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ScienceDirect
Schizophrenia Research 102 (2008) 1 – 18
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Schizophrenia, "Just the Facts" What we know in 2008. 2. Epidemiology and etiology

Rajiv Tandon [a], Matcheri S. Keshavan [b], Henry A. Nasrallah [c]

[a] University of Florida, 3706 Glin Circle, Tallahassee, FL 32309, United States
[b] Wayne State University, Detroit, Michigan, United States
[c] University of Cinncinnatti, Cinncinnatti, Ohio, United States

Received 15 February 2008; received in revised form 31 March 2008; accepted 2 April 2008

Abstract

Although we have studied schizophrenia as a major disease entity over the past century, its causes and pathogenesis remain obscure. In this article, we critically review genetic and other epidemiological findings and discuss the insights they provide into the causes of schizophrenia. The annual incidence of schizophrenia averages 15 per 100,000, the point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.7%. Schizophrenia runs in families and there are significant variations in the incidence of schizophrenia, with urbanicity, male gender, and a history of migration being associated with a higher risk for developing the illness. Genetic factors and gene-environment interactions together contribute over 80% of the liability for developing schizophrenia and a number of chromosomal regions and genes have been "linked" to the risk for developing the disease. Despite intensive research and spectacular advances in molecular biology, however, no single gene variation has been consistently associated with a greater likelihood of developing the illness and the precise nature of the genetic contribution remains obscure at this time. Environmental factors linked to a higher likelihood of developing schizophrenia include cannabis use, prenatal infection or malnutrition, perinatal complications, and a history of winter birth; the exact relevance or nature of these contributions is, however, unclear. How various genetic and environmental factors interact to cause schizophrenia and via which precise neurobiological mechanisms they mediate this effect is not understood. Etiological heterogeneity, complex patterns of gene–gene and gene–environment interaction, and inadequately elucidated schizophrenia pathophysiology are among the explanations invoked to explain our inadequate understanding of the etio-pathogenesis of schizophrenia. The ability to question some of our basic assumptions about the etiology and nature of schizophrenia and greater rigor in its study appear critical to improving our understanding about its causation.
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Keywords: Schizophrenia; Facts; Epidemiology; Genetics; Environmental risk factors; Incidence; Chromosomes; Genes; Prevalence; Linkage; Association; Pregnancy; Etiology; Causes

1. Introduction

Epidemiology is the study of distribution and determinants of disease (MacMahon and Pugh, 1970). Distinguishing characteristics and experiences of persons who develop a disease from those of individuals who do not allows one to identify factors related to causation of that disease. Determinants of disease constitute the essence of epidemiology; with reference to schizophrenia, this includes both genetic and environmental risk factors which need to be considered together since both are important in the etiology of schizophrenia and neither appears to operate in isolation (Tsuang et al., 2004).

In this paper, we summarize major epidemiological findings in schizophrenia and discuss what they tell us about genetic and environmental factors involved in its

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doi:10.1016/j.schres.2008.04.011

causation. We first summarize current knowledge about variations in the occurrence of schizophrenia across populations, socio-demographic characteristics and time. We then briefly review key genetic findings and environmental risk factors linked to the development of schizophrenia and critically discuss our state of understanding about the etiology of schizophrenia. We highlight key conceptual issues, outline approaches to dissecting genetic and environmental contributions to its causation, and consider major challenges towards elucidating the etio-pathogenesis of this disease.

2. Incidence and prevalence

The distribution of a disease is generally expressed in terms of incidence (new cases), and prevalence (total number of cases: existing+new). Incidence rate refers to the number of new cases of the disease that develop over a specific period of time among people who are at risk for developing the disease. Instead of a rate (new cases per population at risk per time), incidence can also be expressed as the probability that an individual will develop a particular disease (e.g., lifetime risk). Differences between the characteristics of people who develop versus do not develop the disease help to define the risk and protective factors for and against development of the disease, respectively. Thus knowledge about the distribution of new disease development (incidence) over time, place, and person points to etiological factors (determinants) for developing the disease. Prevalence refers to the proportion of people in a community who have a particular disease at a given time (point prevalence) or over a given time-span (period prevalence) including both people with pre-existing disease and those who newly develop the disease over this specified time period.

2.1. Incidence and lifetime risk

Since incidence is a measure of the number of *new* cases of a disease occurring among people who are *at risk* for developing the disease over a specified period of *time* (generally one year), it requires knowing who is a case at the beginning (and excluding them from both the numerator and denominator), the number of people at risk for newly developing the disease (denominator), and the number of people who newly develop the disease (numerator) over this specified period of time. The number of new cases can be determined by community surveys or by identifying them as they seek services (first contact with health worker, hospitalization, etc.). Correctly determining the distribution of a disease depends upon having a reliable and valid diagnosis of the disease and the ability to precisely demarcate those with disease from those without it. In the absence of any pathognomonic feature and several impediments to constructing a fully reliable patient clinical profile, it becomes a greater art to diagnose schizophrenia than most other diseases (Eaton et al., 2007). Additionally, consistent case definition (when does a possible case become a case — e.g., persons with prodromal symptoms) and identification (e.g., a person may not seek treatment/s and is thereby missed as a case) can be problematic. Furthermore, although we have made substantial advances over the past two decades in being able to diagnose schizophrenia with greater reliability, it is unclear if we have made any progress with regard to validity (McCormick and Flaum, 2005).

These challenges have contributed, in significant part, to varying estimates of incidence obtained across the multitude of studies. In the only global study that directly generated incidence data (WHO 10-nation study, Sartorius et al., 1986; Jablensky et al., 1992), the annual incidence was found to range from 16–40/100,000/year using broad criteria (ICD-9; World Health Organization, 1978) and 7–14/100,000 using narrow criteria (CATEGO class S+ identifying nuclear schizophrenia; Wing et al., 1974) for diagnosing schizophrenia. A 10-fold higher incidence rate was detected in the U.S.A.-based five community site National Institute of Mental Health Epidemiological Catchment Area (ECA) program (Tien and Eaton, 1992), but these results were derived from community surveys conducted by individuals with minimal or no clinical experience rather than on the basis of service provision and clinician diagnosis, which is how most other studies derived their data; this likely resulted in several false positives (Anthony et al., 1985; Regier et al., 1998). Studies based on service provision, on the other hand, might underestimate rates of schizophrenia because some affected individuals may not seek treatment. A recent meta-analysis of all published studies between 1965 through 2001 obtained a median incidence rate of 15.2/100,000/year with 80% confidence interval rates (10th–90th decile) ranging from 8–43 per 100,000 per year (McGrath et al., 2004). Data were derived from 55 studies conducted across 33 countries. Rates were not found to vary by broad world regions or economic status of the country (Saha et al., 2006). Contrary to prior assumptions of uniform rates of schizophrenia across the world, however, this meta-analysis revealed robust variations in incidence of schizophrenia, with *urbanicity*, *migration*, and *male gender* found to be associated with a higher risk for developing schizophrenia.

