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THE ROLE OF GENDER DIFFERENCES IN THE REDUCTION OF ETIOLOGIC HETEROGENEITY IN SCHIZOPHRENIA

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ABSTRACT. *Recent research has shown a resurgence of interest in the study of gender differences in schizophrenia. Accumulated evidence suggests that, compared with women, men have a higher incidence of schizophrenia, earlier age of onset, poorer course and medication response, poorer premorbid social and intellectual functioning, fewer affective symptoms, lower family morbid risk of schizophrenia and affective disorders, more evidence of obstetric complications in their mothers, and greater structural brain abnormalities. The roles of estrogen, neurodevelopment, and family history of affective disorder are evaluated as co-contributors to the observed gender differences in schizophrenia. Particular emphasis is given to evaluating the hypothesis that men are more prone to a hypothesized poor-prognosis, neurodevelopmental subtype of schizophrenia, for which early environmental brain insults play an important etiologic role, whereas women may be more prone to a hypothesized good-prognosis, affective subtype that is genetically related to the affective disorders. This hypothesis is evaluated in terms of (a) its ability to account for gender differences in schizophrenia, (b) its ability to link differences in clinical presentation to proposed differences in etiology; and (c) its potential to generate testable predictions for future schizophrenia research. © 1998 Elsevier Science Ltd*

GENDER DIFFERENCES IN SCHIZOPHRENIA have been noted since Kraepelin (1919/1971) observed that dementia praecox seemed to be primarily a disorder of young men. In recent years, there has been increased interest in the role of gender in schizophrenia, and epidemiological research supports Kraepelin's contention that schizophrenia is more prevalent among men than women (Iacono & Beiser, 1992). Resurgence of interest in gender differences in schizophrenia is partially attributable to recent research efforts aimed at understanding heterogeneity in schizophrenia. Specifically, it is well known that schizophrenia is highly variable in its clinical presentation, and it is possible that such phenomenological heterogeneity reflects underly-

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ing pathophysiological (e.g., Buchanan & Carpenter, 1994) or etiological heterogeneity (e.g., Tsuang, Lyons, & Faraone, 1990). Identification of etiologically distinct subtypes would likely have a major impact on researchers' understanding of schizophrenia (Tsuang et al., 1990).

Research efforts to date have not yet succeeded in delineating meaningful subtypes of schizophrenia that correspond to different etiologies (McGuffin, Farmer, & Gottesman, 1987). To the extent that there are reliable gender differences in schizophrenia, however, gender may be a potential factor contributing to both phenomenological and etiological heterogeneity. Indeed, some researchers have suggested that gender differences in schizophrenia reflect the differential proneness of men and women to two different subtypes of schizophrenia (e.g., Castle, Sham, Wessely, & Murray, 1994; J. M. Goldstein, Santangelo, Simpson, & Tsuang, 1990). The purpose of this article is to review the evidence for gender differences in schizophrenia and the theories proposed to explain them. Particular emphasis is placed on critically evaluating the theory that men and women are differentially prone to different etiological subtypes of the disorder.

ARE THERE GENDER DIFFERENCES IN SCHIZOPHRENIA?

Gender differences in schizophrenia have been reported in a variety of areas including age of onset, incidence, course, premorbid adjustment, symptomatology and clinical presentation, structural brain abnormalities, family history, history of obstetric complications in their mothers, and fetal exposure to maternal influenza. Evidence for gender differences in each of these areas is briefly reviewed and evaluated separately in the following sections.

Age of Onset

Perhaps the most robust gender difference in schizophrenia is its earlier age of onset in men compared with women (e.g., Bardenstein & McGlashan, 1990; Castle, Abel, Takei, & Murray, 1995; DeLisi, 1992; Flor-Henry, 1985; Lewine, 1988; Lewine, Strauss, & Gift, 1981; Lewis, 1992; Seeman, 1982). Most studies have found that the mean age of onset for men is in the early 20s compared with the mid-to-late 20s for women (J. M. Goldstein, Tsuang, & Faraone, 1989; Katschnig & Lenz, 1988; Lewine, 1981; Lieberman et al., 1993; Loranger, 1984; Shtasel, Gur, Gallacher, Heimberg, & Gur, 1992; Szymanski et al., 1995; Wyatt, Alexander, Egan, & Kirch, 1988)—a mean difference of about 3 to 5 years that does not seem to be an artifact of diagnostic system (Lewine et al., 1981), the age distribution of the general population (Faraone, Chen, Goldstein, & Tsuang, 1994), or age at first hospitalization (Faraone et al., 1994; Häfner et al., 1994; Loranger, 1984; Szymanski et al., 1995). In addition, women have a second peak in illness onset during their mid-to-late 40s that is absent in men (Castle et al., 1995; Castle, Wessely, & Murray, 1993; Flor-Henry, 1990; Häfner et al., 1994).

Although the gender difference in age of onset of schizophrenia is largely uncontroversial, the past 3 years have witnessed renewed attention to this topic, largely because of its relation to another variable of interest (i.e., family history of the disorder). Specifically, recent research has suggested that the gender difference in age of onset holds for sporadic (i.e., nonfamilial) but not familial cases of schizophrenia (Albus et al., 1994; DeLisi et al., 1994; Gorwood, Leboyer, Jay, Payan, & Feingold, 1995; Kirov,

Jones, & Murray, 1994; Leboyer et al., 1992; Walsh et al., 1993). In other words, when considering only those patients with an affected first-degree relative, the gender difference in age of onset disappears.

Incidence

Although previous epidemiological data suggested that schizophrenia occurs equally often in the sexes (Dohrenwend & Dohrenwend, 1974; Lewine, Burbach, & Meltzer, 1984), more recent studies suggest that incidence rates are higher among men than women (see Iacono & Beiser, 1992). Results of a large community-based first-episode study (Iacono & Beiser, 1992) suggest that incidence of schizophrenia is roughly twice as high for men than women regardless of the particular diagnostic criteria used. As Iacono and Beiser (1992) noted, reliance on first-hospital-admission statistics was an important limitation of most earlier incidence studies that found equal prevalence rates of schizophrenia among men and women. For example, these studies were affected by factors including regional differences in hospitalization policies, lack of consistency in diagnostic rules across hospitals, omission of nonhospitalized schizophrenic patients, and inclusion of patients with delusional disorders.

