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Research Strategies for Studying Psychopathology

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Few things in life are more frightening, puzzling, or intriguing than psychopathology. The human body and mind are phenomenal evolutionary achievements, but their proper functioning represents a delicate balance. When that balance is upset—whether by external stressors that push the organism beyond its limits, biological aberrations that predispose the organism to respond inappropriately, or cognitive styles that distort everyday experiences—psychopathology may result. In this chapter, we will examine how psychopathology researchers study the causal factors relevant to mental disorders. Each research method has its own strengths and weaknesses. In conjunction, however, these methods have permitted researchers to make substantial progress toward identifying the causes of many mental disorders.

Asking Questions About Psychopathology

One question often asked by new graduate students in clinical psychology is "Why are research designs necessary in psychopathology?" Beginning students often assume that the causes of psychopathological conditions can be identified solely by examining individual patients. So we open this chapter with these two deceptively complex questions: (1) Why can't years of clinical experience provide adequate answers to questions concerning the causes of psychopathology? and (2) Do we really need research designs to obtain these answers?

Why Research Designs Are Necessary in Psychopathology Research

Research designs are necessary largely because the human brain, although remarkably sophisticated, is nonetheless a highly fallible information processor. The same cognitive strategies that are adaptive in everyday life can sometimes lead us astray in our thinking about research problems. Some social cognition theorists (e.g., Gilovich, 1991) have argued that the human brain was "designed" by natural selection to extract meaning and order from its environment. Such a propensity makes good evolutionary sense given that our external surroundings are often complicated and chaotic. Without an innate tendency to organize the world into meaningful groupings—to make "sense out of nonsense"—we would probably be incapable of functioning adequately in the natural environment. Nevertheless, this generally adaptive tendency sometimes results in *cognitive illusions*—errors in thinking that are subjectively compelling (Nisbett & Ross, 1980). We tend to perceive relationships among variables even when such relationships are objectively absent. Like visual illusions, cognitive illusions often appear "real" even after we are told that they are imaginary by-products of our cognitive apparatus. As researchers we must

recognize our propensities toward cognitive illusions and learn to compensate for them. Research designs assist researchers with precisely this corrective function. Indeed, the failure to use appropriate research designs has often led psychologists to draw faulty inferences concerning the correlates and causes of psychopathology. Two examples will suffice to make this point.

1. Several authors have argued that patients with schizophrenia tend to come from markedly dysfunctional home backgrounds and that such backgrounds may play an important role in the etiology of schizophrenia. Yet when Schofield and Balian (1959) compared patients with schizophrenia to nonpatient comparison subjects, there were few differences between the samples on such life-history variables as quality of maternal, paternal, or sibling relationships, poverty in the home, and parental discord. Indeed, in several cases comparison subjects exhibited higher levels of adverse environmental variables than the patients!

One factor that may account for many clinicians' and researchers' perceptions of a strong association between schizophrenia and negative life experiences is the *fallacy of positive instances*. This fallacy, which affects all of us, is the error of attending only to data that confirm our hypotheses (see Gilovich, 1991). Thus, individuals who expect to observe a relationship between schizophrenia and negative life experiences may pay attention to confirming evidence while ignoring or downplaying disconfirming evidence. The fallacy of positive instances can be overcome only by using research designs that force us to attend to all relevant evidence.

2. Many clinicians are convinced of the validity of projective tests such as the Draw-A-Person (DAP) test. Yet research on the DAP consistently shows that the signs posited by many clinicians to be diagnostic of specific psychopathological characteristics possess little or no validity. How can we account for this stunning discrepancy? Chapman and Chapman (1967, 1969) hypothesized that individuals are prone to *illusory correlations*—perceived relationships between variables that are, in fact, largely or entirely unrelated—and that this tendency is especially strong when the variables intuitively "seem" to be associated with one another. Chapman and Chapman (1967) tested this hypothesis by showing undergraduates a series of fabricated DAP protocols containing certain features (e.g., large eyes, big head), along with a description of the personality characteristics (e.g., suspicious, concerned about intelligence) of the patient who supposedly produced each drawing. Subjects were then asked to estimate the extent to which these DAP features co-occurred with certain personality characteristics. Unbeknownst to the subjects, there was *no correlation* between the DAP features and personality characteristics in this data set. Yet the subjects consistently perceived certain DAP features to be strongly correlated with certain personality features. Moreover, their errors corresponded to their implicit "theories" concerning which variables go together. For example, subjects reported that patients who produced DAP protocols with large eyes tended to be suspicious and that patients who produced DAP protocols with large genitals tended to concerned about their sexuality. Moreover, Chapman and Chapman found that illusory correlations persisted even when the DAP features and personality characteristics were *negatively* correlated in their data. Chapman and Chapman (1969) replicated these findings with another commonly used projective measure—the Rorschach. Thus, many clinicians' convictions regarding the validity of certain projective tests may stem from cognitive propensities to perceive relationships where none exist and from their inattentiveness to disconfirming evidence.

In summary, one major reason why psychopathologists use research designs is *to prevent themselves from being fooled*. Sophisticated psychopathology researchers are aware of their propensities toward cognitive illusions, and take pains to ensure that such ubiquitous errors in thinking do not influence their results. The research methods discussed in this chapter are designed largely to protect investigators from their own perceptual and inferential biases.

Case Study Methodology

Case studies—the detailed examination of single individuals—do play an important role in psychopathology research. In contrast to the *nomothetic* research designs emphasized in this chapter, which involve the derivation of general laws that apply to large groups of individuals, case studies are *idiographic* in nature. That is, they involve an examination of how the unique patterning of life experiences and personality features within each

individual gives rise to that individual's characteristic pattern of thoughts, feelings, and behaviors. Although idiographic approaches can be useful for reconstructing and understanding a given person's life history, they do not provide stringent tests of hypotheses. The distinction between nomothetic and idiographic approaches provides a partial answer to our earlier question of why years of clinical experience cannot provide conclusive answers to questions concerning the etiology of psychological disorders. In general, the case history method lends itself well to a detailed understanding of a given individual's life history, but not to the derivation of general psychological principles.

Case studies are better suited to what philosophers of science call the *context of discovery* than to the *context of justification* (Reichenbach, 1938). Whereas the context of discovery involves hypothesis generation, the context of justification involves hypothesis testing. Thus, although case studies provide a fertile ground for developing interesting hypotheses, they are woefully ill-suited for testing them. Because case studies typically lack the controls found in systematic research, they often result in misleading conclusions. For example, imagine that an individual with bipolar disorder reports that both of her parents were extremely critical of her in childhood. Can we conclude that bipolar disorder is associated with parental criticality? No. Perhaps the parental criticality is specific to this individual. Perhaps most individuals, not just those with bipolar disorder, report that their parents were critical of them in childhood, or perhaps there is something about our interviewing method that tends to elicit reports of parental criticality. No examination of case studies, no matter how meticulous, will permit us to exclude these and other alternative hypotheses. Moreover, because case studies are limited to small numbers of individuals, their generalizability to the broader population is often questionable.

Cause and Effect in Psychopathology Research

The ultimate goal of the psychopathology researcher is to uncover the causes of a disorder. We use the plural (causes) because psychological disorders are probably multiply determined. But what do we mean by cause? Meehl (1977) delineated a number of meanings of causation in the domain of psychopathology, four of which are especially relevant to our discussion. The strongest meaning of the word *cause*—which Meehl calls *specific etiology*—refers to a categorical (all-or-none) variable that is *both necessary and sufficient* for a disorder to emerge. Such cases are probably rare in psychopathology, although they are occasionally found in traditional medicine. For example, a single dominant gene is both necessary and sufficient to produce Huntington's chorea.

A second and weaker form of causation involves a dimensional variable that exerts a *threshold effect*. In other words, only when a critical level of a variable (e.g., a propensity toward anxiety) is exceeded does an individual experience risk for the disorder. Below this threshold, the individual's risk for the disorder is nonexistent. A variant of this second form of causation involves a *step-function*, in which the individual's risk for the disorder increases sharply when a critical level of a variable is exceeded. In a step-function model, unlike a threshold model, the individual's risk for the disorder is low, but not nonexistent, below this critical level.

A third and still weaker form of causation involves a variable that is *necessary but not sufficient* for a disorder to arise. The most common variant of this form of causation is referred to as a *diathesis-stress model*. In a diathesis-stress model, elevated levels of certain variables create a *diathesis*, or vulnerability, to a disorder. This vulnerability, which is often genetically influenced, is actualized only when the individual encounters a psychological or biological stressor. Note that according to a diathesis-stress model, both vulnerability factors and stressors are necessary for a disorder to emerge; neither variable alone can do the trick. Gottesman (1991), for example, argued that the etiology of schizophrenia can best be accommodated within a diathesis-stress model in which a genetic liability to schizophrenia interacts with environmental (e.g., anxiety-provoking life events) and/or biological (e.g., early viral exposure) stressors to produce the disorder.

Finally, a causal factor can be *neither necessary nor sufficient* for psychopathology. Many general risk factors for psychopathology (e.g., excessive reactivity) are probably of this type.

Thus, there are several ways to conceptualize the cause(s) of psychopathology. But what research methods are best suited for inferring these causes?

Experimental vs. Quasi-Experimental Designs

In most research in psychopathology, investigators are placed in a quandary. They want to determine whether one or more factors (e.g., psychosocial stress, early brain trauma) are causes of the psychopathological condition. The design best suited for determining causation is an ***experimental design***, in which subjects are randomly assigned to two different conditions, one of which receives the experimental manipulation (the experimental group), whereas the other does not (the control group). In such a design, the experimenter manipulates the independent variable to ascertain its effect on the dependent variable(s) of interest.

But in most research in psychopathology, it is impossible to randomly assign subjects to conditions, and it would be unethical if it were possible. For example, if one wishes to study the personality characteristics of individuals with schizophrenia, one cannot, for obvious practical and ethical reasons, randomly assign individuals to either a schizophrenic experimental group or nonschizophrenic control group. Consequently, most research designs in psychopathology are ***quasi-experimental.*** In a quasi-experimental design, we compare two or more groups (e.g., depressed vs. nondepressed subjects) that come into our study with certain preexisting characteristics. Because our subjects have not been randomly assigned to conditions, quasi-experimental studies, unlike experimental studies, cannot be used to draw causal inferences. A moment's reflection reveals the reason for this limitation. Because subjects in quasi-experimental designs have not been randomly assigned to groups, the groups often differ on numerous ***extraneous,*** or ***nuisance, variables.*** For example, if we evaluate the personality characteristics of patients with schizophrenia and comparison subjects, it is virtually inevitable that these two groups will differ on variables other than schizophrenia per se. For example, the patient group may be lower than the comparison group in socioeconomic status (SES), IQ, hygiene, quality of diet, and a host of other variables, many of which could affect scores on dependent variables.

To address this problem, researchers who utilize quasi-experimental designs frequently implement a technique known as ***matching,*** in which the groups in a quasi-experimental design are equated on potentially relevant variables. By "potentially relevant" we mean variables that could affect the dependent variable. So, in the example above, the investigator could match schizophrenic and nonschizophrenic groups on variables that might influence scores on personality measures, such as SES, IQ, and gender. Some investigators have tried to *statistically control* for these potentially relevant variables by using techniques such as analysis of covariance, but this technique is problematic statistically when used in this manner and is generally not recommended (Chapman & Chapman, 1973; Lord, 1967).