Recent findings confirm and clarify longstanding suggestions of a link between urbanicity and schizophrenia (Faris and Dunham, 1939). For many decades,

there was controversy about whether this association meant that urban dwelling caused schizophrenia ("breeder hypothesis") or whether persons with schizophrenia migrated to urban settings ("selection hypothesis"). For the past half-century, this argument was seemingly resolved in favor of the later perspective and the observed association was ascribed to the "social drift" of persons with schizophrenia to inner city areas with cheaper accommodation and relative anonymity (Dohrenwend et al., 1992). Even as the social drift phenomenon has been corroborated, well designed recent studies have also confirmed an association between urban birth and upbringing (upto the age of 15) and an increased risk of developing schizophrenia (Lewis et al., 1992; Mortensen et al., 1999; Kirkbride et al., 2006). The finding of a dose–response relationship between degree of urbanicity and risk of schizophrenia strongly supports the proposition that some factor associated with urbanicity may be causally related to schizophrenia (Pedersen and Mortensen, 2001). What that specific risk-modifying factor linked to urbanicity might be, however, is unclear. Several candidates have been proposed — these include urban–rural differences in rates of cannabis and other substance use, prenatal and perinatal health, degree of social stress and social connectedness, poverty, rates and nature of migration, environmental toxins, various infectious diseases, or vitamin D deficiency. Whereas some of these factors have independently been linked to schizophrenia (e.g., migration) and others to urbanicity (e.g., vitamin D deficiency), none has been convincingly linked to both or established as the schizophrenia risk-modifying factor that satisfactorily explains the urbanicity–schizophrenia connection.

Ever since Odegaard (1932) documented a higher occurrence of "schizophrenic breakdown" among Norwegians who had migrated to Minnesota than among those who remained in Norway, several studies have confirmed an association between migration and an increased risk of developing schizophrenia (Malzberg, 1964; Bhugra, 2004). A meta-analysis of 18 studies published between 1977 through 2003 identified a personal or family history of migration as a significant risk factor for schizophrenia (Cantor-Graae and Selten, 2005); the relative risk for developing schizophrenia was found to be 2.7 for first-generation immigrants and 4.5 for second-generation immigrants. Both selective migration (Odegaard, 1932) and diagnostic bias (Sashidharan, 1993) have been cited as explanations; neither of them appears to adequately account for the association. The migration–schizophrenia link has been found to be more robust among individuals migrating from a country where the population is predominantly black to a country where the population is predominantly white; similarly, migrating to areas with a lower density of people with a similar ethnic background has been found to be associated with a higher liability for psychotic illness (Kirkbride et al., 2007; Veling et al., 2008). What factor/s then might mediate the link between migration and schizophrenia? Social adversity associated with being a migrant (social isolation, discrimination and "racism", experience of "social defeat", etc.) has been cited as the major factor (Boydell et al., 2001; Cooper et al., 2008), although "biological" explanations such as vitamin D insufficiency and epigenetic mechanisms have also been suggested (Dealberto, 2007). The association between migration and increased risk of developing schizophrenia provides compelling evidence supporting a role for social factors in its etiology (Cantor-Graae, 2007); the specific risk-mediating factor (social or biological), however, remains to be elucidated.

Estimates of the risk of developing schizophrenia over one's lifetime range from 0.3–2.0% with an average of approximately 0.7% (Saha et al., 2005). Although gender differences in the clinical expression and outcome of schizophrenia have long been recognized (Seeman, 1982), it has generally been believed that the risk of developing schizophrenia over one's lifetime is similar among males and females (e.g., Wyatt et al., 1988). More recent studies have undermined this assumption and two recent meta-analyses revealed that males have a higher lifetime risk of developing schizophrenia with a male–female relative risk of about 1.4 (Aleman et al., 2003; McGrath et al., 2004). The male–female ratio in morbid risk for schizophrenia is found to increase as more stringent current diagnostic criteria are utilized (Beauchamp and Gagnon, 2004). Studies from developing countries have not found such a difference and study samples obtained prior to 1980 were much less likely to reveal a gender difference in the risk of schizophrenia (Aleman et al., 2003). This observed discrepancy between findings of studies conducted in the past two decades and those conducted earlier is of obvious importance but poorly understood, although proposed explanations include differences between the two time periods with regard to diagnostic criteria, case-ascertainment methods, or differential changes in a variety of physical and/or social environment risk factors among the two genders (Hambrecht et al., 1992; Aleman et al., 2003).

2.1.1. Incidence of schizophrenia over time: is schizophrenia a new disease?

Schizophrenia has been more consistently and frequently described over the past two centuries

(Bleuler, 1950; Kraepelin, 1971). Although loose descriptions resembling schizophrenia are obtained in texts dating back several thousand years (Jeste et al., 1985; Ellard, 1987), easily recognizable descriptions of schizophrenia are much less common than those of other psychiatric or neurological disorders (Evans et al., 2003). This has led some to suggest that schizophrenia is a disease that has afflicted humans only over the past two centuries and that some factor related to industrialization, urbanization, or increasing population density may have contributed to the emergence of this disease (Torrey, 1980; Hare, 1988). The broadly even distribution of schizophrenia across the world in the context of its strong genetic underpinnings (Crow, 1995), however, argues against the proposition that it is a recent disease and most experts believe that schizophrenia, like many other diseases, had been present for a long time before its first lucid description in the early 19th century. Resolution of this controversy is unlikely until we have a better understanding of the etiopathophysiology of the illness.