Course of Illness

Accumulated evidence suggests that female schizophrenic patients have a more benign course of illness than men across a variety of operational definitions of course (for reviews, see Angermeyer, Goldstein, & Kuehn, 1989; J. M. Goldstein, 1988; Seeman, 1986), regardless of the particular diagnostic system used. In particular, compared with men, women have fewer hospitalizations (J. M. Goldstein, 1988; Haas, Glick, Clarkin, Spencer, & Lewis, 1990; Salokangas, 1983; Test, Burke, & Wallisch, 1990; but see Angermeyer, Kuhn, & Goldstein, 1990), shorter hospital stays (J. M. Goldstein, 1988; Salokangas, 1983; Test et al., 1990; but see Breier, Schreiber, Dyer, & Pickar, 1992; Haas et al., 1990), longer community survival (Eaton et al., 1992; Hogarty, Goldberg, Schooler, & Ulrich, 1974), more rapid symptom remission (Lieberman et al., 1993), and superior neuroleptic response and lower dose requirements prior to menopause (Andia et al., 1995; Dworkin & Adams, 1984; Seeman, 1983; Young & Meltzer, 1980; and for reviews see Jeste, Lindamer, Evans, & Lacro, 1996; Yonkers, Kando, Cole, & Blumenthal, 1992; but see Pinals, Malhotra, Missar, Pickar, & Breier, 1996). The gender difference in course may, however, be attenuated over time such that female schizophrenic patients do not have a more favorable outcome than male patients over long-term follow-up (i.e., 10 years and beyond; Childers & Harding, 1990; Opjordsmoen, 1991; but see Harrison, Croudace, Mason, Glazebrook, & Medley, 1996) perhaps due to a late deterioration in course for women but not for men (Opjordsmoen, 1991).

Premorbid Adjustment

There is a great amount of empirical literature supporting the longstanding clinical lore that schizophrenic men have poorer premorbid social adjustment than women. Specifically, compared with women, preschizophrenic men are more socially isolated and withdrawn, are less able to maintain friendships and sexual relationships, have lower levels of functioning outside the family (e.g., occupational functioning, commu-

nity involvement; Childers & Harding, 1990; Gittelman-Klein & Klein, 1969; J. M. Goldstein et al., 1989; M. J. Goldstein, Rodnick, Evans, May, & Steinberg, 1978; McGlashan & Bardenstein, 1990; Salokangas, 1983; Salokangas & Stengård, 1990; Shtasel et al., 1992; Westermeyer & Harrow, 1986; Zigler, Levine, & Zigler, 1977), have lower premorbid IQ and poorer school performance (see Aylward, Walker, & Bettes, 1984 for a review; Offord, 1974), exhibit more behavioral problems (e.g., discipline problems at school, criminal behavior) in childhood and adolescence (Salokangas, 1983; N. F. Watt, 1978), and are less likely to get married (Klorman, Strauss, & Kokes, 1977; Reich & Thompson, 1985; Walker, Bettes, Kain, & Harvey, 1985; D. C. Watt, Katz, & Shepherd, 1983; D. C. Watt & Szulecka, 1979; Zigler et al., 1977), although this last finding may be because men are more likely than women to have developed schizophrenia by the time they reach marriage age (D. C. Watt & Szulecka, 1979).

Symptomatology and Clinical Presentation

Although schizophrenic men and women are probably more similar than they are different in terms of clinical presentation (e.g., Bardenstein & McGlashan [1990] reported no gender differences in positive symptoms or thought disorder), there continues to be debate over whether there are gender differences in the clinical expression of the disorder. For example, men with schizophrenia seem to exhibit more antisocial behavior than women (McGlashan & Bardenstein, 1990), whereas women with schizophrenia exhibit more depressive symptoms (J. M. Goldstein & Link, 1988; Lewine, 1985; McGlashan & Bardenstein, 1990; Walker et al., 1985; but see Addington, Addington, & Patten, 1996), self-destructive behavior (J. M. Goldstein & Link, 1988; McGlashan & Bardenstein, 1990), and paranoia (Andia et al., 1995; J. M. Goldstein & Link, 1988) than men. Although several studies have reported that men with schizophrenia have more negative symptoms than women (Gur, Petty, Turetsky, & Gur, 1996; Hambrecht, Maurer, & Häfner, 1992; Lieberman et al., 1993; Nasrallah & Wilcox, 1989; Ring et al., 1991; Salokangas & Stengård, 1990; Shtasel et al., 1992), several others have found no gender differences (Addington et al., 1996; Andia et al., 1995; Breier et al., 1992; Lewine, 1985; Szymanski et al., 1995), and one found that women have more severe negative symptoms than men (Lewine & Meltzer, 1984).

Perhaps one reason for the inconsistencies in findings on gender differences in negative symptoms is the failure to distinguish between deficit and nondeficit negative symptoms, as Carpenter and his colleagues (e.g., Carpenter, Heinrichs, & Wagman, 1988) have advocated. Specifically, it is possible that negative symptoms in women are more likely to be secondary to depressive symptomatology (nondeficit symptoms), whereas negative symptoms in men are more likely to be a primary result of the disease process of schizophrenia (deficit symptoms). Indeed, there is evidence to suggest that men with schizophrenia are more likely than women to meet criteria for what Carpenter and his colleagues have termed the "deficit syndrome," suggesting that negative symptoms expressed by men may be a result of a different pathophysiological process than those expressed by women (Carpenter et al., 1988).

Structural Brain Abnormalities

The findings regarding gender differences in structural brain abnormalities are rather mixed. For example, there has been much recent attention to gender differences in ventricular enlargement, a consistently replicated brain abnormality in

schizophrenia (e.g., Deakin, 1994; Pfefferbaum et al., 1988; Weinberger & Wyatt, 1983; and see also Shelton & Weinberger, 1986, for a review) associated with negative symptoms (Andreasen, Ehrhardt et al., 1990; Andreasen, Olsen, Dennert, & Smith, 1982; Gur et al., 1994; Klausner, Sweeney, Deck, Haas, & Kelly, 1992; Lewis, 1990; Pakkenberg, 1987), poor premorbid functioning (Lewis, 1990; Weinberger, Cannon-Spoor, Potkin, & Wyatt, 1980), illness chronicity (Besson, Corrigan, Cherryman, & Smith, 1987; Klausner et al., 1992), and poor response to neuroleptic treatment (Lewis, 1990; Weinberger et al., 1980). Although the majority of studies reviewed by Goetz and van Kammen (1986) failed to find evidence of gender differences in ventricular enlargement, several more recent studies have suggested that lateral ventricle enlargement may be limited to men with schizophrenia (Andreasen, Ehrhardt et al., 1990; Andreasen, Swayze et al., 1990; Flaum, Arndt, & Andreasen, 1990; Johnstone et al., 1989), and a meta-analysis by Raz and Raz (1990) revealed that samples with larger proportions of men yielded greater ventricular enlargement effects. Nonetheless, although there is some debate (see Zigun, Daniel, Kleinman, & Weinberger, 1991, 1992) about the interpretation of the findings from one of these studies (Andreasen et al., 1990), other studies have yielded opposite findings—that female but not male schizophrenic patients had enlarged lateral ventricles relative to their respective control groups (Flaum et al., 1995; Nasrallah, Schwarzkopf, Olson, & Coffman, 1990), and one study did not find any gender differences (Lauriello et al., 1997).