Although matching is a useful strategy in quasi-experimental designs, it has limitations. First, even if the investigator has equated the groups on 100 potentially relevant variables, it is always possible that the groups differ on a 101st variable—a variable that the investigator had not considered. This unpleasant fact explains why quasi-experimental designs cannot be used to draw definitive causal inferences: It is not possible for the investigator to rule out every conceivable nuisance variable.

Second, matching rests on causal assumptions that may be incorrect. Investigators match on variables implicitly assumed to be nuisance variables. But as Meehl (1971) illustrated, variables traditionally considered nuisance variables, such as social class, could easily be a critical element in a complex causal chain. If the variable on which we match is actually a part of the causal chain, matching will distort the picture and bias our interpretations. Although matching is a valuable control for nuisance variables, it should never be applied in a cookbook fashion without considering the potential causal theories for a disorder.

Third, matching on one variable often results in systematic differences between our sample and the general population (Chapman & Chapman, 1973). For example, if we want to match schizophrenic and comparison groups on IQ, we would have to select high-scoring patients to match low-scoring comparison subjects because patients with schizophrenia tend to score lower on almost every task. The resultant patient group will overrepresent paranoid patients because patients with paranoid schizophrenia tend to be brighter and to show less of the thought disorder that would hinder performance on an IQ test. Similarly, selecting the low-scoring comparison subjects would produce a sample of subjects with lower SES, less education, and a different upbringing because all of these variables are correlated with IQ. So in this case, our

matching strategy leaves us with unrepresentative patient and/or comparison samples.

Because psychopathology researchers typically must rely on quasi-experimental designs, they are limited in their ability to infer cause-and-effect relations. Researchers who use quasi-experimental designs must instead gradually piece together causal inferences from a variety of forms of circumstantial evidence. Such inferences are necessarily tentative and uncertain.

To a limited extent, the problem of causal inferences can be overcome by examining what are sometimes loosely referred to as experiments of nature, which are sudden and typically unexpected events (e.g., natural disasters) that intrude upon individuals in a more or less random fashion. We say "loosely referred to" because such studies should be technically viewed as quasi-experiments rather than true experiments. This is because subjects cannot be randomly assigned to either experience or not experience these life events. As a consequence, even these studies do not permit definitive cause-and-effect inferences. Nevertheless, psychopathology researchers can sometimes capitalize on the opportunities offered by experiments of nature by comparing the psychology symptoms of individuals who have been exposed to a major stressor with those of individuals who were not exposed to this stressor. In an ideal world, the researcher would also have access to data on the psychological status of both groups of individuals prior to the stressor. But because experiments of nature are almost by definition unpredictable, these data are rarely available.

A good example of such a study was conducted by Wood, Bootzin, Rosenhan, Nolan-Hoeksema, & Jourden (1992), who examined the prevalence and content of nightmares following the 1989 Loma Prieta earthquake among college students in the San Francisco area (who experienced the earthquake) and among a comparison sample of college students from Arizona (who did not experience the earthquake). They found that during the three weeks following the earthquake, approximately 40% of the San Francisco area students reported earthquake-related nightmares, compared to 5% of Arizona students. Wood et al. were not able, of course, to randomly assign subjects to earthquake and nonearthquake conditions. Consequently, we cannot conclusively rule out the possibility that San Francisco area students were more prone to earthquake-related nightmares than Arizona students, and that their higher rates of such nightmares were therefore a consequence of preexisting differences rather than the earthquake itself. Nevertheless, the dramatic difference in the prevalence of these nightmares between groups appears to render this explanation unlikely.

Psychopathology researchers often must reconcile themselves to quasi-experimental designs because they cannot expose subjects randomly to stressful life events. Nevertheless, three major research paradigms in psychopathology are experimental in nature and thus allow relatively unambiguous causal conclusions. First, researchers may utilize *analogue experiments*, which involve attempts to produce variants of psychopathology in either human or animal subjects. Imagine, for example, that an investigator is interested in the hypothesis that depression is characterized by underactivation of the left hemisphere. Rather than obtain a large sample of clinically depressed individuals, the investigator might instead use mood-induction procedures to produce mild analogues of depression, such as having subjects read Velten cards (Velten, 1968), which consist of statements that tend to induce sadness in normal individuals. Alternatively, the investigator might induce *learned helplessness* in subjects by presenting them with insoluble puzzles. In both cases, the investigator would then examine subjects' brain wave activity to test the hypothesis of left hemisphere underactivation. Although analogue experiments can be useful, they do have potential pitfalls. In particular, the investigator who conducts such experiments must assume that the analogue provides an adequate model of the psychopathological condition of interest. If, for example, the mild and transient dysphoria that follows a mood induction procedure differs qualitatively from clinical depression, then generalizing from the former to the latter will be misleading (Coyne, 1994).

One variation of the analogue approach uses *animal models* of psychopathology, which involve attempts to produce a simulated form of a mental disorder in nonhumans. For example, some researchers (e.g., Seligman, 1975) have hypothesized that exposing animals to uncontrollable aversive stimuli produces a state of learned helplessness characterized by apathy, passivity, and loss of appetite—a response that is similar to at least some forms of human depression. Nevertheless, because humans may be different from other animals on variables potentially relevant to psychopathology

(e.g., moral development, abstract thinking, language), researchers who use animal models of psychopathology must be cautious in extrapolating their findings to humans. In addition, research using animal models often involves complex ethical considerations (Ulrich, 1991).

Challenge paradigms represent another experimental approach. In the *challenge paradigm*, subjects are randomly presented with stimuli that are thought to trigger a pathological response. Biological challenges, such as CO_2 inhalation, have been used with panic patients to see how reliably and under what circumstances they trigger a panic attack (Barlow, 1988). Of course, challenge paradigms raise ethical issues. They can be used only when the impact on subjects is transitory. Nevertheless, patients will often cooperate with such studies because they want to help advance research that might uncover the mechanisms behind a disorder. In the case of panic, challenge paradigms have given us considerable insight into both the biological and psychological mechanisms behind this disorder (e.g., Gorman, Liebowitz, Fyer, & Stein, 1989).

Finally, researchers interested in the effects of an intervention on a given individual may use *single-subject experimental designs*, in which each subject serves as his or her own control. For example, in an *A-B-A-B*, or *reversal*, design, the investigator measures a relevant aspect of the subject's behavior (e.g., nail biting) at baseline (A) and then again after an intervention (e.g., relaxation training) is introduced (B). To ensure that any change in the subject's behavior at B was not due to factors other than the intervention (e.g., passage of time), the intervention is withdrawn (reversed) in the second A phase and then introduced again in the second B phase. If the subject's behavior improves only after the treatment is presented (i.e., after both B phases), then one can safely conclude that the treatment is effective. This conclusion rests upon several assumptions, however. For example, if the treatment has lasting effects, then one would not expect a return of the subject's behavior to baseline in the reversal phase. Unlike case studies, single-subject designs often permit cause-and-effect inferences because they involve the systematic manipulation of independent variables within a subject. Like case studies, however, these designs are idiographic and are thus often limited in their generalizability.

Most research designs described in this chapter are nonexperimental or quasi-experimental.

Psychometric Issues

The study of any psychological phenomenon, including psychopathology, involves the measurement and interpretation of relevant variables. If we could measure those variables directly and flawlessly, we could proceed immediately to the interpretation stage. But we almost never have that luxury. Therefore, we virtually always need to consider the potential problems introduced by less than perfect measurement.

Reliability

The term *reliability* refers to the consistency of a measure. There are three major types of reliability: *test-retest reliability* (consistency over time), *interrater reliability* (consistency among raters), and *internal consistency reliability* (consistency among the items in the measure). Traditionally, a correlation coefficient is the index of reliability, with +1.00 indicating perfect reliability and 0.00 indicating no reliability. Reliability is the critical first element in evaluating a measure, but as we will see shortly, it does not tell the entire story.

Several types of reliability are relevant in the field of psychopathology. The ability of multiple observers to agree on a diagnosis (assessed by interrater reliability) is critical. This agreement can be indexed with either the traditional correlation or intraclass correlation coefficient (for a continuous variable) or a simple percent agreement index (for a discrete variable). The *Kappa coefficient* (Cohen, 1960) is preferred over a percent agreement index because Kappa takes into account the base rate of the diagnosis. The lower the base rate for a diagnosis, the easier it is for two raters to agree by chance alone. The applicability of test-retest and internal consistency reliability depends on the nature of the variable being measured. For example, some variables are relatively stable over time (e.g., IQ), whereas others are not (e.g., mood). We should expect high test-retest reliability only for stable variables.

The *structured diagnostic interview* represents a critical advance in the reliability of psychiatric diagnoses. Spitzer, Endicott, and Robins (1975) spurred the development of structured interviews, as well as the more detailed and descriptive diagnostic criteria first introduced in *DSM-III*, with their analysis of the sources of diagnostic unreliability. Structured interviews reduce a major con-

tributor to diagnostic unreliability: differences in the information and observations available to different diagnosticians. The combination of structured interviews and more explicit diagnostic criteria improved diagnostic reliability dramatically (Spitzer et al., 1975) and has probably contributed to many of the significant research achievements of the past 20 years. Today, structured diagnostic interviews are the norm in research and increasingly the norm in specialty clinics (Weins, 1990). One commonly used structured interview is the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995), which assesses most of the major mental disorders in DSM-IV.

Validity

Validity refers to the extent to which our measure assesses what it purports to measure. Note that although reliability is necessary for validity, it does not guarantee it. Imagine that a researcher claims that the length of a person's neck is a measure of her "intelligence." Such a measure would be reliable (i.e., repeatable over occasions), but it would (we hope!) have no validity as a measure of intelligence. In psychopathology, we rarely have the luxury of a perfect criterion to judge the validity of our measures. As a consequence, our indices of validity often are intertwined with our theories concerning what we are measuring. We judge the validity of IQ tests, for example, by observing how well they predict criteria that are theoretically related to intelligence. We might validate an IQ test by determining how well it predicts grades in school or performance on a task that we believe requires intellectual skill. This approach to validity is referred to as ***criterion-related validity***. In criterion-related validity it is necessary to specify the criterion. For example, an IQ test may be a valid predictor of school grades but have no validity when used to predict happiness. Criterion-related validity can refer to how well a test relates to either a criterion that is already available (***concurrent validity***) or to a criterion that will only be available in the future (***predictive validity***).

Cronbach and Meehl (1955) integrated many of the above ideas into a concept called ***construct validity***. A construct is an attribute that is not directly observable, such as intelligence, extroversion, or schizophrenia. Cronbach and Meehl argued that in science we are often interested in more than just the reliability or validity of a measure. Instead, we want to know the validity of the theoretical concept that the measure is designed to assess (e.g., an IQ test as a measure of the construct of intelligence). Validating a construct involves a converging operation in which we systematically test predictions derived from our theory. These predictions are embedded within a *nomological network* (an interlocking series of hypotheses derived from one's theoretical understanding of the construct). These predictions may be tested with either reliability or validity indices depending on the nature of the hypothesized relationship. Furthermore, the theory may sometimes predict either strong or weak relationships, so that sometimes we expect large validity coefficients whereas at other times we expect small coefficients. For example, our nomological network of intelligence might include an expectation of stability over time (high test-retest reliability), a generalized ability applicable to many different situations (high internal consistency reliability), strong relationships with current academic achievement (high concurrent validity), and strong relationships with future occupational success (high predictive validity). Construct validity does not yield a single index but rather is evaluated by the broad pattern of theoretically relevant relationships observed. Psychopathology research can be thought of as involving the construct validation of hypothesized theoretical concepts, such as depression and schizophrenia.