What is less controversial is the fact that descriptions of schizophrenia have been fairly consistent over the past two centuries and that its occurrence has been relatively stable over this period even though specific diagnostic criteria have changed. Its presentation has, however, evolved over the past century with a modest improvement in the overall prognosis (Bleuler, 1972; Hegarty et al., 1994) and reduced occurrence of more severe forms of the disease such as hebephrenia and catatonia (Morrison, 1974; Stompe et al., 2002). Some studies suggest a decline in the incidence of schizophrenia (Eagles et al., 1988; Woogh, 2001) whereas others suggest an increase (Tsuchiya and Munk-Jorgensen, 2002; Bray et al., 2006); changing diagnostic criteria and case detection methods make such comparisons difficult (Stromgren, 1987; Kendell et al., 1993).

2.2. Prevalence

Prevalence is a measure of the proportion of individuals in a defined population who either are manifesting a given disease at a particular time (point or period prevalence) or have manifested the disease at any time during their life (lifetime prevalence). Point prevalence thus refers to the proportion of the population with the disease on a given day, period prevalence to the proportion with the disease during a particular time-frame (generally 6 months or one year), and lifetime prevalence to the proportion that ever had the disease at any time during their life regardless of whether they currently do or do not have the disease. Logically, estimates of period prevalence should equal or exceed those of point prevalence and estimates of lifetime prevalence should equal or exceed those of period prevalence. The prevalence of any condition in a community is influenced by several factors including rates of new case development (incidence), duration of the condition, and differential mortality or migration patterns associated with the condition (Fig. 1). Although variable degrees of "recovery" do occur (Harding et al., 1987), complete cures are uncommon and the average duration that an affected person lives with schizophrenia is approximately 30 years. Based on a median incidence rate of 15.2/100,000/year, one would roughly predict a median point prevalence of about 456/100,000 or 4.56/1000 population.

Although findings from the approximately 200 studies are found to vary several-fold, the average is very close to this predicted estimate. Saha et al. (2005) conducted a systematic review of 188 studies from 46 countries and derived a range of different prevalence estimates in schizophrenia. Based on a meta-analysis of 21 studies, they obtained a median *point* prevalence estimate of 4.6 per 1000 persons with 80% confidence interval estimates (10th–90th decile) ranging from 1.9–10/1000. Based on a meta-analysis of 34 studies, they obtained a median *period* (upto 1 year) prevalence estimate of 3.3 per 1000 persons with 80% confidence interval estimates (10th–90th decile) ranging from 1.3–8.2/1000. Based on a meta-analysis of 24 studies, they obtained a median *lifetime* prevalence estimate of 4.0 per 1000 persons with 80% confidence interval estimates (10th–90th decile) ranging from 1.6–12.1/1000. Sixty-seven distinct studies provided data towards these three estimates: two studies for all three meta-analyses, 8 for two of the estimates, and the remainder for just one of these analyses.

Although these estimates of prevalence were somewhat lower than previously believed (e.g., Kessler et al., 1994) and more recently reported (e.g., Perala et al., 2007), this systematic review confirmed our notions of worldwide prevalence with pockets of low and high prevalence. Similar to the observed higher incidence of schizophrenia among migrants, this comprehensive review also found the prevalence of schizophrenia to be higher among this group. In contrast to observed differences in incidence across gender and urban–rural settings, however, no such differences in prevalence were observed. Prevalence was found to be similar among males and females as also among urban and rural dwellers. In comparison to the similar incidence across less developed and more developed countries, on the other hand, a significantly higher prevalence of schizophrenia was observed in more developed versus less

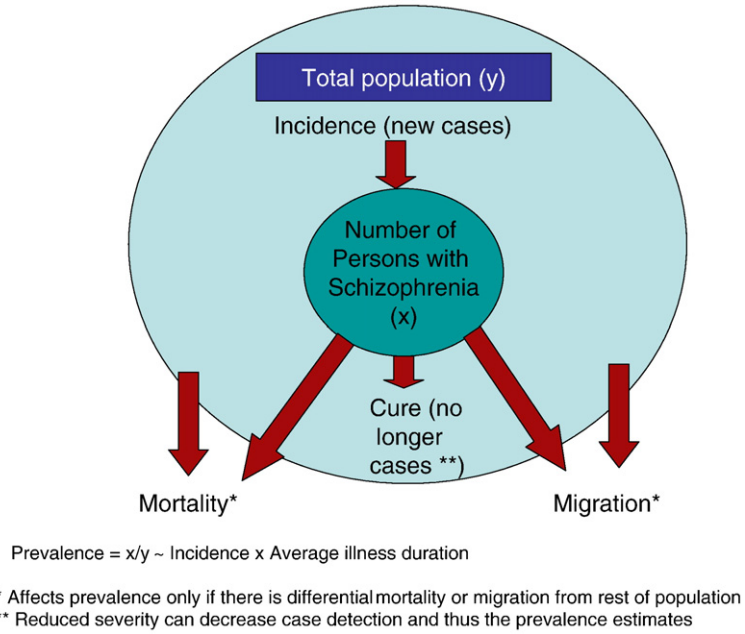


Fig. 1. Relation between incidence and prevalence in a given population.

developed countries. A higher prevalence of schizophrenia among lower versus higher socio-economic classes within communities has also been consistently documented over the past century.

The combinations of incidence-prevalence findings observed in schizophrenia are not easily explained. Variables linked to both higher incidence and prevalence are likely relevant to the etiology and possibly to persistence of the disease. Factors associated with higher incidence but equal prevalence of schizophrenia may be related in complex ways to both etiology and outcome differences (e.g., *hypothetically*, a greater risk of developing the illness along with greater illness-related mortality in males versus females might explain the higher incidence but equal prevalence of schizophrenia among males versus females; alternatively, this set of gender findings could *hypothetically* also be explained by a greater risk of development but higher rate of "cure" among males versus females, Fig. 1). Variables associated with equal incidence but higher prevalence are probably unrelated to etiology but relevant to outcome. Although the basis of these incidence-lifetime risk-prevalence findings is not well understood, they do provide a rich substrate for developing and testing hypotheses about what causes schizophrenia (McGrath, 2007): we need to better understand what these patterns of distribution of schizophrenia are telling us about the specific genetic and environmental risk factors related to its causation and the neurobiological mechanisms that might mediate these effects?