Findings on gender differences in corpus callosal abnormalities are also mixed. Although increased callosal thickness seems to be associated with early onset and negative symptoms (for a review, see Coger & Serafetinides, 1990), poor prognostic factors that may be more common in men than women, three studies failed to find evidence that men with schizophrenia had abnormal corpus callosum thickness (Hauser et al., 1989; Hoff, Neal, Kushner, & DeLisi, 1994; Nasrallah et al., 1986), and two reported that men with schizophrenia had decreased thickness compared with control men (Raine et al., 1990; Woodruff, Pearlson, Geer, Barta, & Chilcoat, 1993). The findings for women with schizophrenia are equivocal, with two studies reporting decreased callosal thickness compared with control women (Hauser et al., 1989; Hoff et al., 1994), two reporting increased thickness (Nasrallah et al., 1986; Raine et al., 1990), and one reporting no significant difference in thickness compared with control women (Woodruff et al., 1993).

One possible confounding variable making it difficult to draw conclusions about gender differences in structural brain abnormalities is family history. Specifically, there is some evidence to suggest that structural brain abnormalities are more common in patients without schizophrenia in their first-degree relatives than in patients with a positive family history of the disorder (see Vita et al., 1994). Moreover, as discussed later, women may be more likely than men to have a positive family history of schizophrenia. One study (Vita et al., 1994) found evidence for an interaction between gender and family history such that a negative family history of schizophrenia (i.e., no affected first-degree relatives) was related to ventricular enlargement for male but not for female schizophrenic patients. Thus, it is important to take family history into account in studies examining gender differences in structural brain abnormalities.

Although the literature on gender differences in ventricular enlargement and callosal volume is rather inconsistent, it is possible that further examination of gender differences both in other specific brain regions and in overall brain structure will reveal clearer pictures. For example, two studies reported greater reduction in hippocampal and basal ganglia volume among men with schizophrenia than women (Bo-

gerts, Ashtari et al., 1990; Bogerts, Falkai et al., 1990), and there is some evidence to suggest that schizophrenic men have more overall evidence of structural brain abnormalities than do schizophrenic women. Specifically, one study (Lewine, Gulley, Risch, Jewart, & Houpt, 1990) found that schizophrenic men more frequently exhibited deviant magnetic resonance imaging (MRI) findings than schizophrenic women, although there was no consistent pattern to these deviant findings. That is, although schizophrenic men clearly had more morphological abnormalities than women, the specific abnormalities that schizophrenic men had were variable. Moreover, none of the schizophrenic women had deviant MRIs.

Family History

Several studies have found that, compared with men, women with schizophrenia have higher rates of the illness in their first-degree relatives (Bellodi et al., 1986; J. M. Goldstein, Faraone, Chen, Tolomiczencko, & Tsuang, 1990; J. M. Goldstein et al., 1989; Murray, Jones, O'Callaghan, Takei, & Sham, 1992; Shimizu, Kurachi, Yamaguchi, Torii, & Isaki, 1987; Wolyniec, Pulver, McGrath, & Tam, 1992) and higher monozygotic twin concordance rates (Kringlen, 1987; Rosenthal, 1970). As discussed previously, among men with schizophrenia, absence of a family history of schizophrenia is associated with increased ventricular enlargement (Vita et al., 1994). Taken together, these findings have led to the speculation that schizophrenic men are more likely than women to have a sporadic form of the illness for which environmental factors contributing to brain injury are particularly important (Castle & Murray, 1991; DeLisi, Goldin, Maxwell, Kazuba, & Gershon, 1987; Nasrallah & Wilcox, 1989).

Schizophrenia and affective disorders co-occur in some families (Kendler, McGuire, Gruenberg, & Walsh, 1995; Maier et al., 1993; M. A. Taylor, 1992), and it is interesting that indirect evidence suggests that family members of schizophrenic women in particular may have an increased morbid risk of affective disorder in addition to their increased morbid risk of schizophrenia. Specifically, studies have consistently reported that good-prognosis schizophrenia with affective features (which is more common in women than men) is associated with an increased risk of affective disorder in family members (DeLisi et al., 1987; Kendler & Hays, 1983; Kendler & Tsuang, 1988; McCabe, Fowler, Cadoret, & Winokur, 1971; Pope, Cohen, Lipinski, & Yurgelun-Todd, 1988; Pope & Lipinski, 1978; Sham, MacLean, & Kendler, 1994). By one estimate, good-prognosis schizophrenic patients, regardless of gender, have two to three times as much affective disorder as schizophrenia in their families, suggesting that good-prognosis schizophrenia is genetically related to affective disorder. The reverse is true for poor-prognosis schizophrenic patients, who have two to three times as much schizophrenia as affective disorder in their families (Pope & Lipinski, 1978). It is interesting to note that schizoaffective disorder is associated with a less chronic course and better prognosis than schizophrenia (Kendler et al., 1995) as well as increased rates of both schizophrenia and affective disorders among relatives (Kendler et al., 1995; Maier et al., 1993). However, cases of good-prognosis schizophrenia do not necessarily meet *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. *[DSM-IV];* American Psychiatric Association, 1994) criteria for schizoaffective disorder. Schizoaffective patients must have diagnosable schizophrenia concurrently with an episode of a major affective disorder for a substantial period of time, while at other times experience hallucinations and delusions in the absence of affective symptoms. Thus, although good-prognosis schizophrenia does not have a one-to-one correspon-

dence with *DSM-IV* schizoaffective disorder, perhaps it is best conceptualized as including, but not limited to, cases of schizoaffective disorder. Indeed, as M. A. Taylor (1992) noted, given evidence of genetic overlap between schizophrenia and affective disorders, the exclusion of schizoaffective disorder from studies examining their relation may be unjustified.

Obstetric Complications and Early Brain Injury

If men with schizophrenia are more likely than women to have a sporadic form of the illness associated with environmental insults to the brain, one might expect schizophrenia in men to be associated with a history of obstetric complications in their mothers (e.g., fetal distress, prolonged labor, breech birth, umbilical cord prolapse), which are often, although not always, associated with cerebral dysfunction. Indeed, obstetric complications and early brain injury have been shown to be associated with early onset, poor-prognosis, nonfamilial schizophrenia (Cantor-Graae, McNeil, Sjöström, Nordström, & Rosenlund, 1994; DeLisi et al., 1987; O'Callaghan, Larkin, Kinsella, & Waddington, 1990) as well as male gender (Nasrallah & Wilcox, 1989; O'Callaghan et al., 1992; Owen, Lewis, & Murray, 1988; but see Verdoux & Bourgeois, 1993).