Defining and Refining the Syndrome

How do researchers establish the validity of psychopathological syndromes? How can they determine if their definition of a psychopathological syndrome is too broad or too narrow? Like other constructs, psychiatric diagnoses represent latent attributes that are not directly observable. To support the construct validity of a hypothesized diagnosis, psychopathology researchers must accumulate *indirect* evidence. In an influential article, Robins and Guze (1970) delineated a comprehensive approach toward establishing the construct validity of psychiatric diagnoses. They argued that a valid diagnosis must accomplish five things:

1. Describe the clinical syndrome with sufficient clarity to permit high interrater reliability.
2. Predict diagnosed individuals' performance

on laboratory (e.g., cognitive/attentional tasks) and psychometric (e.g., personality questionnaires) indices.
3. Predict diagnosed individuals' natural history (i.e., course and outcome).
4. Predict diagnosed individuals' family history of psychiatric syndromes.
5. Differentiate the diagnosis from other, superficially similar, diagnoses.

In addition, although not mentioned by Robins and Guze, a valid diagnosis should ideally:

6. Predict response to treatment.

Robins and Guze's approach is an application of the principle of construct validation to psychiatric diagnoses. Each of these six pieces of information are components of the nomological network in which one's predictions concerning the relations between the hypothesized syndrome and external variables are embedded (Waldman, Lilienfeld, & Lahey, 1995).

We can best understand the Robins and Guze approach with reference to a specific diagnosis, such as schizophrenia. In the case of schizophrenia, there is evidence from numerous studies that the diagnosis of schizophrenia (1) can be reliably differentiated from other, superficially similar diagnoses (e.g., bipolar disorder); (2) predicts performance on laboratory (e.g., smooth pursuit eye tracking) and psychometric (e.g., MMPI) indices; (3) is generally, but not invariably, associated with a chronic course and poor outcome; (4) is associated with a family history of schizophrenia and "schizophrenia spectrum" disorders (e.g., schizotypal and paranoid personality disorders); (5) differs in its external correlates from other, superficially similar conditions (e.g., psychotic mood disorders); and (6) predicts a positive response to dopamine antagonists (Gottesman, 1991). Thus, according to Robins and Guze's approach, the diagnosis of schizophrenia can be said to possess construct validity.

The Robins and Guze criteria can also be used to refine a syndrome. If a revised definition of a syndrome improves the prediction of one or more of these six criteria, this revision is usually accepted. For example, until the publication of *DSM-III*, schizophrenia was defined more broadly in the United States than in Europe. This broad definition included patients we would now call bipolar. Evidence for differential treatment effects between this narrow definition of schizophrenia and bipolar disorder, as well as differential courses, family histories, and other criteria, provided convincing evidence in support of this revision in diagnostic criteria.

The Robins and Guze approach can also be applied to the examination of the construct validity of multiple syndromes. If, for example, two syndromes are characterized by identical external correlates, such as family history and treatment response, these two syndromes may be manifestations of a single disorder. For example, researchers once distinguished manic-depression (manic episodes plus depressive episodes) from unipolar mania (manic episodes only). Subsequent research indicated, however, that mania with associated depression did not differ from mania alone in terms of natural history, family history, response to treatment, and other correlates (Depue & Monroe, 1978). Consequently, *DSM-IV* regards both mania with associated depression and mania alone as aspects of one overarching syndrome known, perhaps misleadingly, as bipolar disorder.

How should the researcher proceed if a proposed diagnosis fails to meet some or all of the Robins and Guze criteria for construct validity? One possible reason for such low validity is that the proposed diagnosis is too broad—that is, the individuals it encompasses are too ***heterogeneous***. A researcher who has either theoretical or empirical reasons to believe that a diagnostic category is heterogeneous can use several approaches to reduce this heterogeneity. First, the researcher may elect to divide the syndrome into one or more subtypes on the basis of rational or theoretical criteria. For example, numerous researchers have argued that the diagnosis of alcohol dependence (alcoholism) is heterogeneous and have proposed ways of meaningfully subdividing this diagnosis. Some have suggested, for instance, that alcoholism that appears prior to another psychiatric disorder (i.e., primary alcoholism) tends to be characterized by an earlier onset and more negative prognosis than alcoholism that appears following another psychiatric disorder (i.e., secondary alcoholism) (Goodwin & Guze, 1989). Once these putative subtypes are proposed, the researcher can use the Robins and Guze framework to determine whether they differ in their external correlates. This was the approach adopted in the earlier example of narrowing the syndrome of schizophrenia.

The researcher may also use statistical techniques to divide the syndrome into narrower and—it is hoped—more etiologically homogeneous, subtypes. For example, the technique of *factor analysis* allows researchers to ascertain whether the relations among symptoms can be accounted for by one or more underlying dimensions and may even shed light on the nature of these dimensions. For example, factor analyses of measures of schizophrenic symptoms suggest that these symptoms may be underpinned by two factors: a positive symptom factor (excesses, such as delusions and hallucations) and a negative symptom factor (deficits, such as flat affect and withdrawal) (Schuldberg, Quinlan, Morganstern, & Glazer, 1990). Such data are consistent with the hypothesis that positive symptom and negative symptom schizophrenia are etiologically distinct conditions, although construct validational studies using Robins and Guze's framework will be needed to further validate this distinction (Andreasen, Flaum, Swayze, Tyrell, & Arndt, 1990).

Another technique used to subdivide syndromes is *cluster analysis*, which can be used to sort symptoms (or, in some cases, patients with these symptoms) into different categories. This sorting procedure is performed by taking mathematical measures of similarity among the variables in question, and creating different clusters that are as homogeneous as possible. Unlike factor analysis, which examines only the variance shared by variables, cluster analysis examines the total variance of these variables. Although cluster analysis can be useful for generating hypotheses concerning the existence of subtypes that may be nested within a broader diagnosis, this technique often yields quite different results depending on the clustering algorithm used (Meehl & Golden, 1982) or the variables selected (Meehl, 1990).

Epidemiological Studies: Gathering Clues to Etiology

What Is Epidemiology and How Is It Relevant to Psychopathology?

How common is a psychological disorder in the general population? What characteristics are associated with its frequency in the general population? How often do cases of this disorder arise and disappear? These questions are addressed by epidemiological methods. Although the term *epidemiology* derives from *epidemic*, epidemiologists concern themselves with far more than the spread of diseases. Epidemiology can be defined as the study of the (1) distribution of disorders in a given population and (2) the variables that are statistically associated with this distribution (Rutter, 1994). Thus, an epidemiological study of antisocial personality disorder (ASPD) would probably focus on the frequency of ASPD in the general population and the factors (e.g., gender, social class, and family history of antisocial behavior) that covary with the frequency of ASPD in the population.

Why do epidemiologists want to know these things? Research on the rate of a disorder in a population provides a baseline for comparison with the rates in various subpopulations. For example, the co-twins of monozygotic ("identical") twins with schizophrenia (see "The Twin Study Paradigm" later in this chapter) have approximately a 50% chance of developing schizophrenia (Gottesman, 1991). This 50% figure takes on full meaning only when compared to the general population prevalence of schizophrenia—approximately 1%. Thus, epidemiological data permit us to determine that having a monozygotic twin with schizophrenia increases one's risk of schizophrenia approximately fiftyfold.

Research on the characteristics that covary with the frequency of a disorder in a population may provide important leads to its etiology. For example, epidemiological studies have revealed that ASPD is more common in males than females, is more common among individuals of lower social class, and is associated with a family history of ASPD and criminality (see *DSM-IV*). Such data might suggest clues to the etiology of ASPD. For example, the finding that ASPD is more common in males than females might point to biological or socialization variables that show marked sex differences and that potentially increase individuals' risk for antisocial behavior. Such variables might include levels of testosterone (Dabbs & Morris, 1990) or adults' tendency to differentially reinforce physical aggression in boys and girls (Serbin, O'Leary, Kent, & Tonick, 1973).

This strategy of identifying factors associated with the frequency of a disorder in the population has yielded several spectacular successes in medicine. For example, the cause of cholera was identified in London in 1848 by Snow (1855), who constructed a detailed map of the distribution of

affected cases during an epidemic. In this way, Snow traced the origin of the epidemic to a specific water pump (Tsuang, Tohen, & Murphy, 1988). Subsequent investigators were able to identify the bacterium that produces cholera. Thus far, such remarkable success stories have eluded epidemiologists investigating the causes of psychopathology. For example, although Faris and Dunham's (1939) classic epidemiological study revealed that the rates of schizophrenia in Chicago progressively increased as one moved from the outskirts of the city to its centrally located slums, their investigation and others like it have shed little light on the causes of schizophrenia. Nevertheless, the hope remains that epidemiological research may help to pinpoint risk factors for psychological disorders and may ultimately provide clues to their etiology.

Epidemiology is the study of *who* has *what*, *where*, *when*, and *how* (Costello, 1990). In other words, epidemiologists strive to determine which individuals are affected with which disorders, the geographical distribution of these disorders, the time course of the appearance and spread of these disorders, and (ideally) the processes that give rise to these disorders. The last of these goals,—*how*—is the ultimate goal of epidemiological research because an understanding of the etiology of a disorder often provides the information needed to treat or prevent it.

Critical Concepts and Terms in Epidemiology

Several concepts and terms are crucial for a full understanding of epidemiological methods. The two most critical are prevalence and incidence. ***Prevalence*** refers to the percentage of a population afflicted with a disorder during a given time period (e.g., one month or one year). ***Point prevalence*** is defined as the percentage of a population that is afflicted with a disorder at a single point in time (e.g., January 1, 1999). ***Period prevalence*** is defined as the percentage of a population afflicted with a disorder during a specified time period (e.g., from January 1, 1999, to January 1, 2001). ***Lifetime prevalence*** is the percentage of the population that develops the disorder sometime during their lifetime. The term ***base rate*** is often used to refer to lifetime prevalence (Meehl & Rosen, 1955).

Incidence, which is often confused with prevalence, refers to the percentage of ***new cases*** that arise during a specified time period (Regier & Burke, 1985). For example, if in a population of 1 million individuals, 1,000 individuals develop bipolar disorder during a one-year interval, then the one-year incidence of bipolar disorder in this population is .1%. A moment's reflection leads to the conclusion that prevalence and incidence will be similar only if the disorder in question is brief in duration. Incidence is assessed with a longitudinal design in which a sample of unaffected individuals is followed over time to ascertain what proportion develop the disorder in question.