3. The genetic basis for schizophrenia

It is well known that schizophrenia aggregates in families. Although over two-thirds of the cases occur sporadically, having an affected family member substantially increases the risk of developing schizophrenia. This risk increases as the degree of genetic affinity with the affected family member increases (Kendler et al., 1993). Although a genetic basis for schizophrenia has long been suggested (Kallman, 1946), family dynamic and interactional explanations were commonly invoked to explain this familiality until the 1960s (Bateson et al., 1956; Lidz et al., 1965). To differentiate between these explanations, a series of seminal studies (Heston, 1966; Kety et al., 1968) examined the risk of schizophrenia in the adopted-away offspring of parents with schizophrenia raised by parents without the illness and adopted-away offspring of parents without schizophrenia raised by parents with the illness; they found that the risk of schizophrenia was related to the presence of the illness in biological parents but not in the adoptive parents. In keeping with the genetic basis for schizophrenia implied by this finding, twin studies have consistently found more than a three-fold greater concordance for the

disease among monozygotic twins than among dizygotic twins (Gottesman et al., 1987; Sullivan et al., 2003) (Table 1). Dizygotic twins share 50% of their genetic material and if one twin has schizophrenia the risk of the other having the illness is 10–15% (similar to that in siblings of a person with schizophrenia — who also share 50% of their genes). In contrast, monozygotic twins share 100% of their genetic material and if one twin has schizophrenia, the risk of schizophrenia in the other is about 40–50%.

Twin concordance rates are also utilized to estimate the heritability of a disease. Heritability refers to the proportion of variance in liability for an illness in the general population that is accounted for by genetic effects — by themselves and through interactions with environmental factors, they contribute about 80% of the liability for schizophrenia (Cannon et al., 1998; Cardno et al., 1999; Sullivan et al., 2003).

In reviewing the role of genetic factors in schizophrenia twenty years ago, Gottesman et al. (1987) suggested that the above clinical genetic data merely provided clues to the "real" genetics of schizophrenia which would be elucidated by the thousands of molecular genetic studies (linkage, association, gene knock-out, etc.) that were to follow in the next two decades. In assessing the genetic underpinnings of a disease, clinical genetic studies provide information about the presence and extent of genetic contributions to its development, chromosomal and linkage studies about where in the genome relevant risk genes for the disease may exist, association studies about which particular gene variation modifies the risk for the disease, and gene knock-out and related studies about what specific brain processes may be affected by such genetic variations and how this may result in schizophrenia. Gottesman et al. (1987) had subtitled their review "A decade of modest gains while playing for time". Despite phenomenal advances in the science and technology of molecular biology over the past two decades highlighted by the mapping of the human genome seven years ago, it could be argued that we have not learned very much more and that we are still playing for time (Sullivan, 2008); although a genetic basis for schizophrenia is now clearly established, the precise mechanism of inheritance still remains obscure.

3.1. Chromosomal abnormalities and linkage studies: Where on the human genome are the risk genes for schizophrenia?

Although a number of "structural" chromosomal abnormalities have been described in schizophrenia (MacIntyre et al., 2003), the three most often noted are deletion of 22q11, a balanced reciprocal translocation of 1q42/11q14, and involving the X chromosome (DeLisi et al., 1994; Blackwood et al., 2001; Williams et al., 2006b) implicating them as chromosomal regions which might harbor a risk gene or genes for schizophrenia. The complete mapping of the human genome in the past decade (Lander et al., 2001; Venter et al., 2001) has allowed a more detailed assessment of the linkage of specific chromosomal segments to differences in liability for schizophrenia. Linkage analysis utilizes genetic information from families with multiply affected

Table 1
Estimates of relative risk for schizophrenia due to various genetic and environmental risk factors

Risk factor	Average relative risk of schizophrenia if risk factor present (approximate)	References
Family history of schizophrenia	2–70	Gottesman et al. (1987); Kendler et al. (1993); Sullivan et al. (2003)
Monozygotic twin	50–70	
Both parents affected	40–60	
Dizygotic twin or 1st degree relative	9–18	
2nd degree relative (e.g., grandparent)	3–6	
3rd degree relative (e.g., 1st. cousin)	2–3	
Any specific single gene variant	1.1–1.5	Allen et al. (2008)
Urbanicity	2–3	Pedersen and Mortensen (2001)
Migration	2–3	Cantor-Graae and Selten (2005)
1st or 2nd trimester maternal infection or malnutrition	2–3	Penner and Brown (2007)
Winter birth	1.1	Davies et al. (2003)
Obstetric and perinatal complications	2–3	Geddes and Lawrie (1995); Geddes et al. (1999); Byrne et al. (2007)
Cannabis or stimulant use	2–3	Semple et al. (2005)
Paternal age >35 years	1.5–3	Wohl and Gorwood (2007)
Male gender	1.4	Aleman et al. (2003)

individuals with schizophrenia and seeks to identify regions of the genome *linked* to the illness; i.e., which chromosomal segments are shared among affected relatives but not among unaffected relatives. More than thirty genome-wide scans have been conducted in schizophrenia and two meta-analyses (Badner and Gershon, 2002; Lewis et al., 2003) both pinpointed chromosomal regions 8p21–22 and 22q11–12 as harboring schizophrenia risk genes. Lewis and co-workers meta-analyzed results from 20 genome scans and in descending likelihood identified chromosomal regions 2p12–q22, 5q23–q34, 3p25–p22, 11q22–q24, 6pter–p22, 2q22–q23, 1p13–q23, 22pter–q12, 8p22–p21, 6p22–p21, 20p20–p11, 14pter–q13, 16p13–q12, 18q22–qter, 10pter–p14, 1q23–q31, 15q21–q26, 6q15–q23, and 17q21–q24 as containing susceptibility genes for schizophrenia. A genome-wide scan for linkage in sibling pairs (DeLisi et al., 2002) also identified chromosomal regions 10p15–p13, 2 centromere, and 22q12.