Maternal Influenza

Maternal influenza has received some attention as a possible environmental contributor to schizophrenia etiology because several studies have reported that exposure to world-wide influenza epidemics, particularly in the second trimester of gestation, is associated with an increase in schizophrenic births (Adams, Kendell, Hare, & Munk-Jørgensen, 1993; Barr, Mednick, & Munk-Jørgensen, 1990; Fahy, Jones, Sham, Takei, & Murray, 1993; Kunugi, Nanko, & Takei, 1992; Mednick, Huttunen, & Machon, 1994; Mednick, Machon, & Huttunen, 1990; Mednick, Machon, Huttunen, & Bonett, 1988; O'Callaghan, Sham, Takei, Glover, & Murray, 1991; Sham et al., 1992; Takei et al., 1994, 1996; Welham, McGrath, & Pemberton, 1993). Of those studies that examined the influenza effect separately by gender, some reported that it is confined to the birth of schizophrenic women (Adams et al., 1993; Mednick, Machon, Huttunen, & Barr, 1990; O'Callaghan et al., 1991; Takei et al., 1994), whereas others did not find such gender differences (Mednick et al., 1988; Takei, Van Os, & Murray, 1995; Takei, Lewis et al., 1996). It is possible that the influenza effect acts in conjunction with the genetic predisposition to cause schizophrenia (Castle et al., 1995; Mednick et al., 1988; Murray, Jones et al., 1992; Pulver et al., 1992). Consistent with this notion, one study found that schizophrenic women born in winter or spring (who would have had an increased likelihood of fetal exposure to influenza) had a higher than expected familial loading for the illness (Pulver et al., 1992). As Mednick et al. (1988) suggested, perhaps exposure to influenza leads to schizophrenia only when a genetic predisposition is also present. Conversely, as Murray, Jones, et al. (1992) speculated, perhaps the genetic predisposition itself is related to a propensity to respond abnormally to exposure to influenza.

Summary and Integration of Findings

In sum, the gender-differences literature on schizophrenia suggests that men and women do differ and that these differences span a variety of areas. The most robust

and consistently replicated findings seem to be that, compared with women, men have an earlier age of illness onset, poorer course and outcome, fewer affective symptoms, poorer premorbid functioning, a greater history of obstetric complications in their mothers, and a lower familial loading for schizophrenia and affective disorder.

Existence of gender differences in schizophrenia seems clear; however, an important question to consider is whether these differences are specific to the diagnosis of schizophrenia or whether they are similar to gender differences in other disorders (J. M. Goldstein & Tsuang, 1990). There is also the possibility that some gender differences in schizophrenia reflect an overlay of gender differences in normal personality. For example, among psychiatric and normal populations, antisocial behavior seems to be more common among men than women (Bardenstein & McGlashan, 1990; McGlashan & Bardenstein, 1990). In contrast, there is evidence to suggest that several of the gender differences reviewed previously are specific to schizophrenia. For example, the direction of the gender difference in age of onset for unipolar depression is the opposite of that for schizophrenia—Men tend to have a later onset than women (Bardenstein & McGlashan, 1990; Lewine, 1981; Lewine et al., 1981). Similarly, in contrast to schizophrenia, bipolar illness is characterized by higher remission rates for men than women (Bardenstein & McGlashan, 1990).

Clearly, there is evidence for systematic gender differences specific to schizophrenia; however, it is important to point out that (a) not all schizophrenic men and women differ on these variables (J. M. Goldstein & Tsuang, 1990) and that (b) another variable, age of onset, has also been found to have strong associations with the same variables that are related to gender (Lewine, 1981). For example, early onset schizophrenia is associated with poor premorbid adjustment (Lewine, 1981), negative symptoms (Katschnig & Lenz, 1988), poorer course (Eaton et al., 1992), and obstetric complications in mothers (Kirov et al., 1996; McNeil & Kaij, 1978; Murray, 1994; Nasrallah & Wilcox, 1989). Thus, it seems unlikely that schizophrenia consists simply of a male subtype and a female subtype. Researchers including Goldstein and her colleagues (e.g., Goldstein, Santangelo et al., 1990; J. M. Goldstein et al., 1989) have suggested that it is more likely that there are two subtypes of schizophrenia for which men and women are at different risks: (a) an early onset type that is more prevalent in men, which is characterized by a chronic course and poor prognosis, poor premorbid adjustment, negative symptoms, structural brain abnormalities, and obstetric complications, and (b) a later onset type that is more prevalent in women, which is characterized by a more remitting course and better prognosis, better premorbid adjustment, affective symptoms, and a family history of affective psychosis.

Results of several studies support the notion that gender differences in schizophrenia reflect differential risks for different subtypes of the disorder. Goldstein et al. (1989) found that men with schizophrenia had earlier onset, poorer premorbid functioning, lower family morbid risk of schizophrenia, lower remission rates, higher rehospitalization rates, and poorer social and occupational functioning compared with women. Similarly, results of two studies using latent class analysis suggest that schizophrenia can be divided into subtypes that are not restricted on the basis of gender but have different prevalence rates among men and women (Castle et al., 1994; Goldstein, Santangelo et al., 1990). Specifically, one study found support for two well-defined subtypes: one characterized by early onset, poor premorbid social functioning, and restricted affect (which was more than twice as likely to appear in men than women) and a second characterized by later onset and persecutory delusions with a roughly equal sex ratio. A third subtype, characterized by dysphoria and persecutory delu-

sions, was largely confined to women and received less clear empirical support (Castle et al., 1994). Similarly, another study (J. M. Goldstein, Santangelo et al., 1990) found support for two subtypes, the first characterized by low family morbid risk, deficit symptomatology, poor premorbid functioning, and winter birth (which was more prevalent in men) and the second characterized by dysphoria, persecutory delusions, and higher family morbid risk (which was more prevalent in women). Nonetheless, the subtypes did not have a one-to-one correspondence with gender, as some men met criteria for the predominantly female subtype and some women met criteria for the predominantly male subtype. Thus, both of these studies suggest that men and women can express one of two subtypes of schizophrenia but are at different risks for each of these on the basis of their sex.