Two other important epidemiological terms are the comparison group and the case-control method. Epidemiological researchers often select samples of affected individuals from settings in which the rates of a disorder are known to be elevated (e.g., an inpatient unit, a mental health clinic). This strategy is more efficient and economical than sampling affected individuals from the general population, particularly if the prevalence of the disorder is low. For example, if one were interested in examining the characteristics of individuals with autistic disorder, which occurs in no more than 5 out of 10,000 individuals in the general population (*DSM-IV*), one would have to sample 200,000 individuals to obtain a sample of 100 autistic subjects. Instead, one could probably obtain enough autistic subjects by sampling only a handful of inpatient child psychiatry units or mental retardation clinics. Having identified a sample of autistic individuals, one would then need to compare the findings from this sample with those from a sample of individuals without autistic disorder. Because this latter sample serves as a baseline with which the rates of various characteristics in the former group can be compared, it is referred to as a ***comparison group***. This group is also sometimes referred to as a ***control group***, although this more traditional term is misleading. Unlike a true control group in experimental research, in which extraneous differences between groups are minimized by the process of random assignment, a comparison group often differs from the affected group in many characteristics (e.g., age, gender, social class). The term control group should technically be reserved for groups that have been created by randomly assigning individuals to conditions. Nonetheless, tradition dies hard. The comparison of groups of individuals with and without a disorder (or, in some cases, with a different disorder) is typically referred

to as the *case-control design* (even though the term case-comparison design would be more technically accurate).

Methods of Sampling

Thus far, we have discussed how epidemiological researchers examine the distribution of disorders in a population. But unless the population of interest is small, it is not feasible to assess all members of a population. Instead, the investigator must be content to obtain a sample that provides a good approximation to the population from which it is drawn.

How should a population be sampled? The answer to this question is not as simple as it appears, as there are at least three ways in which sampling can be performed. In the first approach, *random sampling*, every individual in the population has an equal chance of being selected. The resulting sample is designed to be as representative as possible of the larger population from which it is drawn. Random sampling is frequently used by political polling organizations to obtain representative samples of registered voters.

The second approach, *stratified random sampling*, is used when the researcher wants to ensure that one or more subgroups within the population are adequately represented in the sample. Imagine, for example, that you were interested in investigating the prevalence of bipolar disorder across different religious groups in the United States. If you used a random sampling approach, there might not be sufficient numbers of individuals in certain religious groups (e.g., Hindu, Shinto) to permit a statistically meaningful examination of the rates of bipolar disorder in such groups. To deal with this problem, you could oversample from these underrepresented religious groups and later apply an adjustment factor to correct for the fact that different religious groups have been sampled in differing proportions. Specifically, you could weight subjects individually based on the probability of their selection in the sample (Regier & Burke, 1985). This approach is called stratified random sampling because the investigator samples extensively from one or more *strata* (i.e., "layers" or subgroups) within the population.

The third approach is called *cluster sampling*, which is typically used when the investigator does not have access to a list of every member of the population. This often occurs when the population is very large. Thus, the researcher can instead sample from clusters of individuals, such as housing projects or apartment complexes. Within clusters, samples of households can then be selected through either random or stratified random sampling (Regier & Burke, 1985).

Potential Biases in Epidemiological Research

Epidemiologists must be careful to avoid biases that may distort the results of their investigations. Perhaps the most crucial of these is *selection bias*, which results when a sample is chosen on the basis of a characteristic that is not representative of the population to which the investigator intends to generalize (Burke & Regier, 1988). An example of this bias can be found in the work of Freeman (1979), who examined the relation between giftedness in children and their risk for psychopathology. When Freeman sampled from an association for the families of intellectually gifted children, she found a high rate of psychological disturbance in these children. But when she sampled gifted children from the general population, she found a low rate. Had she relied exclusively on the former sample, her conclusions would have been misleading. Interestingly, Freeman found that the parents of this sample reported high levels of divorce and conflict. Apparently, parents who join organizations for gifted children are not a random sample of all parents with gifted children. Perhaps high levels of familial dysfunction lead parents to seek out emotional support or camaraderie (Rutter, 1994); or perhaps gifted children with psychopathology tend to increase the likelihood of parental turmoil.

The most common example of selection bias in psychopathology research involves the use of clinical samples drawn from different populations across studies. When this occurs, replication failures often result. For example, Luchins (1982) argued that inconsistent findings across studies of cerebral ventricular enlargement in schizophrenia were a consequence of examining clinical samples drawn from substantially different populations. Luchins noted that the studies that reported enlarged ventricles examined chronic patients with neuropsychological deficits, whereas studies that reported normal ventricles examined acute patients

with normal neuropsychological functioning. As another example, Gorenstein (1982) reported that psychopathic personalities exhibited deficits on a number of measures of frontal lobe dysfunction. Hare (1984) failed to replicate Gorenstein's findings despite using the same measures of frontal lobe functioning. Hare explained this discrepancy by noting that Gorenstein's sample, unlike his, was characterized by high rates of alcohol abuse, which can produce frontal lobe damage.

Using clinical samples can also result in misleadingly high estimates of *comorbidity* (Feinstein, 1985)—that is, the overlap of two or more diagnoses within an individual (see Lilienfeld, Waldman, & Israel, 1994). Comorbidity can result from either Berksonian bias (Berkson, 1946), clinical selection bias (du Fort, Newman, & Bland, 1993), or both. *Berksonian bias* is purely mathematical, and results from the fact that an individual with two disorders can seek treatment for either disorder, so that individuals with comorbid disorders will be overrepresented in clinical settings. *Clinical selection bias* results from an increased likelihood of treatment seeking for individuals with one condition because of the presence of another condition. Individuals with alcoholism, for example, may be unlikely to seek treatment unless they are also depressed or anxious (Lilienfeld et al., 1994). Clinical selection bias can be thought of as the "straw that breaks the camel's back" effect. Individuals with a single disorder may not be motivated to obtain help until they find themselves unable to cope with a second disorder. Both of these biases will produce comorbidity rates that are higher in clinical settings than those derived from studies of the general population.

Epidemiological studies are a valuable tool for identifying potential causal or contributory factors. Nevertheless, epidemiological work alone is almost never able to establish specific links between pathology and potential causal influences. But when you are faced with a field filled with haystacks, it is helpful to know which one is likely to hold the needle that you are looking for. Epidemiological studies serve that role well.

Studying Genetic and Environmental Influences

We often take for granted that our family has had an enormous influence on our personalities. We readily point to specific experiences that we feel have shaped our thinking, attitudes, and sense of who we are. Nevertheless, in reality we often have little idea how our families have influenced our development, and more often than not, our impressions leave out one of the most potent family influences—our genetic heritage.

In an intact family, in which biological parents raise their offspring, we are influenced by both the genetic and the environmental contributions of our parents. These independent effects are impossible to separate in a natural environment. Furthermore, it is likely that genetic and environmental influences interact, meaning that individuals with different genetic makeups react differently to different environments. In other words, the dual influence of genes and environment may be more potent than the sum of the individual effects. For example, adoptees with a genetic predisposition toward antisocial behavior are especially likely to develop antisocial behavior if they are reared with antisocial parents (Cadoret, Cain, & Crowe, 1983).

There is now a general consensus that both genetic and environmental influences contribute to virtually every form of psychopathology, but that has not always been the case. From the 1940s well into the 1970s, professionals generally favored exclusively psychogenic theories for most forms of psychopathology. For example, the cause of schizophrenia was attributed to such factors as the "schizophrenogenic mother" (Fromm-Reichman, 1948) or the "double-bind" (Bateson, Jackson, Haley, & Weakland, 1956), even though the data in support of these models were equivocal at best. The Zeitgeist during the middle of the 20th century was to pin the cause of psychopathology on the environment—especially the parents—and the Zeitgeist was maintained in the face of growing evidence of a genetic contribution to a variety of psychopathologies. For example, Kallman (1938) argued that genetics played a significant role in schizophrenia, and he published data consistent with this position. By the early 1960s, there was extensive data supporting the position that genetics played a significant role in schizophrenia (see Gottesman & Shields [1972] for a review). Yet Meehl's classic 1962 paper proposing a genetic diathesis for schizophrenia was considered revolutionary by many and implausible by many more.

Behavior genetics is the study of genetic influences on behavior. The designs discussed below only scratch the surface of the paradigms available.

More behavior genetics research has been conducted on animals than on humans because of the experimental control possible with animal models (Plomin, DeFries, & McClearn, 1990). But even without experimental control, powerful paradigms allow us to probe genetic influences on human behavior. Complete coverage of these approaches is beyond the scope of this chapter. Interested readers are referred to Plomin et al. (1990) for more details.

Demonstrating a Genetic Influence

Behavior genetics uses the concept of *heritability*, which is the extent to which individual differences in a characteristic (e.g., a mental disorder) are attributable to genetic factors. Genetic factors can be subdivided into additive genetic influences and nonadditive genetic influences. *Additive* genetic influences involve the direct effects of genes, whereas *nonadditive* genetic influences involve interactions among genetic elements, including interactions within genes (*dominance*) and interactions among genes (*epistasis*) (Plomin et al., 1990). Because only additive genetic effects are directly transmittable from parent to offspring, these effects are of considerable interest to animal breeders. The distinction between additive and nonadditive genetic influences has implications for the definition of heritability. We use the term *broad heritability* to refer to both additive and nonadditive genetic effects and the term *narrow heritability* to refer to additive genetic effects only (Loehlin, 1992).

Research on the heritability of psychopathological conditions typically uses one of three approaches—the family, twin, or adoption paradigms. Each paradigm has advantages and disadvantages. Traditionally, each paradigm starts by sampling patients with specific characteristics. These initial patients are referred to as *probands*. Probands are selected by both diagnosis and certain nondiagnostic features. For example, if we were conducting a twin study of the genetics of bipolar disorder, we would select probands who have bipolar disorder and who are twins. Once probands are selected, their relevant relatives are identified and diagnosed, where the definition of *relevant* depends on the paradigm. The effectiveness of each of the paradigms rests on how carefully the proband cases are sampled and how accurately the diagnoses of relatives are made.

Sampling is critical because a biased sample will produce biased, and usually erroneous, results. The best sampling technique is random sampling or some variation on this method, although true random sampling is rarely possible. A common strategy is to select all patients admitted to certain treatment facilities during a specified period who meet all the selection criteria. The advantage of this approach is that it avoids subtle biases that may result from less systematic selection procedures, such as having professionals in the community refer suitable cases. For example, professionals may be more likely to refer a case for a study of the genetics of a disorder if they know that there is an unusually high level of pathology in the patient's family. Such cases, although perhaps more clinically interesting, are often unrepresentative of the population. Virtually all sampling techniques have potential biases. Selecting probands from state hospital admissions will overrepresent individuals who lack supportive families or other resources that permit them to stay in the community despite significant pathology, and it will underrepresent individuals who have the financial resources for private treatment. One should always detail the specific sampling procedures to allow other researchers to make reasoned judgments about potential biases.