Linkage analysis does not, however, identify the particular susceptibility genes themselves and the total number of genes in chromosomal regions linked to schizophrenia suggested by the above meta-analyses approximates 4000 genes (about *one-quarter of all known genes*), which indicates the extreme lack of precision of this approach by itself. The power to detect linkage depends on the available samples; unfortunately, the samples currently available worldwide may be insufficient to detect genes of relatively small effect (odds ratio ~1.8, as is believed to be the case in schizophrenia) (Risch and Merinkangas, 1996; Moldin, 1997). Genetic heterogeneity, or the presence of several independent risk genes, further reduces the sensitivity of linkage analysis (Sawa and Snyder, 2002; Fanous and Kendler, 2005). Finally, the difficulties in finding large multiplex families for such analyses and technological advances that allow relatively inexpensive rapid throughput genome-wide scanning have diminished interest in this approach to locating likely schizophrenia susceptibility genes.

3.2. Association studies and susceptibility genes: Which genes cause schizophrenia?

Linkage analysis (which requires family samples) and association studies (which can be conducted on samples of related or unrelated individuals) are two complementary molecular approaches to connecting genes to disease. Genetic association studies evaluate the relationship between specific gene variants and the risk of developing schizophrenia. Such studies are more suitable than linkage analysis for detecting genes of relatively small effect but require careful attention to the possibility of false positive (type 1 error) and false negative (type 2 error) results in view of the large number of gene variants that can potentially be evaluated (Hunter and Kraft, 2007). Publication of an extensive catalogue of common human DNA variants (International HapMap Consortium, 2005), development of sophisticated data-analytic tools, ready availability of high-throughput methods of genomic analysis, increased sharing of genetic materials across research groups, and broad international collaboration have significantly facilitated the search for the association between specific variations of defined genes and the risk for developing schizophrenia. Variations in specific gene sequences are compared between individuals with and without schizophrenia and variants found with significantly different frequency among those with schizophrenia considered to confer susceptibility to the disease. As such associations may also be detected due to numerous artifacts, replication is a critical sine qua non (Hunter and Kraft, 2007). After case–control comparisons of the gene variant, the next steps are assessment of whether the protein product of the gene is expressed in the brain and its function, if the different forms of the gene yield functionally different proteins, whether there is differential expression of the gene product in persons with schizophrenia, and if the gene product may plausibly be relevant in terms of the hypothesized pathophysiology of the illness.

Over the past decade, several genetic associations for schizophrenia (Owen et al., 2005; Gogos and Gerber, 2006; Straub and Weinberger, 2006) have been reported and these have been supported by varying amounts of evidence. There are several ongoing efforts to collate and update these data (e.g., Becker et al., 2004; Lin et al., 2006; Allen et al., 2008); despite these resources, staying on top of these association findings can be challenging in view of the sheer volume and discrepancies. In addition to data suggesting an association between gene variants and risk for schizophrenia, messenger RNA of many of these genes is expressed in the brain and varying amounts of data suggest that they may be differentially expressed in individuals with the illness. Furthermore, neurobiological data plausibly link many of these genes to pathophysiological processes considered relevant in schizophrenia (Harrison and Weinberger, 2005; Law et al., 2006; Lang et al., 2007; O'Tuathaigh et al., 2007; Tan et al., 2007a; Talkowski et al., 2008). Some of the genes (with their protein products) that are currently of etio-pathogenetic interest in schizophrenia include NRG1 (neuroregulin 1), DTNBP1 (dysbindin), DRD1-4 (dopamine receptors D1–D4),

DISC1 (disrupted in schizophrenia 1), COMT (catechol-*O*-methyl-transferase) and GRM3 (metabotropic glutamate receptor), (Duan et al., 2007; Lewandowski, 2007; Li and He, 2007; Nicodemus et al., 2007; Tan et al., 2007b; Chubb et al., 2008; Hanninen et al., 2008; Munafo et al., 2008; Schwab et al., 2008; Talkowski et al., 2008). Even for these "most promising" genes, however, there is a remarkable failure to replicate exactly the same markers and haplotypes across studies and a lack of consistency in implicating particular alleles in liability for schizophrenia (Alkelai et al., 2008; Sanders et al., 2008; Sullivan, 2008). There are findings that do not easily fit and although there are ways to explain discrepancies, the veracity of these explanations has not been adequately tested.

Therefore, we cannot as yet assert with certainty that any particular gene variant increases the risk for schizophrenia and we have considerable work to do before we will be able to precisely define the pathogenetic mechanisms mediating the effects of various risk genes to "cause" schizophrenia. The several large case-controlled whole genome association studies (e.g., GAIN, 2008; Kingsmore et al., 2008) currently underway will hopefully provide useful insights.

3.3. The genetic basis of schizophrenia, Circa 2008. The promise and the challenge

Is the glass half-full or half-empty? Genetic factors are critically important and our increasingly powerful technological tools are enabling us to better study the nature of these genetic contributions to the etiology of schizophrenia. But failures of clear and consistent replication need to be considered in the context of our history of previous highly publicized "solid" genetic findings in schizophrenia that could subsequently not be confirmed (e.g., Sherrington et al., 1988; Brzustowicz et al., 2000). Four broad issues that warrant specific consideration include the desirability of adopting standards for interpretation of future genetic studies, explaining the evolutionary-genetic paradox of the relatively constant incidence of schizophrenia over the past century despite its evolutionary disadvantages, suitability of our current genetic framework of schizophrenia, and whether schizophrenia is the appropriate phenotype for us to be conducting these genetic studies on.

There is considerable disagreement in our field about the degree of appropriate concern about our failure to consistently and unambiguously replicate findings implicating a particular gene variant as a risk factor for schizophrenia (DeLisi, 2000). Some experts suggest that this is only to be expected in view of the fact that schizophrenia is a heterogeneous disease with multiple genes of small effect (Owen et al., 2005) that might vary across populations with different genetic ancestry, and that the allelic diversity (leading to discrepant findings) being observed in schizophrenia is no different from that seen in other complex genetic disorders (Straub and Weinberger, 2006); these experts caution against an overly rigid "nihilistic" approach and argue for the need to pursue each "promising lead" in order to avoid type 2 errors in our difficult search for the precise genetic basis for schizophrenia. Other experts suggest, however, that more consistent genetic findings have been noted in other complex genetic diseases (Welcome Trust Case Control Consortium, 2007) and there is no obvious reason why schizophrenia should be considered more complex (Sullivan, 2007); they provide a strong case for "hard" replication in order to avoid type 1 errors (Ioannidis, 2005; DeLisi and Faraone, 2006). Both concerns merit attention and a balanced "middle-of-the-road" approach would entail vigorous pursuit of all leads in a rigorous manner in conjunction with explicit testing of explanations offered for discrepant findings. In any event, a key concern should be the power of a particular study to replicate prior reports.