FACTORS CONTRIBUTING TO GENDER DIFFERENCES IN SCHIZOPHRENIA

The Role of Psychosocial Factors

Some researchers have suggested that gender differences in schizophrenia are a result of differential susceptibility to stress. Three separate arguments have been presented: (a) that men experience more interpersonal stress than women, (b) that men are more vulnerable to adverse effects of stress, and (c) that stressful role demands occur earlier for men than for women (Lewine, 1981). However, there is very little empirical support for these psychosocial explanations. For example, although Maccoby and Jacklin (1974) reported that nonill men experience more interpersonal aggression than women, recent data from the National Comorbidity Survey (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) indicate that certain types of interpersonal trauma are more prevalent among men than women (e.g., physical attack, threat with a weapon), whereas other types are more common among women than men (e.g., rape, molestation, physical abuse). Furthermore, there is no empirical evidence to suggest that exposure to interpersonal aggression is important in the etiology or course of schizophrenia. Similarly, although there is evidence that environmental stress has more deleterious consequences for male rats than for female rats (e.g., Feldon & Weiner, 1992), it is difficult to argue that humans show similar sex differences. Humans experience a wide variety of environmental stressors, and there is some evidence to suggest that some of these are more aversive to men and others more aversive to women (Al-Issa, 1985; Mednick et al., 1978). Finally, the third psychosocial hypothesis presents the problem of operationalizing the concept of "role demands," and it is unable to account for the fact that similar gender differences have been observed across cultures despite cultural differences in gender role demands. Moreover, none of these psychosocial stress explanations is likely to account for the gender differences in structural brain abnormalities or family history of schizophrenia.

Gender differences in social behavior have also been proposed as potential contributors to gender differences in schizophrenia. Specifically, preschizophrenic girls are more shy and less sociable than other girls, whereas preschizophrenic boys are more aggressive and delinquent than other boys (N. F. Watt, 1978). Seeman (1985) suggested that sociability (which preschizophrenic girls lack) may be a protective factor for women, whereas aggressive behavior (which preschizophrenic boys exhibit in excess) may be a precipitating factor in men. However, the suggestion that poor social skills or aggressiveness are causal factors in the development of schizophrenia is entirely speculative and lacking in empirical support. In addition, this line of reasoning

ignores the obvious alternative interpretation that the abnormal behavior of preschizophrenic children is a premorbid manifestation of the disease process.

The Role of Estrogen

Several researchers have argued that estrogen has antipsychotic effects similar to neuroleptic drugs and thus may have a protective effect in schizophrenic women (Al-Issa, 1985; Castle et al., 1995; Seeman, 1982; Seeman & Lang, 1990). Dopamine overactivity is thought to play an important role in accounting for some of the symptoms of schizophrenia (Davis, Kahn, Ko, & Davidson, 1991; Meltzer, 1992). Estrogen, like neuroleptic drugs, seems to achieve its antipsychotic effect by blocking or decreasing the sensitivity of dopamine receptors or by inhibiting dopamine synthesis (Häfner, Behrens, DeVry, & Gattaz, 1991; Seeman & Lang, 1990). Clinical observations as well as empirical data suggest that, when estrogen levels are low (i.e., premenstrually, postpartum, and postmenopause), schizophrenic women tend to experience symptom exacerbations, and when psychotic they do not differ from men in the severity of their positive symptoms. In contrast, when estrogen levels are high (i.e., during pregnancy), women experience psychotic symptom remission (Riecher-Rössler, Häfner, Stumbaum, Maurer, & Schmidt, 1994; Seeman & Lang, 1990). As discussed previously, premenopausal schizophrenic women also respond to lower doses of neuroleptic medication than schizophrenic men and postmenopausal women.

Estrogen may also contribute to the later age of onset in women as opposed to men with schizophrenia. Specifically, binding to the D2 dopamine receptor peaks later in women than in men, perhaps due to the differential effects of sex hormones (Wong et al., 1984). As Weinberger (1986) suggested, such peak in dopamine activity during early adulthood makes it a time of particularly high risk for onset of psychosis. Thus, the gender difference in age of onset in schizophrenia may be largely a function of sex per se rather than a function of illness subtype. This possibility is consistent with the findings of Goldstein, Santangelo et al. (1990), which indicate that schizophrenic men tend to have an earlier age of onset than women regardless of which subtype they express. In contrast, Szymanski et al. (1996) found no gender differences in age of onset among a sample of neuroleptic treatment refractory schizophrenic patients (who tend to have a more severe course and poor prognosis), consistent with the notion that age of onset is a function of subtype rather than sex. Clearly, additional research is necessary to determine whether age of onset is a function of sex or subtype.

If gender differences in the age of onset of schizophrenia are largely a function of sex rather than subtype, we are left with the problem of explaining why the gender difference in age of onset of schizophrenia disappears when considering only familial cases of the illness. Some have interpreted these findings as evidence that the later age of onset in women is not simply a function of the protective effects of estrogen (Murray, 1994). Although it is possible that estrogen plays a role in delaying schizophrenia onset in women, in the presence of a high genetic loading for the illness (i.e., as in the case of one or more affected first-degree relatives), genetic factors may override the effects of sex hormones in determining age of onset (DeLisi, 1992; DeLisi et al., 1994).

Estrogen may also help to explain other gender differences in schizophrenia. Specifically, the menopausal decline in estrogen levels may leave women more vulnerable to onset of psychosis, perhaps contributing to women's second peak in onset during the mid-to-late 40s and attenuation of gender differences in long-term outcome. Similarly, the neuroleptic-like effects of estrogen are likely to contribute to women's supe-

rior response to neuroleptic medication. That is, women may require less neuroleptic medication than men to achieve symptom remission because estrogen acts like a natural neuroleptic.

The protective effects of estrogen seem to contribute to some of the gender differences in schizophrenia (e.g., age of onset, severity of course, response to neuroleptic treatment), but alone hormonal influences cannot account for the fact that not all schizophrenic men and women differ on these variables. Similarly, the estrogen hypothesis cannot adequately account for the role of obstetric complications and structural brain abnormalities in the etiology of schizophrenia. Clearly, other influences are implicated in contributing to schizophrenia gender differences.

The Role of Neurodevelopment

As noted before, evidence for gender differences in schizophrenia is consistent with the hypothesis that men and women are at different risks for different subtypes of the disorder. Several researchers, particularly Castle and Murray and their colleagues (Castle & Murray, 1991; Castle et al., 1995, 1994, 1993; Murray, 1994; Murray, O'Callaghan, Castle, & Lewis, 1992), have further argued that the predominantly male form of schizophrenia is characteristic of a neurodevelopmental disorder, whereas the predominantly female form may be etiologically related to the affective disorders.

Although researchers initially thought that structural brain abnormalities in schizophrenia resulted from a neurodegenerative process (Murray, Jones et al., 1992), recent research supports the idea that the process is neurodevelopmental rather than neurodegenerative in nature. For example, structural brain abnormalities are associated with poor premorbid adjustment in childhood (Harvey, Ron, de Boulay, & Wicks, 1993; Murray, Jones et al., 1992; Shelton & Weinberger, 1986) and are not correlated with the duration of schizophrenic illness (Bogerts, 1989), suggesting that brain impairment has effects long before the onset of psychosis. Also consistent with a neurodevelopmental rather than a neurodegenerative process, gliosis (i.e., the normal response of glial cells to neuronal damage) has been found to be absent among schizophrenic patients (Bogerts, 1989; Bogerts, 1993; Falkai, Bogerts, & Rozumek, 1988; Roberts, 1991). In addition, evidence that schizophrenic patients have reduced hippocampal volume (Bogerts, Ashtari et al., 1990; Bogerts, Falkai et al., 1990; Bogerts, Meertz, & Schonfeldt-Bausch, 1985; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990) is also consistent with neurodevelopmental damage. Because the hippocampus reaches its adult volume by 2 years of age, decreased volume in schizophrenic patients suggests neurodevelopmental impairment occurring before the onset of the illness.