Once a sample of probands has been gathered, the next task is to identify and diagnose the relatives that are relevant for each paradigm. That task can be formidable. Simply identifying the relatives and tracking them down can be very difficult; some relatives may have moved away and others may have died. Once relatives have been identified and located, the process of diagnosing each relative is far from simple. Three approaches have been used. One approach, the *family history method*, uses the secondary reports of cooperative relatives to make the diagnosis. This is the least expensive procedure, but also the least effective and most biased. Evidence suggests that the family history method tends to produce high false negative rates (not identifying affected family members) but low false positive rates (incorrectly labeling a family member as affected) (Andreasen, Endicott, Spitzer, & Winokur, 1977). Relatives may also be poor observers of relevant behavior and therefore provide the researcher with inadequate information. The two most widely used procedures for obtaining diagnoses are the *individual interview approach* (Gottesman & Shields, 1972) and the *records review approach* (Kety, Rosenthal, Wender, & Schul-

singer, 1968). The most valid procedure, but also the most costly and time-consuming, is to interview each relative individually. When relatives are unavailable for an interview, secondary sources of diagnostic information may be used, although traditionally analyses are carried out separately for (1) the primary data (obtained from direct interviews) and (2) the more complete data sets (where some of the data are obtained from these secondary sources). A less costly approach is to rely on standardized records, although such records are not always available. Many behavior-genetic studies have been conducted in countries with socialized medicine, such as Denmark, because these countries maintain extensive standardized medical and psychiatric records. Interviews tend to produce higher estimates of psychopathology than a review of hospital records. Generally, the more extensive the information researchers have available, the more likely they will find evidence of pathology if it exists.

Because each approach varies in its likelihood of uncovering psychopathology, one should include a comparison group and evaluate all subjects blindly (i.e., without knowledge of whether the family member is from the proband or comparison group). Comparison groups are formed by identifying subjects who are similar to the proband sample, except for the diagnostic variable that defined probands, and then finding their relevant family members.

We will briefly describe each of the three most commonly used behavior-genetic paradigms below. We will use schizophrenia as the example in our discussion even though these paradigms have been used to investigate many other disorders.

1. The family study paradigm. The family study paradigm evaluates the prevalence of relevant psychiatric disorders in relatives of patients with a specific disorder. In the study of schizophrenia, the most relevant psychiatric disorder is schizophrenia, although we often probe for related disorders as well (e.g., the so-called schizophrenia-spectrum disorders—schizoaffective disorder, paranoid personality disorder, schizotypal personality disorder). The family study paradigm starts with a sample of proband cases (patients diagnosed with schizophrenia) and proceeds to identify and diagnose as many relatives as possible. We break down the analysis by comparing the rates of schizophrenia, schizophrenia spectrum disorders, or both by the degree of genetic relatedness to the proband case. Parents, children, and full siblings share, on average, 50% of a person's genes and are referred to as *first-degree relatives*. Grandchildren, grandparents, half-siblings, aunts, and uncles (*second-degree relatives*) share, on average, 25% of a person's genes, and first cousins (*third-degree relatives*) share, on average, 12.5% of a person's genes. If schizophrenia is heritable, as the degree of genetic relatedness to the proband drops, we expect the rates of schizophrenia to drop. A comparison group should always be included—in this case, family members of subjects who do not have schizophrenia. And, of course, all diagnostic evaluations should be done blindly (i.e., without knowledge of whether the subject under evaluation is from a proband or comparison family).

The major drawback in family studies is that genetic and environmental influences are confounded. Thus, the finding that psychopathology runs in families does not establish that genetic factors are responsible because environmental influences would produce the same results. On the other hand, a finding that psychopathology does not run in families all but rules out the possibility of genetic influences, although it is remotely possible that certain nonadditive genetic influences may not show up in family studies (Lykken, McGue, Tellegen, & Bouchard, 1992).

2. The twin study paradigm. The twin study paradigm[1] addresses the major weakness of the family study paradigm (the fact that environmental and genetic influences are confounded). Twin studies handle this confounding by attempting to hold environment constant. We begin by identifying probands who have developed schizophrenia and are twins. Co-twins are then located and two classifications are performed. Each twin pair is classified as either identical (also called *monozygotic* or *MZ*) or fraternal (*dizygotic* or *DZ*). MZ twins share 100% of their genes, whereas DZ twins share 50% of their genes on average. Because environment and sex-linked genes can vary dramatically for men and women, typically only same-sex DZ twins are used.[2] When a co-twin of the proband also qualifies for a diagnosis of schizophrenia, the twins are said to be *concordant*. The potential role of genetics is evaluated by comparing the concordance rate for MZ and DZ twins. Because both MZ and DZ twins are raised together, it is assumed that the environmental influences on

these two types of twins are approximately equal (termed the *equal environments assumption*). Therefore, any difference in concordance rates between MZ and DZ twins should be due to the difference in level of shared genes. The raw concordance rates may be corrected statistically to take into account the fact that it is twice as easy to sample a concordant twin pair than a nonconcordant twin pair because a concordant pair has two potential probands in the population from which the sample is drawn.

This paradigm has been used in over a dozen studies of schizophrenia, but perhaps the most influential study was conducted by Gottesman and Shields (1972). These investigators identified 24 MZ twin pairs and 33 DZ twin pairs from the Maudsley Twin Register. After carefully determining zygosity (i.e., MZ or DZ), these investigators obtained extensive clinical information in order to determine concordance rates. In addition to the normal diagnostic information, they obtained case histories, family histories, and MMPIs from most of their subjects. They then obtained independent and blind diagnoses for each of their subjects from six of the best diagnosticians of the time. The comparison between MZ and DZ twins was consistent with previous studies in showing higher MZ than DZ concordance, but the real strength of this study was that the immense wealth of data allowed these investigators to examine potential markers for genetic risk, as well as optimal diagnostic criteria for identifying a homogeneous sample of patients with schizophrenia. These data have shaped selection criteria for hundreds of subsequent studies of schizophrenia, and their influence is clearly evident in the current diagnostic manual.

3. **The adoption study paradigm.** The adoption paradigm[4] deals with the confounding of environmental and genetic influences by studying individuals who have been separated from their biological relatives. For obvious ethical reasons, the separation from their biological relatives is not under experimental control; hence, this is a quasi-experimental design. Often one begins with probands who have developed schizophrenia and who were adopted at birth. These individuals have both a genetic heritage contributed by their biological family and an environmental heritage contributed by their adoptive family. By comparing the rates of schizophrenia in both biological and adoptive relatives, one can gauge the relative contribution of environment and genetics to the development of the disorder. As with the family study paradigm, a comparison group is selected by finding suitable subjects who have not developed schizophrenia but who were adopted, and the level of psychopathology in their biological and adoptive relatives is evaluated.

Kety et al. (1968) used the adoption study paradigm to study the potential genetic and environmental influences on schizophrenia. Using the remarkably complete record system in Denmark, they identified 33 proband cases who had developed schizophrenia and had been adopted shortly after birth, and they selected a comparison group matched with these subjects on a host of potentially confounding variables (e.g., social class of adoptive and biological parents, age at adoption). They then identified all biological and adoptive relatives for these subjects and obtained their psychiatric records. On the basis of those records, they established that there was an elevated risk for schizophrenia (approximately fivefold) only in the biological relatives of the proband cases. This remarkably rich data set has been reanalyzed over the years from other perspectives (e.g., Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978).

Kety et al.'s approach is known as the *adoptees' relatives approach* because it begins with schizophrenic and nonschizophrenic probands and examines the rates of psychopathology in their relatives. There are other adoption paradigms. For example, Rosenthal et al. (1968) investigated the risk for psychopathology in the adopted offspring of patients with schizophrenia. They found a tenfold increase in the rate of schizophrenia in these offspring relative to the comparison group. This approach is known as the *adoptees' study method* because it begins with schizophrenic and nonschizophrenic parents and examines the rates of psychopathology in their adopted-away offspring.

Cautionary Notes in Using These Paradigms Although the twin and adoption paradigms provide powerful tests of the hypothesis that genetics play a role in the development of schizophrenia, there are limitations to these paradigms. For example, the equal environments assumption in twin studies may not always be strictly true. Nevertheless, this assumption has generally been upheld in a number of studies (Kendler, 1983). An issue with adoption studies is that adoptive parents are not chosen ran-

domly by the social service agencies entrusted with the task of placing children. The screening process likely eliminates potential parents who show obvious signs of psychopathology, which tends to reduce the level of pathology in the adoptive relatives. Presumably this screening process should affect the proband and comparison samples equally. In addition, adoption agencies often place adoptees with parents who are more similar to the adoptees' biological parents than would be expected by chance. Such selective placement can sometimes distort the findings of adoption studies. Researchers can sometimes deal with this problem by measuring the degree of selective placement and correcting for it statistically.

It should also be noted that different behavior-genetic paradigms may yield different estimates of heritability. The heritability estimates for personality traits derived from twin studies, for example, tend to be somewhat higher than those derived from adoption studies (Tellegen et al., 1988). Although several factors may account for this difference, one factor is that twin studies provide estimates of broad heritability, whereas adoption studies provide estimated of narrow heritability (Loehlin, 1992). The heritability estimates derived from twin studies may therefore provide a truer reflection of reality than estimates derived from adoption studies.

Finally, psychopathology researchers never have the experimental control over breeding available to genetic researchers who use animals as subjects. It is unlikely that the random matings assumed by many statistical models are actually occurring. Nonrandom matings (called *assortative matings*) distort estimates of population parameters such as gene frequency. Such assortative matings may be common in the domain of psychopathology; individuals with schizophrenia, for example, are more likely to mate with individuals with schizophrenia-spectrum disorders than would be expected by chance (Gottesman & Shields, 1982).

We have documented several limitations in the paradigms used to study genetic influences on psychopathology. Still, these paradigms have produced reasonably consistent data on genetic influences for many types of psychopathology, including schizophrenia. The convergence of findings from diverse paradigms gives us reasonable confidence in the results, even though each individual paradigm has its weaknesses.

Probing the Nature of Genetic Influences

Population genetics is the study of departures from genetic equilibrium resulting from such factors as selective pressures, mutation, migration, or nonrandom mating. Population genetics relies heavily on the statistical analysis of population base rates and changes in those base rates over generations. A question of interest to population geneticists is the well-documented negative selective pressure in schizophrenia. Patients with schizophrenia have approximately half as many offspring as the general population (Gottesman, 1991), yet the rate of schizophrenia does not appear to be dropping dramatically from generation to generation. Such data make certain genetic models unlikely. For example, if schizophrenia were due to a single dominant gene with complete penetrance, we would expect a 50% drop in the frequency of this gene and the rate of schizophrenia in each generation. Studying factors like this can provide indirect evidence concerning many questions of interest to psychopathology researchers.

Genetic paradigms can also be used to zero in on the exact locations for genetic defects. One such approach is the *linkage study*, in which the pattern of transmission of a disorder is compared with the pattern of transmission of other genetically determined characteristics, where the specific locus on the chromosome of the genetic influence for those characteristics is known (see Schizophrenia Bulletin, 1989, for detailed examples). Using a linkage approach with a sample of families from Iceland and England, Sherrington et al. (1988) isolated a genetic risk factor for schizophrenia on chromosome 5. The families in their study had unusually high rates of schizophrenia, making their *pedigrees* (the chart that shows the genetic relatedness of family members and identifies which individuals have the trait under study) especially informative. The rate of schizophrenia in most families is much lower than in the families included in this study, which raises the issue of whether the latter families are representative.

