the dependence of sibling data to document the extent to which siblings with a specific risk factor in common (e.g., a depressed parent) have similar outcomes (e.g., a history of major depression), and also to attempt to identify salient environmental factors that result in similarity between siblings (shared environmental influences) as well as those that lead to differences between siblings (nonshared environmental influences).

Analytic tools to address such questions are currently available (e.g., Hetherington et al., 1994). One new approach is to capitalize on the dependence of observations in high-risk studies to model statistically the degree to which siblings at risk have similar outcomes of interest (Rende, Wickramaratne, Warner, & Weissman, 1995). In this approach, sibling resemblance is estimated via the pairwise odds ratio, which explicitly quantifies the degree of statistical resemblance between dependent observations. Using this approach in a study of offspring at high and low risk for depression, we (Rende et al., 1995) found that sibling aggregation in the high-risk cohort was more notable for anxiety than for depression, suggesting that the familial influences common to siblings at risk for depression may operate more strongly in producing anxiety.

Cohort Effects

There is increasing evidence that "cohort effects" (i.e., differences across generations) are observed for some psychiatric disorders, in that younger cohorts have higher lifetime rates of disorders than older cohorts. For example, the lifetime risk of having a major depressive disorder has increased dramatically, and the average age of onset has decreased (Weissman et al., 1993); another study, using a sibling design, documented a secular increase in childhood mood disorders (Ryan et al., 1992). Hence family studies that combine information from multiple cohorts must control for potential cohort effects by including year of birth as an independent variable in multiple-regression models (Weissman et al., 1986).

Another strategy is to focus on specific cohorts, such as same-age siblings and cousins, which are by definition subject to the same cohort or period effects (Todd et al., 1993). An example of this approach is a family study of substance misuse that found considerably higher rates of drug misuse in the siblings than in the parents of misusers (Luthar, Anton, Merikangas, & Rounsaville, 1992). Hence it has been suggested that siblings or children of addicts may constitute far more suitable groups for studying familial aggregation of drug misuse than parents may (Luthar & Rounsaville, 1993).

Age of Onset

The major outcome in a family study is usually the rate of a disorder in relatives over their lifetimes, termed "morbid risk" or "lifetime prevalence." In this sense, "lifetime risk" refers to the risk of onset of a particular disorder between birth and a particular age, such as the age of the individual when an interview is conducted. However, because age of onset varies for a given disorder and usually encompasses a rather wide range, studies must account for the fact that some individuals in a study may not yet have a disorder because they have not passed through the typical period in which first onset is usually noted. In addition, the rates of disorders in relatives must be interpreted according to the age range of the cohort under study, and not simply assessed in raw terms.

Several statistical methods have been developed to adjust for variable age of onset in relatives (see Weissman et al., 1986). One approach utilizes the general strategy of survival analysis. Survival-analytic techniques treat age of onset of disorder as a survival time, and a survival function—or lifetime risk at a given time—may be estimated by different methods (Cutler & Ederer, 1958; Kaplan & Meier, 1958). These approaches should be considered in family designs specifically focused on children and adolescents. For example, in a bottom-up study, the age range of parents may be quite wide, and hence adjustments based on age of onset should be made before determining lifetime rates of disorders in parents. In a high-risk study, if the ages of children at risk vary, adjustments may be necessary because different subjects will pass through the typical age-of-onset period at different time points in the study.

Another consideration concerning age of onset is that, in general, early-onset forms of disorders tend to be more familial than late-onset forms of disorders. As such, it is useful to consider age of onset in both probands and relatives as a factor when one is analyzing family data. One example of this approach is the demonstration that early-onset major depression is more familial than late-onset depression (Weissman et al., 1984). Considering age of onset may lead to crucial distinctions between familial and nonfamilial forms of disorders, as has been proposed, for example, by Todd et al. (1993).

NATURE, NURTURE, AND PSYCHOPATHOLOGY

Traditionally, psychiatric genetic research has followed a hierarchy in searching for genetic influences on psychiatric disorders. A first step is to conduct family studies to establish the familial nature of a disorder; a second step is to conduct behavioral genetic studies to demonstrate significant genetic influence on a disorder; and a third step is to conduct molecular genetic studies to pinpoint specific regions on the chromosome that are linked to the disorder.

Within this hierarchy, family studies represent a limited approach because they cannot disentangle genetic and environmental influences. However, as a concluding theme to this chapter, we wish to emphasize the continuing importance of family designs in the search for genetic influences on the development of psychopathology. Perhaps the most salient point to consider at this time is that molecular genetic approaches to childhood and adult psychopathology will proceed more slowly than may have been thought even a few years ago. The major obstacle is that although there are powerful methods for detecting single genes, which are necessary and sufficient causes of some disorders, most psychiatric disorders do not appear to follow simple patterns of inheritance; instead, that multiple genetic loci and environmental influences appear to contribute to phenotypic expression in a probabilistic manner. Hence, given the complex nature of psychopathology, family studies may contribute much useful information to the search for genetic underpinnings of disorders.

Three points are especially important to consider. A first point is that a given disorder may be due to various etiological influences that result in a similar phenotype. When genetic influences are considered, this situation is referred to as "genetic heterogeneity," in which specific genes may be involved in the expression of only some types of a disorder (e.g., Plomin & Rende, 1991). If genetic heterogeneity is important for a disorder, then family studies can be instrumental in identifying highly familial subtypes of the disorder that may be due to genetic influence. There is hope that such a strategy may be successful in research on disorders in childhood and adolescence, such as early-onset mood disorders (Todd et al., 1993).

A second point is that different disorders may in fact reflect common genetic etiologies. The preponderance of comorbidity in childhood and adolescent disorders (e.g., Caron & Rutter, 1991) suggests that family studies may be especially important in determining whether comorbid conditions reflect common familial influences. For example, recent studies have suggested that attention-deficit/hyperactivity disorder and mood disorders may share a common familial influence (Biederman et al., 1992), whereas panic disorder and major depression do not (Weissman et al., 1993). Such studies may be especially useful in identifying clusters of symptoms that may be due to common genetic etiologies, and others that are etiologically distinct (Wickramaratne & Weissman, 1993).

A third point is that strategies used for conducting family studies may yield some clues on the potential genetic etiology of disorders. Two approaches mentioned earlier in this chapter are relevant. One approach is to examine second- and third-degree relatives in addition to first-degree relatives in family studies; because a range of genetic relatedness is available, testing of hypotheses of genetic influence is possible (e.g., Todd et al., 1993). Another approach is to capitalize on the preponderance of non-nuclear family structures to develop behavioral genetic designs, which may sort out the effects of genes and environment on psychopathology. For example, two potential designs include quasi-adoption strategies, in which children with a history of psychopathology in biological relatives are reared by unaffected nonrelatives, and designs that compare the similarity of full siblings and half-siblings (Rende et al., 1993). All of these strategies represent ways in which prototypical family designs may help to sort out the effects of nature and nurture on psychopathology.

As a concluding comment, we wish to emphasize the importance of environment in the development of psychopathology. Because most psychiatric disorders will have complex etiologies involving both genetic and environmental sources of influence, family studies will continue to yield data on the role of environmental risk factors, as exemplified by the research on proximal risk factors for psychopathology in childhood and adolescence discussed earlier (e.g., Richters & Weintraub, 1990). The importance of these research strategies should not be minimized, given the current interest in the genetics of childhood and adolescent disorders, because it is becoming increasingly clear that both nature and nurture plays a significant role for most forms of psychopathology. In this sense, methodologies used in family studies will continue to play an essential part in the search for etiological factors involved in the expression of psychopathology in childhood and adolescence.

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