Consistent with a neurodevelopmental origin, male schizophrenic patients, more often than female patients, have evidence of structural brain abnormalities and histories of obstetric complications. Moreover, men seem to have a lower genetic loading for the illness than women. These findings together suggest that certain types of early environmental brain insults (e.g., obstetric complications) may be more important in the pathogenesis of schizophrenia among men than women (Castle & Murray, 1991; DeLisi et al., 1987; Nasrallah & Wilcox, 1989). Moreover, as is characteristic of other neurodevelopmental disorders, schizophrenia in men is frequently associated with poor premorbid social adjustment, low premorbid IQ, and poor school performance. Finally, negative symptoms may be more common in men than women, and they seem to occur in association with structural brain abnormalities (Andreasen et al., 1990; An-

dreasen & Olsen, 1982; Crow, 1985; Kemali et al., 1987; Klausner et al., 1992; A. O. Williams, Reveley, Kolakowska, Ardern, & Mandelbrote, 1985).

In a particularly interesting series of studies examining the childhood home movies of schizophrenic patients, Walker and her colleagues reported evidence consistent with a neurodevelopmental etiology in a subgroup of patients. Specifically, they (Walker, Grimes, Davis, & Smith, 1993; Walker & Lewine, 1990) found that, compared with their healthy siblings, preschizophrenic children were less responsive to others, showed less positive affect, and poorer motor coordination, again suggesting existence of early neurological damage predating the onset of the disorder. Although the small number of women in this sample limited the ability to examine gender differences, further research (Neumann, Grimes, Walker, & Baum, 1995) revealed that preschizophrenic children could be subdivided into two clusters, one of which showed more progressive behavior problems (i.e., worsening over time), greater neuromotor abnormalities, and an earlier age of onset than the other. The authors concluded that presentation of this subgroup was consistent with neurodevelopmental schizophrenia.

Evidence from twin studies supports the hypothesis that early environmental brain insult contributes to etiology of this proposed neurodevelopmental form of schizophrenia. Specifically, two studies found that schizophrenic probands have significantly larger cerebral ventricles than their unaffected monozygotic co-twins (Reveley, Reveley, Clifford, & Murray, 1982; Suddath et al., 1990). Because cerebral ventricle size is usually highly correlated among monozygotic twins, these results suggest that some environmental insult (e.g., obstetric complications) affected one twin more than the other, contributing to development of schizophrenia in that twin (Murray, Jones et al., 1992).

Existence of a neurodevelopmental form of schizophrenia that occurs primarily in men is also consistent with evidence that, in general, men have a higher prevalence of neurodevelopmental disorders such as autism, mental retardation, stuttering, and dyslexia (Castle et al., 1995; Castle & Murray, 1991; Geschwind & Galaburda, 1985; Murray, Jones et al., 1992). Men seem to be more prone than women to such disorders primarily because of sex differences in the development of the central nervous system that leave males more vulnerable to neurological insult. First, the central nervous system develops more slowly in males than in females, leaving male brains vulnerable to insult for a longer period of time (Geschwind & Galaburda, 1985; Seeman, 1989; D. C. Taylor, 1969). Second, there is evidence that male brains show greater hemispheric lateralization than female brains, perhaps resulting in decreased ability to compensate for early damage to one hemisphere (Al-Issa, 1985; Diamond, 1989; Flor-Henry, 1985; McGlone, 1980; Seeman, 1982). Specifically, both dichotic listening (Hiscock, Inch, Jacek, Hiscock-Kalil, & Kalil, 1994) and tachistoscopic (Hiscock, Israelian, Inch, Jacek, & Hiscock-Kalil, 1995) paradigms suggest that the left hemisphere is more specialized for language among men than women. Furthermore, evidence that residual speech disorders following stroke or left temporal lesioning are more severe in men than in women (for a review, see McGlone, 1980) is consistent with the suggestion that males are less able than females to compensate for unilateral brain damage. Third, there is some limited evidence suggesting that males are more prone than females to prenatal abnormalities of neuronal migration (Geschwind & Galaburda, 1985), obstetric complications (Cantor-Graae et al., 1994), and preterm birth (Berkowitz & Papiernik, 1993). Furthermore, it is well established that males more often than females suffer neurological impairment as a result of such complications (e.g., Rantakallio & von Wendt, 1985). Thus, if a form of schizophrenia is neurodevelopmental in origin, it is not surprising that men would be more prone to it than women.

The Role of Family History of Affective Disorder

Whereas neurodevelopmental schizophrenia may be more common among men, a second subtype of schizophrenia, which is genetically related to affective disorder, may be more common among women (Castle & Murray, 1991; Castle et al., 1995, 1993; Flor-Henry, 1990; Sham, MacLean, & Kendler, 1994). Recall that women with schizophrenia tend to have more affective symptomatology than men and have increased family morbid risk of affective disorder. Thus, the hypothesis that women do indeed tend to have a subtype of schizophrenia that is genetically related to affective disorders could help to explain their later age of onset, more benign illness course, better premorbid social and intellectual functioning, and relative absence of structural brain abnormalities and obstetric complications. Consistent with an affective subtype of schizophrenia, Grimes and Walker (1994) found that expression of negative emotion (perhaps reflecting depression) among preschizophrenic children was associated with a later age of onset and good prognosis, although the small number of women in their sample precluded their ability to examine gender differences.

If a good-prognosis form of schizophrenia is genetically related to affective disorders, it remains unclear why some individuals predisposed to affective disorder later develop an illness diagnosed as schizophrenia. Some researchers (e.g., Murray, O'Callaghan et al., 1992) have suggested that the gene(s) implicated in this illness can vary phenotypically, being expressed alternatively as affective psychosis, schizoaffective disorder, or a form of schizophrenia. Another possibility is that fetal exposure to maternal influenza redirects women predisposed to affective disorder to schizophrenia, a scenario that Takei and colleagues (Takei, O'Callaghan, Sham, Glover, & Murray, 1993) refer to as "phenotypic diversion." Indeed, these researchers have reported that the increase in births of schizophrenic females following an influenza epidemic was accompanied by a corresponding decrease in births of females diagnosed with ICD 8 or 9 (World Health Organization, 1978) affective psychosis. The authors speculated that exposure to influenza during a crucial time in pregnancy may cause subtle neurodevelopmental changes in fetuses predisposed to affective disorder such that they later exhibit clinical phenomenology resembling schizophrenia (Takei et al., 1993). Although this hypothesis has yet to be directly tested, there is some evidence that fetal exposure to influenza during the second trimester is associated with neurodevelopmental deviance. Specifically, among schizophrenic patients, exposure to influenza during this time period has been linked to obstetric complications and low birth weight (Wright, Takei, Rifkin, & Murray, 1995) and to enlargement of cerebrospinal fluid spaces, particularly the sylvian fissure in the temporal lobe (Takei, Lewis, Jones, Harvey, & Murray, 1996). Nonetheless, it is important to recognize that only a small proportion (e.g., 1–4%) of cases of schizophrenia is associated with fetal exposure to influenza (Barr et al., 1990; Sham et al., 1992). Thus, even if influenza does cause phenotypic diversion from affective disorders to schizophrenia, this effect would only hold for a small minority of individuals.