Linkage studies may soon be much more powerful as the Human Genome Project dramatically increases the number of identified human genes and their specific locations. This information will make the task of identifying linkages easier, and may even allow the use of virtually any pedigree in

linkage studies. Such advances may permit us to identify genes that increase risk for specific disorders, although identifying the mechanism for that risk will still require the skills of the psychopathology researcher.

Environmental Studies

Traditionally, psychopathologists have discussed the environment as if it were a monolithic or uniform entity. More recently, however, researchers have recognized two types of environmental influences: shared and nonshared. *Shared environmental influences* make individuals within the same family similar to one another, whereas *nonshared environmental influences* make individuals within the same family different from one another. If a father is highly anxious and succeeds in making all his children anxious by overprotecting them, his anxiety would be a shared environmental influence.[5] Alternatively, if a parent severely mistreats one child but not another, the parental mistreatment would be a nonshared environmental influence. The distinction between these two types of influence is critical in psychopathology research because an increasing body of evidence indicates that nonshared, but not shared, environment plays a major role in the etiology of most mental disorders and personality traits (Bouchard, Lykken, McGue, & Segal, 1990; Plomin, 1990).

1. Behavior-genetic studies. Behavior-genetic designs are often thought of as paradigms for studying genetic influences on psychopathology. Nevertheless, they can also provide a sensitive platform for studying both shared and nonshared environmental influences (Loehlin, 1992). For example, the similarity between adoptive parents and their adopted offspring on a trait can be interpreted, in the absence of selective placement, as an estimate of shared environment on this trait because the only factor accounting for their resemblance is by definition environmental. The discordance rate of MZ twins for a mental disorder can be interpreted as an estimate of nonshared environment on this disorder. Because MZ twins share 100% of their genes, the only factor accounting for their discordance is environmental. Indeed, the study of MZ twins discordant for schizophrenia has provided a fertile ground for the examination of potential nonshared environmental influences on this disorder (Torrey, Bowler, Taylor, & Gottesman, 1994; Wahl, 1976). It should be noted, however, that estimates of nonshared environment typically include errors of measurement (Loehlin, 1992). Thus, if one's diagnoses of schizophrenia are unreliable, this will inflate both the MZ twin discordance rate of schizophrenia and the estimate of nonshared environmental influence on schizophrenia.[6]

2. Correlational studies. Correlational studies can be thought of as extensions of epidemiological studies. In epidemiological studies, one often finds that certain hypothesized causal variables (e.g., age, ethnicity, socioeconomic status, or other demographic variables) are associated with increased risk for a disorder. Demonstrating a correlation between a hypothesized causal element and the presence of psychopathology provides evidence consistent with one's hypothesis. Nevertheless, every undergraduate research methods textbook warns us, and for good reason, that *you cannot infer causation from a correlation*. A and B may be correlated because (1) A causes B, (2) B causes A, (3) or some third variable, C, causes both A and B. Because variable C could be anything, we have a nearly infinite number of possible interpretations of our correlation. Still, it can be tempting to overinterpret a correlation because our favored causal hypothesis seems so plausible. We should note that although correlation does not necessarily imply causation, causation does necessarily imply correlation. Thus, if a variable does not correlate with risk for a given disorder, the hypothesis that this variable is involved in the etiology of this disorder can be effectively excluded.

3. Analogue studies. The most direct test of an environmental hypothesis involves the manipulation of an environmental variable to observe its effects. Ethical and practical constraints make such a manipulation impossible except in very low "doses." We have already discussed the analogue study approach, which often represents an ethically acceptable way to perform this manipulation. The human analogue study attempts to create mild and temporary effects in the direction predicted by the researcher's hypothesis. The effects must be mild and temporary to make this approach ethically viable. This approach has been used to verify that conditions that create the feeling of helplessness will lead to behavior and feelings consistent with depression (e.g., Alloy, Peterson, Abramson, & Seligman, 1984). In addition, a variety of environmental manipulations (e.g., relaxed atten-

tion, speeded performance), referred to as schizomimetic conditions, have been shown to generate, at least temporarily, mild symptoms of psychosis (see Chapman & Chapman, 1973, for a review). A positive finding in such analogue studies indicates that the variable under study could create such symptoms, but never provides evidence that the symptoms normally develop in this way. For example, by providing selective reinforcement and sufficiently powerful incentives, we could probably get college students to bark like dogs, but no one would entertain the notion that dogs bark for similar reasons.

4. Treatment studies. If it is ethically unacceptable or practically impossible to create symptoms, an alternative strategy is to try to alleviate symptoms in individuals with a particular pathology. Such a strategy provides evidence consistent with the hypothesis that an environmental variable plays a role in the etiology or maintenance of psychopathology, but it also has limitations. Taking two aspirin may well relieve a headache, but few people would consider this evidence that headaches are caused by a deficiency in the level of aspirin. This simple example highlights the *ex juvantibus* ("reasoning backward from what helps") error of using treatment response to draw inferences concerning etiology. In spite of this limitation, treatment outcome can provide crucial data if other lines of evidence exist. The role of familial expressed emotion (Vaughn & Leff, 1976) in contributing to relapse in schizophrenia and other psychiatric disorders was rendered more plausible by the finding (Honig et al., 1995; Randolph, Eth, Glynn, & Paz, 1994) that treating the family of patients with schizophrenia reduces the level of expressed emotion and the patients' rate of relapse. Of course, we still need to be cautious in our conclusions because the treatment may have reduced relapse through other mechanisms.

Biological Studies

Biological studies provide invaluable insights into the nature of a disorder and the mechanisms that may underlie it. They may even contribute insights into both biological and psychological treatment strategies. In this section, we will discuss psychophysiological and brain imaging technologies—two approaches that have contributed extensively to our understanding of psychopathology.

Psychophysiological Research Methods

Psychophysiology is the study of individuals' psychological processes as indicated by their involuntary physiological responses (Lykken, 1982). These involuntary physiological responses can be thought of as windows that provide a useful glimpse into individuals' underlying psychological states. But these windows are almost always somewhat foggy, in part because the responses typically studied by psychophysiologists are influenced by many factors other than current psychological state. For example, a subject's brain is engaged in a host of activities (e.g., regulation of breathing and heart beat, maintenance of overall alertness) in addition to responding to the researcher's stimuli.

Psychophysiology can be distinguished from *physiological psychology* in that the former typically uses behavioral independent variables and physiological dependent variables, whereas the latter typically uses physiological independent variables and behavioral dependent variables (Stern, 1964). For example, a psychophysiologist might administer stressful stimuli (e.g., repeated loud tones) to subjects and monitor their levels of skin conductance in response to these stimuli. In contrast, a physiological psychologist might lesion an area of a rat's limbic system and examine the effects of this lesion on aggressive behavior. Psychophysiology should also be distinguished from *psychophysiological* (i.e., psychosomatic) *medicine*, viz., the study of physical disorders that can be caused or exacerbated by psychological factors (e.g., essential hypertension, asthma). Whereas the researcher who studies psychophysiological disorders is typically interested in physiological reactions, such as blood pressure increases and respiratory difficulties, the psychophysiologist is typically interested in these reactions only insofar as they represent *indicators*—albeit fallible indicators—of underlying psychological processes (Lykken, 1982).

The fundamental armamentarium of the modern psychophysiologist includes a polygraph, a variety of electrodes and transducers, and one or more computers. A *polygraph* is a multichannel device that records physiological signals from the subject. The signals arriving from different physio-

logical systems (e.g., heart, brain) are amplified and then filtered to eliminate extraneous noise, such as the ubiquitous 60 cycle per second noise emitted by electrical devices. These signals are routed to pens, which display several simultaneous channels, producing the "squiggles" so familiar to psychophysiologists. Often these signals are simultaneously sent to a computer via an *analogue to digital (A/D) converter*, a device that transforms signals into numerical form. Virtually all modern psychophysiology laboratories are automated, with computers administering the stimuli and recording and analyzing the data.

Polygraph signals come from either electrodes or transducers. *Electrodes* typically are small metal disks that are placed on the subject's skin to record electrical signals—either those produced by the subject (e.g., electroencephalogram or EEG) or those passed through part of the subject's body (e.g., skin conductance or SC). *Transducers* convert changes in temperature, pressure, or other forms of energy to electrical signals that can be detected by a polygraph. A thermister changes its electrical resistance in response to temperature alterations; a strain gauge changes its electrical resistance in response to movement, such as the chest motions occurring during respiration; a pupillometer converts changes in the amount of light reflected by the pupil to voltage (Stern, Ray, & Davis, 1980).

The polygraph can record a variety of physiological reactions including skin conductance (SC), heart rate (HR), blood pressure (BP), brain waves (EEG), muscle activity (electromyogram or EMG), eye movements (electro-oculogram or EOG), respiration, and pupillary dilation. We will focus on SC, HR, and EEG because these are perhaps the three signals most frequently used in psychopathology research. In addition, these three variables have been used to examine a wide variety of disorders and thus have broad applicability in psychopathology research. Because of space constraints, we will not review psychophysiological variables that are relevant primarily to a single disorder. One example of such a variable that has received considerable attention in the past two decades is smooth pursuit eye movement dysfunction (SPEM), which exhibits promise as a biological marker of schizophrenia. The interested reader is referred to Clementz and Sweeney (1990) for an overview of this literature.

Skin Conductance The eccrine sweat glands, which are most densely concentrated on the palms of the hand and soles of the feet, are activated by the sympathetic nervous system and are therefore primarily responsive to psychological stimulation. They differ from the apocrine glands of the armpits and pubic area, which are primarily responsive to temperature changes. Presumably, the eccrine sweat glands evolved in our primate ancestors to facilitate adhesion to tree branches and other dry surfaces. These glands become moist during psychological arousal, including anxiety. Because water facilitates the passage of electrical current, the psychophysiologist passes a weak current (~ .5 volts) between electrodes placed on the fingers and measures the changes in conductance (Lykken & Venables, 1971). The resulting measure (SC) is among the most commonly assessed signals in psychophysiological research.

Several skin conductance measures are available. The skin conductance level (SCL) refers to the slow (*tonic*) changes in electrodermal activity that typically reflect the subject's state of arousal. The skin conductance response (SCR) refers to a rapid (*phasic*) change in electrodermal activity in response to an external stimulus. Fowles (1980) argued that SCR activity is an indicator of sensitivity to signals of punishment or threat. The spontaneous skin conductance response (SSCR) refers to a phasic electrodermal response in the absence of identifiable external stimulation. The frequency of SSCR fluctuations has been interpreted as a marker of arousal, anxiety, or both (Dawson, Schell, & Filion, 1990).

The study of SC has a long history in psychopathology research. For example, a subset of patients with schizophrenia (hyporesponders) exhibit diminished electrodermal reactions to stimuli, whereas another subset (hyperresponders) exhibit excessive electrodermal reactions to stimuli (Katkin & Hastrup, 1982). This finding may help to clarify the etiological heterogeneity of schizophrenia. For example, hyporesponders are more likely to show a negative symptom pattern, whereas hyperresponders are more likely to show a positive symptom pattern (Cannon, Mednick, & Parnas, 1990). SC measures have also been used extensively in the study of psychopathy and criminality. Psychopaths exhibit smaller SCRs in classical conditioning paradigms involving aversive stimuli (Lykken, 1957) and lower SCLs and fewer SSCRs

in anticipation of aversive stimuli (e.g., Hare & Craigen, 1974).