How has schizophrenia persisted across world populations at a relatively stable rate despite its obvious evolutionary disadvantages such as decreased reproductivity and increased mortality (Svensson et al., 2007; Tandon et al., 2008)? While some may question the premise that incidence rates of schizophrenia have been stable over time, this assertion appears to be well-founded at least over the past two centuries (see section on incidence above). Although we do not have definitive explanations, it has been suggested that the genes for schizophrenia may also be relevant to adaptive human evolution and thereby confer evolutionary advantages to unaffected family members (Crow, 1995; Williams et al., 2006a; Crespi et al., 2007). There has also been much debate about other models to explain the persistence of schizophrenia in the context of the plausibility of mutation rates that such models invoke (Doi and Hoshi, 2007).

Currently, the predominant genetic view of schizophrenia is that it is a heterogeneous, polygenic/multifactorial disease (Risch, 1990; Lichtermann et al., 2000) with multiple common genetic polymorphisms, each of which contributes a small effect to disease susceptibility. This "common disease-common alleles with multiple genes of small effect" (Chakravarti, 1999) model of schizophrenia is the basis for the large-scale genetic association studies conducted around the world in the past decade and the current emphasis on population case–control genome-wide association studies. Some

experts suggest that our genetic conceptualization of schizophrenia is wrong and this flawed model is the reason for our difficulties in elucidating the precise nature of the genetic basis for schizophrenia (McClellan et al., 2007; Crow, 2007a). They instead provide two alternate genetic models for schizophrenia that they suggest are more appropriate. McClellan et al. (2007) suggest that instead of viewing schizophrenia as resulting from the combined effects of multiple common and weakly penetrant genetic polymorphisms, it is better conceptualized as a highly heterogeneous genetic entity caused by multiple, highly penetrant and individually very rare mutations that may be specific to single cases or individual families. This model points to a very different approach towards elucidating the genetic basis for schizophrenia emphasizing intensive study of individual cases or single families. While recent findings of increased runs of homozygosity that reveal highly penetrant recessive loci in schizophrenia (Lencz et al., 2007) are suggestive, there are several limitations to this idea (Craddock et al., 2007; Crow, 2007b). Another genetic model proposed for schizophrenia is that it is not DNA sequence variation but heritable changes in gene expression that explain its genetic origins (DeLisi et al., 2002; Costa et al., 2006; Crow, 2007a). Such epigenetic factors exert their effect on genomic functions principally through DNA methylation and histone remodeling of chromatin structure. Although epigenetic explanations for the genetic basis for schizophrenia bear much promise, our understanding of the role of epigenetic factors in the etio-pathogenesis of complex diseases such as schizophrenia is still in its infancy. While it is conceivable that epigenetic mechanisms are relevant in schizophrenia (Mill et al., 2008), the extent and precise nature of their contributions remain unclear. Copy number variations account for a substantial proportion of human genomic variation and have been found to be relevant to the expression of various neurodevelopmental disorders; their specific role in risk for schizophrenia remains to be clarified (Sutrala et al., 2007; Kirov et al., 2008; Mulle, 2008).

The phenotypic heterogeneity of schizophrenia has been cited as another reason for the difficulties in precise delineation of its genetic basis and it has been suggested that the "schizophrenia genes" do not code for schizophrenia *per se*, but for some broader clinical construct such as psychosis (Kendler et al., 1998; Weiser et al., 2005; Craddock and Owen, 2007) or neurocognitive deficits that occur in schizophrenia and other conditions (Whalley et al., 2005; Toulopoulou et al., 2007). Increasingly, the use of intermediate phenotypes (endophenotypes) to improve etiological homogeneity and thereby reduce the problem of nonreplication in genetic association studies is being advocated (Gottesman and Gold, 2003; Bearden et al., 2007; Braff et al., 2007; Glahn et al., 2007; Gur et al., 2007; Owen et al., 2007; Tan et al., 2008). Although this approach is being found to be useful (Greenwood et al., 2007), the extent to which it will facilitate the elucidation of the genetic basis of schizophrenia is still an open question. Another approach towards reducing etiological heterogeneity is to utilize subtypes or dimensions of schizophrenia as the phenotype for genetic association studies (Jablensky, 2006). Even if such approaches lead to more consistent genetic findings, the question of how and why different dimensions or endophenotypes co-occur in schizophrenia would still need to be answered.

What is the status of our understanding of the nature of genetic contributions to the etio-pathogenesis of schizophrenia in 2008? To the best of our knowledge, this is what we do know:

(i) Heritability is high and genetic factors contribute about 80% of the liability for the illness.
(ii) There is no 'major' gene locus that could explain a substantial portion of the heritability and a large number of candidate susceptibility genes may contribute to the liability for the illness.
(iii) No gene appears to be either sufficient or necessary for the development of schizophrenia.
(iv) Although there are many "findings" of genetic variations being linked to differential risk for developing the illness, inconsistent replication prevents the consideration of any single allelic variant as a gene for schizophrenia with absolute certainty at this time.

4. Environmental risk factors

A variety of specific environmental exposures have been implicated in the etiology of schizophrenia (Table 1). These include both biological and psychosocial risk factors during the antenatal and perinatal periods, early and late childhood, adolescence and early adulthood (Maki et al., 2005).

In the antenatal period, maternal infections and nutritional deficiency during the first and early second trimesters of pregnancy have been linked to an increased liability for developing schizophrenia (Penner and Brown, 2007; Meyer et al., 2007); these associations have not, however, been consistently detected (Crow and Done, 1992). Although maternal influenza is the infection most frequently linked to an increased risk of developing schizophrenia (Mednick et al., 1988), other maternal infections (e.g., rubella, toxoplasmosis, etc.) during this

period have been associated with an increased liability for developing schizophrenia as well (Brown et al., 2001, 2002). Although the precise neurobiological mechanism whereby this increased risk might be mediated is not clearly understood, a role for cytokines and an aberrant immune response to these infections that interfere with normal fetal brain development during this period is commonly invoked (Ashdown et al., 2006). Severe nutritional deficiency (Susser et al., 1996; St Clair et al., 2005) and severe adverse life events (Khashan et al., 2008) experienced by the mother during the first trimester of pregnancy have been linked to an increased risk for developing schizophrenia; these effects are hypothesized to be mediated by "stress sensitization" (Koenig et al., 2005; Yuii et al., 2007) and a predisposition to subsequent hyperdopaminergia (Lipska et al., 1993).