CONCLUSIONS AND FUTURE DIRECTIONS

Together, theories about the roles of estrogen, neurodevelopment, and family history of affective disorder are compelling, largely because of their power to integrate the wide variety of findings of gender differences in schizophrenia. Estrogen may contribute to gender differences in age of onset and illness course, whereas gender differ-

ences in neurodevelopmental deviance and family history of affective disorder may contribute to poorer premorbid functioning, more severe negative symptoms, fewer affective symptoms, less family history of schizophrenia and affective disorders, and more evidence of structural brain abnormalities and obstetric complications in mothers among men than women.

Although research on gender in schizophrenia has been fruitful thus far, revealing differences between men and women across a wide variety of domains, the incontrovertible fact remains that not all men and women differ. Thus, if etiologically distinct subtypes of schizophrenia do exist, they are not likely to be defined strictly along the lines of gender. That is, although men may be more likely to express the hypothesized neurodevelopmental subtype of schizophrenia and women the affective subtype, the former is not limited to men and the latter is not limited to women.

It is important to note that several researchers (e.g., Cardno & Farmer, 1995; Crow, 1995; Goldberg & Weinberger, 1995; McGuffin et al., 1987) have argued against etiologic subtypes in schizophrenia on the grounds that phenotypic heterogeneity in schizophrenia may not reflect underlying etiologic heterogeneity but rather quantitative differences along a continuum of severity (Goldberg & Weinberger, 1995) or genetic liability (McGuffin et al., 1987). Thus, it is crucial that future research examine the evidence that the putative neurodevelopmental and affective subtypes reflect discrete disease entities. Cloninger and colleagues (Cloninger, Martin, Guze, & Clayton, 1985) have outlined progressive criteria for the validation of a disease construct at three levels: clinical syndrome, discrete clinical disorder, and pathophysiologic entity. For example, to demonstrate that neurodevelopmental schizophrenia comprises a clinical syndrome, research must show that it is a homogeneous classification associated with a temporally stable pattern of intercorrelated signs and symptoms occurring within the same patients and that these signs and symptoms distinguish it from affective schizophrenia. At the next level, establishing that neurodevelopmental and affective schizophrenia are discrete clinical disorders requires that each has explicit inclusion and exclusion criteria and distinct boundaries from each other as well as other disorders (e.g., symptoms of the two subtypes should be bimodally distributed, and mixed cases of neurodevelopmental and affective schizophrenia should be rare). At the third level, demonstrating that the putative subtypes are distinct pathophysiologic entities requires the identification of genetic and environmental risk factors for each and the pathophysiological pathways by which these risk factors lead to the disease subtype.

Another step in the validation process will be to determine which variables of interest are related to subtype and which are related to gender per se. To tease apart the relations among gender, subtype membership, and variables of interest, researchers must develop operational criteria with which to categorize schizophrenia patients with either the neurodevelopmental or affective subtypes. Then, comparisons on variables of interest (e.g., age of onset, deficit symptomatology, structural brain abnormalities) could be made not only among subtypes but between genders within each subtype. In conducting this research, it is also important to keep in mind the role of estrogen by taking into account age, menstrual status (e.g., pre- or postmenopausal), and stage in the menstrual cycle when conducting (particularly psychopharmacological) studies with women.

Operational criteria for neurodevelopmental and affective schizophrenia should include variables that (a) are reliably linked to the given subtype and (b) can be rated with a high degree of interrater reliability. Lewis (1992) offered the following criteria

for the neurodevelopmental subtype: age of onset before 25, no family history of schizophrenia, and the presence of premorbid deficits, neurodevelopmental abnormality (e.g., cognitive or motor delays), and childhood neurological disorder. Several issues need to be considered, however, before adopting these criteria. First, it is unclear whether age of onset should be included as a criterion for either the neurodevelopmental or the affective subtypes in light of the possibility that this variable is more reliably related to gender per se than to the particular subtype expressed. Second, the nature of the premorbid deficits needs to be specified. For example, patients scoring below a predetermined cutoff score on premorbid social adjustment rating scales might be classified as having premorbid deficits. Third, a decision rule must be adopted specifying the required number of criteria necessary for a patient to be classified as having neurodevelopmental schizophrenia. It seems unlikely that many patients would satisfy all of the aforementioned criteria, particularly childhood neurological disorder. That is, it is possible that the neurodevelopmental abnormality in schizophrenia may be too subtle to be recognized in childhood. Perhaps this criterion could be replaced with evidence of obstetric complications in mothers, although this information may be frequently unavailable or difficult to obtain. Criteria for the affective subtype could be operationalized in a similar way. For example, these might include positive family history of schizophrenia or affective disorder, prominent affective symptomatology (e.g., dysphoria), good premorbid functioning, and no history of obstetric complications in mothers.

Perhaps a useful starting point for researchers would be to categorize as neurodevelopmental schizophrenia all cases in which there is evidence of developmental anomaly (e.g., premorbid social or intellectual deficits, obstetric complications) in the absence of clear-cut affective symptomatology and family history of affective disorder. Conversely, all cases in which there is evidence of clear-cut affective symptomatology or family history of affective disorder in the absence of developmental anomaly could be categorized as affective schizophrenia.

It is important to point out that it is unlikely that the proposed neurodevelopmental and affective subtypes will account for all cases of schizophrenia, and further research may reveal evidence for additional subtypes. Alternatively, some cases of schizophrenia may be difficult to classify or may be conceptualized as mixed cases of neurodevelopmental-affective schizophrenia, such as those in which there is evidence of neurodevelopmental anomaly in conjunction with affective symptomatology or family history of affective disorder. As discussed previously, however, establishing the rarity of such mixed cases is one of the goals for validating a clinical syndrome. Thus, existence of such mixed cases does not necessarily invalidate the typology.