Heart Rate The human heart consists of a left and right pump, each including an atrium and ventricle (its upper and lower chambers, respectively). The contraction of the heart—the *systolic* phase—ejects blood into the aorta. This contraction is triggered by a strong electrical impulse. The *diastolic*, or relaxation, phase occurs between successive phases of ventricular contraction. Because heart rate (HR) is such a powerful electrical signal, it can be detected by placing two electrodes between almost any two areas on the subject's body. The most common placement is one electrode on the right arm and one on the left leg (Stern et al., 1980). The pronounced spike (termed *R spike*) of the *electrocardiogram* (EKG) is produced by the electrical innervation of the ventricles, which precedes their contraction by approximately 50 milliseconds (Katkin & Hastrup, 1982). A device known as a *cardiotachometer* calculates the time difference between successive R spikes and outputs a signal inversely proportion to this difference. This signal can be read directly as a measure of HR.

HR, like several other psychophysiological variables, obeys the *law of initial values* (Wilder, 1950). According to this law, there is a negative correlation between individuals' baseline levels and their subsequent responses to stimuli (i.e., the higher subjects' baseline levels, the lower will be their responses). In part, the law of initial values stems from the fact that many physiological systems possess homeostatic mechanisms that set limits on their maximum output (Stern et al., 1980). It should be noted, however, that the "law" of initial values is characterized by numerous exceptions, and does not apply to all psychophysiological systems (Katkin & Hastrup, 1982).

HR measures have been used extensively in psychopathology research. For example, criminal and pre-criminal individuals tend to exhibit lower HRs than other individuals during resting conditions (Raine, 1993), and psychopaths tend to exhibit *larger* HR responses than nonpsychopaths in anticipation of aversive stimuli (Hare & Quinn, 1971). This latter finding superficially runs counter to studies demonstrating lower SCL in psychopaths prior to such stimuli, illustrating a phenomenon known as *directional fractionation* (Lacey, 1967) in which different indicators of arousal change in opposite directions. How can we explain psychopaths' simultaneous high HR levels and low SC levels prior to noxious events? According to the *intake-rejection hypothesis* (Lacey & Lacey, 1978), HR decreases reflect increased attention (i.e., intake) and HR increases reflect decreased attention (i.e., rejection) toward the external environment (for a contrasting view, see Obrist, 1976). Thus, psychopaths' HR increases in anticipation of aversive stimuli may indicate active attempts to reduce environmental input, and their low SC level may indicate that such attempts are successful (Hare, 1978).

EEG The human brain is a three-pound organ consisting of approximately 100 billion neurons. The simultaneous firing of these neurons can be detected by placing electrodes on the subject's scalp. The resulting record, the *EEG*, is an index of the brain's electrical activity. The EEG record is typically subdivided by frequency. *Delta* waves occur in the 1–3 cycle per second (cps) range, *theta* waves in the 4–7 cps range, *alpha* waves in the 8–12 cps range, and *beta* waves at 13 cps or above. These waves are associated with different states of consciousness; delta waves, for example, are commonly observed during slow wave sleep, whereas beta waves are commonly observed during alertness. Although these rhythms can be assessed by inspecting the raw EEG record, modern psychophysiologists almost always use a *Fourier transformation* to analyze brain wave signals. This mathematical transformation decomposes a series of brain waves into its component frequencies (Stern et al., 1980).

Psychophysiologists may examine *resting*, or spontaneous, EEG activity (subjects' brain waves while they are not responding to stimuli delivered by the researcher) or *evoked responses* to discrete stimuli presented to the subject (e.g., tones, lights). Evoked responses are almost never apparent in the raw EEG record because the brain is busily carrying out a multitude of activities in addition to responding to these stimuli. Psychophysiologists measure evoked responses by repeatedly presenting the subject with an identical stimulus, and then averaging the EEG response to this stimulus across all presentations. The rationale underlying this averaging procedure is that the EEG activity irrelevant to the stimulus—which can be thought of as "random" in the sense that its fluctuations constitute unsystematic background noise—will cancel out, whereas the EEG activity relevant to the stim-

ulus will be highlighted. The EEG signal produced by this averaging process is known as an *event-related potential* (ERP) because it is believed to be a relatively "pure" measure of the brain's response to a given event (i.e., stimulus). An ERP typically consists of several wave components, some of which exhibit positive voltages and others negative voltages. ERP wave components are categorized along two parameters: (1) their voltage (positive or negative); and (2) their time lag following the stimulus. An N100 wave component, for example, is a negative voltage occurring approximately 100 milliseconds (msec) following stimulus onset. In general, early ERP components are believed to reflect sensory processing of the stimulus, whereas later ERP components are believed to reflect higher order cognitive processing of the stimulus (Katkin & Hastrup, 1982). One ERP component that has received considerable attention in the psychopathology literature is the *P300*. The P300 is most commonly elicited by means of an "oddball" paradigm, in which an aberrant stimulus (e.g., low frequency tone) is presented periodically, although rarely, amid a large number of identical stimuli (e.g., high frequency tones). Although controversy persists regarding the P300's functional significance, there is an emerging consensus that it reflects context updating—that is, a revision of one's mental model of the environment (Donchin & Coles, 1988). This hypothesis is consistent with the finding that the P300 tends to be elicited by novel or unexpected stimuli.

A number of psychological conditions are characterized by aberrant resting EEG findings. Patients with schizophrenia, for example, tend to exhibit reduced levels of alpha and increased levels of delta in their resting EEG (Iacono, 1982; Sponheim, Clementz, Iacono, & Beiser, 1994), and psychopaths tend to exhibit elevated levels of theta waves in their resting EEG (Syndulko, 1978). Because theta waves are often associated with boredom and drowsiness, however, psychopaths' high levels of theta may reflect only their relative absence of anxiety during EEG examinations. Depressed individuals exhibit less left frontal EEG activation (specifically, alpha activity) than nondepressed individuals (Henriques & Davidson, 1991), a finding that may reflect a deficit in biologically based approach systems among depressed individuals.

Several ERP components show considerable promise in the study of psychopathology. Begleiter, Porjesz, Bihari, and Kissin (1984), for example, found that sons of alcoholics exhibited lower P300s compared to sons of normal parents, although this finding has not been uniformly replicated (e.g., Polich & Bloom, 1988). The meaning of this finding and its specificity to alcoholism are unclear. Jutai and Hare (1983) reported that psychopaths exhibited lower N100s than nonpsychopaths in response to tones while playing a video game. Because the N100 appears to reflect selective attention (Coles, Gratton, & Fabiani, 1990), Jutai and Hare suggested that psychopaths tend to ignore extraneous stimuli while engaged in tasks of immediate interest.

Brain Imaging Technology

In the study of psychopathology, it is extremely helpful to be able to document the structure and functioning of the brain as a means of investigating potential causes of a disorder. Prior to modern imaging techniques, we had to rely on autopsy results and rather crude imaging techniques. Not surprisingly, few patients consent to a premature autopsy, even in the name of science, which limited the effectiveness of this paradigm. Early imaging techniques (e.g., the pneumoencephalogram) produced poor images, were uncomfortable for patients, and carried a significant mortality risk (about 1%). Modern brain imaging technology produces clear images, at a reasonable cost, and with minimal risk and discomfort to the patient. They have contributed significantly to the field of psychopathology and will likely contribute more in the future.

Observing Brain Structure: CAT Scans and MRIs

CAT (computerized axial tomography) *scans* and *MRIs* (magnetic resonance imaging) produce remarkably detailed pictures of the structure of the brain. Both techniques take images from different angles. The images are produced by X-rays in the case of the CAT scan, and by the magnetic properties of certain atoms in the brain in the case of the MRI. A mathematical technique is applied to these multiple images to create a three-dimensional picture of the structure necessary to produce that set of images—a technique ingenious enough to have led to a Nobel Prize. This three-dimensional mathematical model can be manipulated to produce detailed photos of any section of the brain desired. Structural brain imaging techniques have been used to investigate structural abnormalities in schizo-

phrenia (e.g., Sudath, Christison, Torrey, Casanova, & Weinberger, 1990), memory disorders (e.g., Jernigan, 1994), and personality disorders (e.g., Goyer, Konicki, & Schulz, 1994), to name but a few.

Observing Brain Functioning: PET Scans and fMRI Studies Detailed pictures of the brain are of little value unless you suspect that there is a structural abnormality. If the structure is normal but the functioning abnormal, CAT scans and MRIs are uninformative. Instead, we need procedures that can observe brain functioning.

We have already discussed one measure of brain functioning—the EEG. Two additional measures of brain functioning are the *fMRI* (functional MRI) and the *PET* (positron emission tomography) *scan*. The fMRI looks at changes in the magnetic properties of brain regions as an indication of the level of activity. The PET scan utilizes a harmless radioactive isotope, which is absorbed by brain tissue in proportion to its functional activity level. The decay of the isotope releases subatomic particles that collide with electrons to produce the photons that are detected and form the image. All of these measures, including the EEG, allow us to investigate unusual patterns of brain activity in individuals with various forms of psychopathology. Over- or underactivation of a brain region may suggest deficits in that region or a compensatory response to a deficit in another region. These techniques have been used to investigate dysfunctions in depression (e.g., Kravitz & Newman, 1995), schizophrenia (e.g., Liddle, 1995), and Alzheimer's disease (e.g., Foster, 1994), among other conditions.

High-Risk Research Approaches

Longitudinal designs have an advantage over most designs in psychopathology research. Following subjects over time allows one to observe the developmental course of a disorder and to measure the environmental factors that influence that course. But longitudinal designs are costly, especially in the low-yield environment of psychopathology research. The longitudinal design is used frequently in cases in which virtually all subjects are expected to pass through roughly the same developmental course. Therefore, each subject provides valuable data on developmental processes. But few randomly selected individuals will develop a specific psychiatric disorder. The base rates for most psychiatric disorders range from 10% to a fraction of 1%. For a disorder such as schizophrenia, with a base rate near 1%, we would need to follow 10,000 individuals for at least 20 years in order to obtain 100 subjects who develop schizophrenia. This would not be a good choice for a dissertation topic.

An alternative to the traditional longitudinal study is the *high-risk paradigm*. Mednick and Schulsinger (1968) were among the first to propose this strategy. Their idea was simple and elegant—use information about subjects to select those whose risk for developing a particular disorder is substantially above the population base rate. Because schizophrenia runs in families, Mednick and Schulsinger selected first-degree relatives of patients with schizophrenia as their subjects—specifically, offspring of mothers with schizophrenia. One could expect approximately 10% of this group to develop schizophrenia based on available research—a tenfold improvement in the yield of a longitudinal study. The approach used by Mednick and Schulsinger is referred to as the *genetic high-risk paradigm* because it relies on selecting experimental subjects on the basis of their genetic relationship to an individual with a particular disorder. An alternative approach—the *behavioral high-risk paradigm* (e.g., Chapman, Chapman, Raulin, & Edell, 1978)—selects at-risk subjects on the basis of behavioral characteristics.