A range of obstetric and perinatal complications have been linked to an approximate doubling of the risk of developing schizophrenia in the offspring (Geddes and Lawrie, 1995; Cannon et al., 2002b; Byrne et al., 2007); there are, however, some discrepant findings (Done et al., 1991). Although the precise mechanism whereby exposure to obstetric/perinatal complications might increase the risk for developing schizophrenia has not been delineated, fetal hypoxia is most commonly cited as the mediating factor (Geddes et al., 1999; Byrne et al., 2007).

Although *maternal* risk factors for schizophrenia during the prenatal–perinatal period receive the most attention (Patterson, 2007), older paternal age at conception has been linked to an approximate doubling of the risk for developing schizophrenia (Malaspina et al., 2001; Byrne et al., 2003; Wohl and Gorwood, 2007). While we do not understand the precise mechanism whereby this increased risk is mediated, impaired spermatogenesis leading to an increased likelihood of de novo mutation and aberrant epigenetic regulation have been advanced as explanations (Byrne et al., 2003; Perrin et al., 2007; Cheng et al., 2008).

Birth during late winter or early spring has been associated with a 5–10% greater likelihood of developing schizophrenia (Torrey et al., 1997; McGrath and Welham, 1999; Davies et al., 2003), although some statistical artifacts are inadequately explained (Lewis, 1989). This season of birth effect appears to become stronger with increasing latitude and increasing severity of winter. How this season of birth effect might be mediated is not fully understood, but it is suggested that it represents a proxy for one of the above three factors (prenatal infection, prenatal malnutrition, or risk of mutation).

Although a range of risk factors in childhood have been suggested as increasing the risk for schizophrenia, confidence in any of these associations is limited by discrepancies in findings and several methodological constraints. Such factors include childhood trauma (Read et al., 2005; Morgan and Fisher, 2007), head injury (Wilcox and Nasrallah, 1987; David and Prince, 2005), parental separation or death (Morgan et al., 2006), adverse child rearing (Tienari et al., 2004), and infection (Dalman et al., 2008). As earlier discussed in the section on incidence, urbanicity during the childhood years and migration are important risk factors for developing schizophrenia.

During adolescence, cannabis use has been linked to an increased risk of developing schizophrenia (Semple et al., 2005; Moore et al., 2007). Although an etiological role is probable, some experts question this cause–effect relationship and suggest instead that cannabis use might precipitate schizophrenia in vulnerable individuals or otherwise modify the expression of schizophrenia but not the risk for developing it (Degenhardt and Hall, 2006; Barnes et al., 2006). Although social adversity and stressful life events have long been linked to the precipitation of schizophrenia (Norman and Malla, 1993); some suggest that these might actually increase the liability for developing the illness (Harrison, 2004; Allardayce and Boydell, 2006).

Delayed attainment of various developmental milestones (e.g., language) and a range of "premorbid" impairments during childhood and adolescence (cognitive — e.g., specific impairments and poor academic achievement, physical — "minor physical anomalies" and "soft neurological signs", and social — e.g., "schizotaxia" and poor social adjustment) have been linked to an increased likelihood of developing schizophrenia (Walker and Lewine, 1990; Fish et al., 1992; Jones et al., 1994; Cornblatt et al., 1999; Cannon et al., 2002a; Keshavan et al., 2005). It is unclear, however, whether such impairments represent risk factors for developing schizophrenia or are instead early manifestations of the disease itself.

A range of environmental risk exposures have thus been linked to liability to develop schizophrenia, but their exact relevance remains unclear. Many associations have been suggested by less reliable observational studies and several putative environmental factors (e.g., urbanicity, migration, and ethnicity) are proxies for some other specific risk exposure whose nature remains obscure. None of the environmental risk factors appear sufficient or necessary to cause schizophrenia and no single factor fully satisfies the nine epidemiological criteria for an exposure-disease cause–effect relationship (Hill, 1965).

Although a role for both genetic and environmental risk factors in the etiology of schizophrenia has long

been proposed, previously these were considered dichotomously and questions such as "is it genetic or environmental in origin" and "what is different about the schizophrenia caused by genetic versus environmental factors" focused upon. It is only in the past couple of decades that investigators have instead seriously begun to explore issues such as "exactly how do genetic and environmental elements interact to cause schizophrenia" (Tienari et al., 2004; Caspi et al., 2005; Krabbendam and van Os, 2005; Benzel et al., 2007; Cougnard et al., 2007; Mathew et al., 2007; Nicodemus et al., 2007; Sei et al., 2007; Zammit et al., 2007; Cheng et al., 2008; Hanninen et al., 2008). How these factors might interact to cause schizophrenia and what neurobiological processes

Table 2

Epidemiological "facts"	Reproducibility	Whether primary to illness?	Durability of finding over time	Key questions
Annual incidence = 8–40 per 100,000 per year with relatively similar incidence across broad regions and countries.	***	**	***	What specific causal factors — social or biological — explain differences in incidence?
Higher incidence associated with urbanicity.	**	**	**	Does a dose–response relationship exist for specific factors?
Higher incidence associated with migration.	**	**	**	
Lifetime risk = approximately 0.7%	**	**	**	What specific factors explain sex differences?
Greater lifetime risk in males	**	**	*	
Point prevalence = 2–10/1000 with pockets of high and low prevalence.	***	*	***	To what extent do variations in diagnostic criteria/case-ascertainment methods explain variations?
Higher prevalence among lower socio-economic classes.	***	*	***	
Schizophrenia is highly heritable and genetic factors contribute to approximately 80% of the liability for the illness.	***	**	***	What genetic model best explains these genetic contributions?
There is genetic heterogeneity, with multiple genes (no single one of which is necessary or sufficient by itself) related to risk of illness.	**	**	**	Why is consistent identification of any single susceptibility gene variant proving so difficult?
Multiple chromosomal regions across the genome are linked to illness liability.	**	**	*	What do the risk genes code for — schizophrenia, psychosis, cognitive deficit, physiological abnormality, endophenotype?
Specific gene variants of small effect in several genes have been linked to illness liability and/or illness expression.	*	*	*	
Several environmental factors of small effect have been associated with an increased risk of developing schizophrenia.	**	**	**	What neurobiological mechanisms mediate these effects?