The neurodevelopmental-affective subtyping scheme is not the first attempt to reduce the heterogeneity in schizophrenia. However, there is little evidence to suggest that existing subtyping schemes reflect underlying etiologic heterogeneity in schizophrenia. For example, the *DSM-IV* (American Psychiatric Association, 1994) currently distinguishes among paranoid, disorganized, catatonic, and undifferentiated types of schizophrenia, and empirical support has been found for Tsuang and Winokur's (1974) similar phenotypic distinction between paranoid and hebephrenic subtypes (Farmer, McGuffin, & Gottesman, 1984; Farmer, McGuffin, & Spitznagel, 1983; J. Williams, Farmer, Wessely, Castle, & McGuffin, 1993). However, considering Farmer et al.'s (1984) finding that co-twins of hebephrenic probands had elevated rates of both hebephrenic and paranoid schizophrenia, these subgroups are likely to reflect differences in severity rather than etiology (Goldberg & Weinberger, 1995; J. Williams et al., 1993).

Other typologies postulate syndromes with different pathologies but not necessarily different etiologies. Crow's (1985) typology distinguishes between Type I and Type II syndromes, which are conceptualized as independent but not etiologically distinct processes. Both Type I (a drug-responsive syndrome related to dopaminergic transmission and associated with positive symptoms) and Type II (a drug-nonresponsive syndrome related to structural brain abnormalities and associated with negative symptoms and poor prognosis) can co-occur in a given patient. Similarly, the deficit–nondeficit distinction (Carpenter et al., 1988) differentiates between negative symptoms that are hypothesized to be a direct result of the disease process and those that are secondary to other symptoms or medication effects. Although the Type I–Type II and deficit–nondeficit distinctions are not identical to the neurodevelopmental-affective subtyplogy, there is likely a good deal of overlap between these classifications. Further research might examine the hypotheses that the Type II and deficit syndromes are more common in neurodevelopmental schizophrenia, whereas the Type I and nondeficit syndromes are more common in affective schizophrenia.

The neurodevelopmental-affective distinction was largely empirically derived through the use of statistical clustering methods such as latent class analysis. The advantage of such a typology is in its potential to lead to more reliable and homogeneous classification of schizophrenic patients (Skinner, 1981). Thus, although the neurodevelopmental-affective subtyping scheme is empirically derived, it is nonetheless grounded in a theoretical model from which researchers can make testable predictions. For example, longitudinal studies could test the prediction that patients meeting the criteria for neurodevelopmental schizophrenia will have a poorer course and outcome than patients meeting the criteria for affective schizophrenia. Evidence that subtypes differ as predicted on variables of interest would suggest that the proposed categorization criteria have predictive validity and that the theoretical framework (i.e., the distinction between neurodevelopmental and affective schizophrenia) is meaningful. In contrast, the failure to confirm these predictions would suggest either (a) the need to revise criteria by which the subtypes have been operationally defined or (b) the need to revise the theory on which these predictions were based (Skinner, 1981).

Neuropsychology will undoubtedly be a particularly important area of emphasis for future research in this area. Studies should test the prediction that the putative neurodevelopmental and affective subtypes of schizophrenia will be associated with differential performance on neuropsychological tests. Specifically, patients with the neurodevelopmental subtype of schizophrenia might be expected to do more poorly than patients with the affective subtype on neuropsychological tests. Consistent with this prediction, one study (J. M. Goldstein, Seidman, Santangelo, Knapp, & Tsuang, 1994) found that adult schizophrenic patients who had early developmental problems (e.g., educational problems) showed more impairment in verbal ability, attention, abstraction, motor speed, and verbal and visual memory than other schizophrenic patients. Moreover, the group with early developmental problems and neuropsychological impairment consisted entirely of men.

In contrast, findings from the few studies that have examined gender differences, rather than subtype differences in neuropsychological test performance, have been inconsistent. Although Seidman et al. (1997) found that men with schizophrenia showed more dorsolateral prefrontal impairment than women, as evidenced by performance on the Wisconsin Card Sorting Test, other studies have not found evidence for greater neuropsychological impairment among men than women. Indeed, one study (Lewine, Walker, Shurett, Caudle, & Haden, 1996) found that men with schizo-

phrenia outperformed women on verbal and spatial memory as well as visual processing. Interestingly, unlike men, women with schizophrenia were relatively more impaired in right hemisphere compared with left hemisphere functioning. Because right hemisphere impairment has been associated with affective disorder (for a review, see Claridge, 1994), the authors concluded that their findings are consistent with the view that schizophrenia in women has a strong affective component; however, their findings need to be replicated. Two other studies (Goldberg, Gold, Torrey, & Weinberger, 1995; Perlick, Mattis, Stastny, & Teresi, 1992) reported few significant gender differences in neuropsychological test performance, and differences that were found were in reverse of the predicted direction. In particular, men performed better than women on spatial (Goldberg et al., 1995), attentional (Goldberg et al., 1995; Perlick et al., 1992), and conceptualization tasks (Perlick et al., 1992). However, the latter two studies may have limited generalizability because of their use of particularly severe, early onset female schizophrenic patients. Also, given their lack of normal comparison groups, it is difficult to conclude that these gender differences were specific to schizophrenia. Finally, and perhaps most important, all of these studies made comparisons solely on the basis of gender (i.e., schizophrenic men will perform more poorly than schizophrenic women) rather than subtype. Although gender may be a marker for different subtypes of schizophrenia, it is not thought to have a one-to-one correspondence with these subtypes. Therefore, the most meaningful predictions of the neurodevelopmental hypothesis will be based on differences between the two hypothesized subtypes: poor-prognosis, neurodevelopmental schizophrenia and good-prognosis, affective schizophrenia.

Rather than examining gender differences in isolation, Lewine, Haden, Caudle, and Shurett (1997) recently subdivided schizophrenic patients by both sex and age of onset, and they surprisingly found that early onset, compared with late onset, was associated with greater neuropsychological impairment and less lateralization among men, whereas late onset, compared with early onset, was associated with greater neuropsychological impairment and less lateralization among women. These intriguing but puzzling findings highlight the importance of taking into account the interaction between gender and other illness variables.

In closing, the research on gender differences in schizophrenia has been a major contributor to the development of the neurodevelopmental-affective subtype distinction. However, it is important to reiterate that, although gender may be a marker for distinct etiological subtypes of schizophrenia, gender and subtype undoubtedly have a less than perfect overlap. Although gender affects which subtype of schizophrenia individuals are likely to express, gender per se is not theoretically linked to etiology. In contrast, the neurodevelopmental-affective subtyping scheme is grounded in etiological theory, which allows for specific predictions about prognosis and treatment. Thus, although the role of gender in schizophrenia needs further examination, it should be explored it the context of research on the predictive validity of the neurodevelopmental-affective subtype distinction. This type of research is essential in helping to elucidate which variables of interest in schizophrenia are related to gender and which are related to subtype.

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