Genetic High-Risk Paradigm

The genetic high-risk paradigm traditionally assumes a significant genetic contribution to a disorder, although technically this assumption is not needed. All we need to know is that there is an elevated risk in family members, which could be genetically transmitted, environmentally transmitted, or both. Subjects are selected by both their familial relationship to someone with the disorder and their age. Most disorders have well-defined *age-of-risk profiles* (the cumulative frequency graph of the age of the first appearance the disorder). If most people develop a disorder in their 20s, then one wants to select subjects prior to that period of risk. Selecting older subjects will leave out those who have already developed the disorder, and selecting younger subjects will substantially increase the time that one must wait to determine

which subjects develop the disorder. A comparison sample is selected, which is usually matched on variables that might confound the results if left uncontrolled (e.g., age, sex, social class). Both groups are then evaluated and followed over time.

The initial evaluation of the at-risk and comparison groups provides a basis for an immediate test of certain hypotheses. Whatever predisposing factors there might be for the disorder should be overrepresented in the at-risk group relative to the comparison group. The sensitivity of this comparison will depend on the proportion of individuals in the at-risk group who are truly "at risk" for the disorder. For example, we know that roughly 10% of the offspring of mothers with schizophrenia will develop schizophrenia. Nevertheless, that figure is likely an underestimate of the number of at-risk individuals because it is unlikely that every at-risk individual will actually develop the disorder. The discordance rate for MZ twins (about 50%) demonstrates that nonshared environmental variables play an important role in the development of schizophrenia. So we would expect at least 20% of the offspring of mothers with schizophrenia to be genuinely at risk because they possess whatever genetic risk factor(s) are specific to schizophrenia. Actually, the figure is probably higher than that because discordant MZ twins presumably share not only the specific genetic risk factor(s) for schizophrenia but also other genetically influenced characteristics—what Meehl (1990) calls polygenic potentiators—which may further increase the risk for psychiatric deterioration. Note that the logic of this paradigm does not depend on our knowing which of the at-risk subjects are truly at risk, only that we know that the experimental group differs from the comparison group in the base rate of the risk factor(s). Having a procedure that reliably identifies groups at differential risk allows us to identify potentially superior selection variables for future studies, a process dubbed *bootstrapping* (lifting oneself up by one's bootstraps) by Dawes and Meehl (1966).

Even through we can use bootstrapping operations without waiting to see who develops the disorder under study, the longitudinal design has some distinct advantages. In the Mednick and Schulsinger (1968) study, for example, subjects were matched in triplets (two at-risk and one comparison subject) on several potentially confounding variables. Because only a small proportion of the at-risk subjects would develop schizophrenia, this procedure provided both a matched comparison subject and a matched at-risk subject for each of the at-risk subjects who later developed schizophrenia. Comparing the at-risk and comparison groups at the initial assessment proved valuable, but the more sensitive comparison was between the subjects who went on to develop schizophrenia and their two matched "controls" (the matched at-risk subject and the matched comparison subject). This powerful and sensitive analysis was not possible until the subjects had been followed long enough to see which of them decompensated.

Behavioral High-Risk Paradigm

Identifying at-risk individuals on the basis of their familial relationship to someone with the disorder is one high-risk approach. Nevertheless, some disorders have weak genetic or familial contributions, rendering the genetic high-risk approach impractical. Even when there is a strong genetic or familial component, the genetic high-risk approach may produce a biased sample. For example, 95% of all patients who develop schizophrenia do not have a schizophrenic parent (Gottesman & Shields, 1972). These patients will not be represented in the genetic high-risk paradigm described above.

The behavioral high-risk paradigm identifies at-risk samples on the basis of behavior or life experiences. Chapman et al. (1978) identified individuals presumed to be at risk for schizophrenia on the basis of traits that Meehl (1964) argued were indicators of genetic risk for schizophrenia (e.g., anhedonia, intense ambivalence, body-image aberration, and magical ideation). A 10–12-year follow-up study (Chapman, Chapman, Kwapil, Eckblad, & Ainser, 1994) confirmed that these subjects are at elevated risk for severe psychopathology, although not necessarily schizophrenia. Nevertheless, long before the follow-up study had been completed, dozens of construct validation studies had been published suggesting that subjects identified by these trait measures exhibited characteristics that one might expect to find in someone at risk for schizophrenia. For example, these subjects showed mild forms of psychotic symptoms (e.g., Chapman et al., 1978), poor social functioning (e.g., Beckfield, 1985), and cognitive processing deficits (e.g., orienting response; Simons, 1981) similar to those reported in patients with schizophrenia. These studies increased confidence in the hypothesis that these subjects were at risk for psychopathology.

The behavioral high-risk strategy has also been used successfully by Depue and his collegues (e.g, Klein & Depue, 1984) in their studies of individuals at risk for bipolar disorder.

Computer Simulations

Parallel distributed processing (PDP) models are mathematical representations, implemented on a computer, of how a heavily interconnected system such as the brain might work. They produce what appears to be rule-based behavior without ever being taught rules, and they seem to learn in much the same way as humans, even to the point of producing similar errors during the learning process.

Cohen and Serban-Schreiber (1992) used PDP models in a series of studies of schizophrenic psychopathology. Because dopamine has been implicated in schizophrenia, they included a "gain" function in each of their simulations (i.e., a mathematical modulator for the overall operation of the model) to simulate the modulatory effect that dopamine would have on the system. They constructed three PDP models to simulate three very different cognitive tasks: (1) the Stroop Effect, (2) the Continuous Performance Test (CPT), and (3) a lexical ambiguity task. The relative performance of patients with schizophrenia had already been well established for the Stroop and CPT tasks. Without going into the technical details, they produced a model to simulate Stroop performance and trained it to perform as normal subjects are known to perform. They then adjusted the gain function until they produced the pattern of results shown by patients with schizophrenia. This first study showed that a systematic manipulation of a single parameter that was designed to simulate the effect of dopamine was sufficient to take a model that reproduced the pattern of results found in normals and make that model reproduce the pattern of results found in patients with schizophrenia. They then built and trained models to reproduce the performance of normals on the CPT, a measure of sustained concentration on which patients with schizophrenia tend to do poorly, and a lexical ambiguity task, on which patients with schizophrenia performed more poorly than normals in one condition but not in another (Cohen, Targ, Kristoffersen, & Spiegel, 1988). As in the Stroop Effect model, Cohen and Serban-Schreiber included a gain parameter in each of these models. They found that adjusting the gain function in these models to the same value that reproduced the pattern of Stroop performance found in patients with schizophrenia also reproduced the pattern of performance on these tasks shown by patients.

The studies reported by Cohen and Serban-Schreiber are an excellent set of construct validation studies. They took what we know about how the brain is wired (i.e., interconnected), what we know about the role of dopamine in normal brain activity (i.e., a modulatory effect), and the fact that dopamine appears to be important in schizophrenia. They then took several areas of cognitive functioning known to be disordered in schizophrenia and simulated each of them with a PDP model. By manipulating the single parameter of gain (designed to be analogous to the action of dopamine), they were able to simulate dramatically different deficits found in schizophrenia. Furthermore, they reproduced the finding in the lexical decision task that patients with schizophrenia are not deficient under certain circumstances, thus ruling out the possibility that the gain parameter simply lowers general performance. This study ties together the research literatures on brain structure and neurochemical and cognitive functioning in both normals and patients with schizophrenia. The manipulation of a single parameter repeatedly reproduced the pattern of findings from previous studies—findings that had previously been explained by invoking different constructs. A single construct (the presumed effect of dopamine) was able to explain each of these disparate findings—clearly an elegant and parsimonious solution to the problem of what underlies the deficits found in schizophrenia. In science, parsimony is considered a virtue (Popper, 1959).

Although the study by Cohen and Serban-Schreiber appears to be radically different from some of the other research approaches discussed in this chapter, it is conceptually identical to the paradigms already presented. The PDP models created by these authors are simply theoretical models of a complex process. These models may be too complex to be diagrammed in a simple flow chart, but they are theoretical models nonetheless. Once created, these computer models can be used to generate specific predictions that can be tested empirically. In effect, that is what Cohen and Serban-Schreiber did, except that the empirical data already existed in the literature. The PDP framework allows us to model complicated cognitive and per-

ceptual processes. In theory at least, this approach could identify promising variables to study in schizophrenia and may even pinpoint variables sufficiently sensitive to the pathology of schizophrenia to serve as markers of the disorder. But even with the "gee wiz" special effects of the computer, it remains a construct validation approach that is dependent on linking the predictions of the models to empirical data.

Conclusion

In this chapter, we reviewed a variety of research methods used by psychopathologists to identify the correlates and causes of mental disorders. Two consistent themes guided this chapter. First, psychopathological conditions are almost certainly multiply determined, and probably involve a complex interplay of both genetic and environmental influences. Second, each methodological approach has its own set of potential advantages and disadvantages. Both of these considerations suggest that the ideal research program in psychopathology incorporates several methodological approaches. By utilizing a number of these approaches in tandem, the researcher seeks to uncover converging evidence across diverse paradigms and thereby triangulate upon the etiology of a given form of psychopathology.

Because each methodological design is best suited for detecting certain potential causal factors, it is unlikely that a single design will ever provide a complete picture of the etiology of any mental disorder. For example, although epidemiological methods are well suited for ascertaining risk factors for psychopathology, they generally provide little information concerning either the genetic or environmental origins of these factors. In turn, although behavior-genetic methods are well suited for ascertaining the relative genetic and environmental influences on risk factors for psychopathology, they generally tell us little about how these influences are linked to the functioning of the central nervous system. For this information, we must instead turn to psychophysiological, neuropsychological, and brain-imaging studies, which, like epidemiological studies, cannot by themselves disentangle the relative contributions of genetic and environmental factors. In addition, because each of the methodological approaches discussed in this chapter is characterized by liabilities and potential biases, an exclusive reliance on one approach will often result in misleading conclusions.

As a result of these limitations, psychopathology investigators have increasingly turned to hybrid designs that simultaneously incorporate multiple methodological approaches. For example, many high-risk researchers have included indices of psychophysiological and neurotransmitter functioning in their investigations. A number of behavior-genetic researchers have included explicit measures of environmental factors in their studies, including those emphasized by epidemiologists (e.g., the social class and education of the adoptive parents). It is only by gradually and painstakingly piecing together evidence from a variety of admittedly imperfect approaches that researchers can hope to arrive at a better understanding of the causes of psychopathology.

Notes

1. A common misconception is that all twin studies involve studying twins that have been reared apart. Although the twins-reared-apart design has been used to study genetic influences, it is impractical in studying genetic influences in most forms of psychopathology because of the low base rate for these disorders.
2. Of course, MZ twins will always be the same sex because sex is genetically determined.
3. The Maudsley Twin Register was compiled from consecutive admissions (1948–1963) of patients to a large outpatient and a short-stay inpatient department at Maudsley Hospital in England.
4. Note that that adoption paradigms used in psychopathology research include all adopted probands and do not restrict their sample to just twins.
5. Of course, to conclusively determine whether this were so, one would have to rule out the possibility that the parent's genes also contribute to the child's anxiety.
6. Note that we tend to think of environment as the social environment of the individual. *Environment* actually refers to any external influence on the individual, and it might well include, for example, differences in diet or medical history.
7. The likelihood of each at-risk subject developing schizophrenia was approximately .10, Therefore, the likelihood of both members of a matched at-risk pair developing schizophrenia is only .01 (.10 × .10).

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