– To *** SCALE to be used to score reproducibility, specificity, and durability of each "fact"

1. *Replicability*
–: very few studies OR Few–Fair number of studies with contradictory findings
*: Few studies with consistent replication OR Fair–Many studies with inconsistent replication
**: Fair number of studies with consistent replication OR Many studies with fairly consistent replication
***:Many independent studies with consistent replication and no contradictory findings
2. *Whether primary to schizophrenia*
–: finding certainly because of some other confounding variable and definitely not related to schizophrenia.
*: finding possibly because of some other confounding variable but may be related to schizophrenia.
**: finding probably not because of some other confounding variable and likely related to schizophrenia.
***: finding certainly not because of some other confounding variable and definitely related to schizophrenia.
3. *Long-term durability*
–: very new finding (<5 years) not in previous 2 versions of "FACTS" in 1998 and 1999.
*: relatively new finding (5–15 years). Not in 1988 version, but may have been noted in 1999 version
**: fairly established finding (15–30 years). Listed in 1999 and may have been noted in 1988 versions
***: long established finding, well known for over 30 years. Listed in both 1988 and 1999 versions

From Table 1, Tandon et al., 2008. "Schizophrenia, Just the Facts, Circa 2008".

might mediate such gene–gene, gene–environment, and environment–environment interactive effects is not understood at this time.

5. Etiology: what do genetic and environmental "facts" tell us about the causes of schizophrenia

Although it appears that our understanding of the causation of schizophrenia has substantially increased over the past two decades, what we can confidently assert is essentially the same — both genetic and environmental factors are important, but exactly which specific exposures and exactly how they cause schizophrenia is still unknown (Table 2). For the past twenty years, we have been biding time and asserting that *certain* etiological information is just around the corner (Gottesman et al., 1987); we still wait (Sullivan, 2008). A reconsideration of our basic strategies and fundamental assumptions may be in order.

To make progress, we may need to exert substantially greater rigor in evaluating findings, better identifying and explaining discrepancies, developing clear and testable hypotheses (and then actually testing them!), and explicitly discarding explanations or assumptions that are disproved by these efforts. We need to be more precise in defining the contribution of each putative risk factor. Assuming that a particular risk factor is convincingly linked to liability for developing schizophrenia, precisely what is the role of that risk factor and exactly how are its effects mediated? Does this factor itself modify the risk for developing schizophrenia or does it moderate the effect of some other factor (Bauman et al., 2002; Fanous and Kendler, 2005). Alternatively, is this factor found to be linked to schizophrenia not because it is a risk modifier, but a risk mediator (Edwards and Lambert, 2007); if so whose effects does it mediate? Finally, does this putative factor modify the risk for developing schizophrenia or does it instead influence its expression (e.g., Cougnard et al., 2007; Shaner et al., 2007)? Table 3 summarizes a set of critical questions that *must* be answered with regard to each risk factor (genetic or environmental) in order for us to acquire a better understanding of its role in the etio-pathogenesis of schizophrenia.

There is also a clear need to effectively integrate the vast amounts of epidemiological data generated across different fields of inquiry by research groups around the world utilizing an assortment of paradigms and approaches. Otherwise, our field at large runs the risk of being buried under a plethora of unrelated and undigested findings (Tandon, 1999). As individual research groups, we are confronted with the challenge of keeping up with new findings whose veracity we cannot ascertain and whose significance we cannot comprehend. This leads to different research groups working in relative silos and ignoring large swaths of established findings or worse misinterpreting and misrepresenting them. In addition to appreciating the need for and importance of meaningful integration, we need to invest substantial effort and discipline in order to make this happen. In our individual research endeavors, greater rigor and healthy skepticism, a more inductive ("hypothesis-testing") approach, in conjunction with clear and precise explication of our findings would be useful. In our areas of expertise, it would be helpful to

Table 3
Critical issues that need to be addressed for all putative etiological factors linked to schizophrenia

Substantial specific questions

1. Is this the "*real" risk-modifying factor* or merely a surrogate marker for some other etiological factor?
2. Does a *dose–response relationship* exist between intensity of exposure to this risk factor (genetic or environmental) AND risk of developing the illness?
3. Does this factor *modify* the risk of developing schizophrenia, *moderate* the risk of some other etiological factor, or *mediate* the effect of some other risk factor?
4. Is the risk factor *necessary* or *sufficient* to cause schizophrenia? [No factor can be both necessary and sufficient to cause schizophrenia as that would mean that it is the sole cause for the disease and we know multiple etiological factors are relevant].
5. What *specific neurobiological mechanisms* mediate the effects of this risk factor to "cause" schizophrenia?
6. *Exactly what disease or group of diseases* does the risk factor increase the risk for (e.g., schizophrenia OR some psychotic disorder OR some disorder with specific cognitive impairment, etc.)?
7. *Exactly how* do different genetic risk factors interact with each other and with environmental risk factors to modify risk of developing the illness?
   a) is there a summing of risk factors that determines individual liability?
   b) are there interactions between specific sets of risk factors that lead to development of schizophrenia?
   c) are there windows of time (e.g., based on age or developmental phase) when exposure to the factor (or to specific interactions between a set of factors) leads to increased risk of developing schizophrenia?
8. Are these effects similar across *different populations* and if not, why not? Exactly how do these environmental and genetic risk factors interact in different populations?

General or methodological

1. Might *variations in diagnostic criteria* or *case-ascertainment methods* explain observed differences in incidence across different populations?
2. Can findings be replicated, *exactly replicated*? If not, are explanations of failure to replicate *explicitly tested*?
3. What *specific* causal factors (genetic and/or environmental and/or interactional) explain differences in incidence across different populations (e.g., differences based on gender, migration/ethnicity status, urbanicity, etc.)?

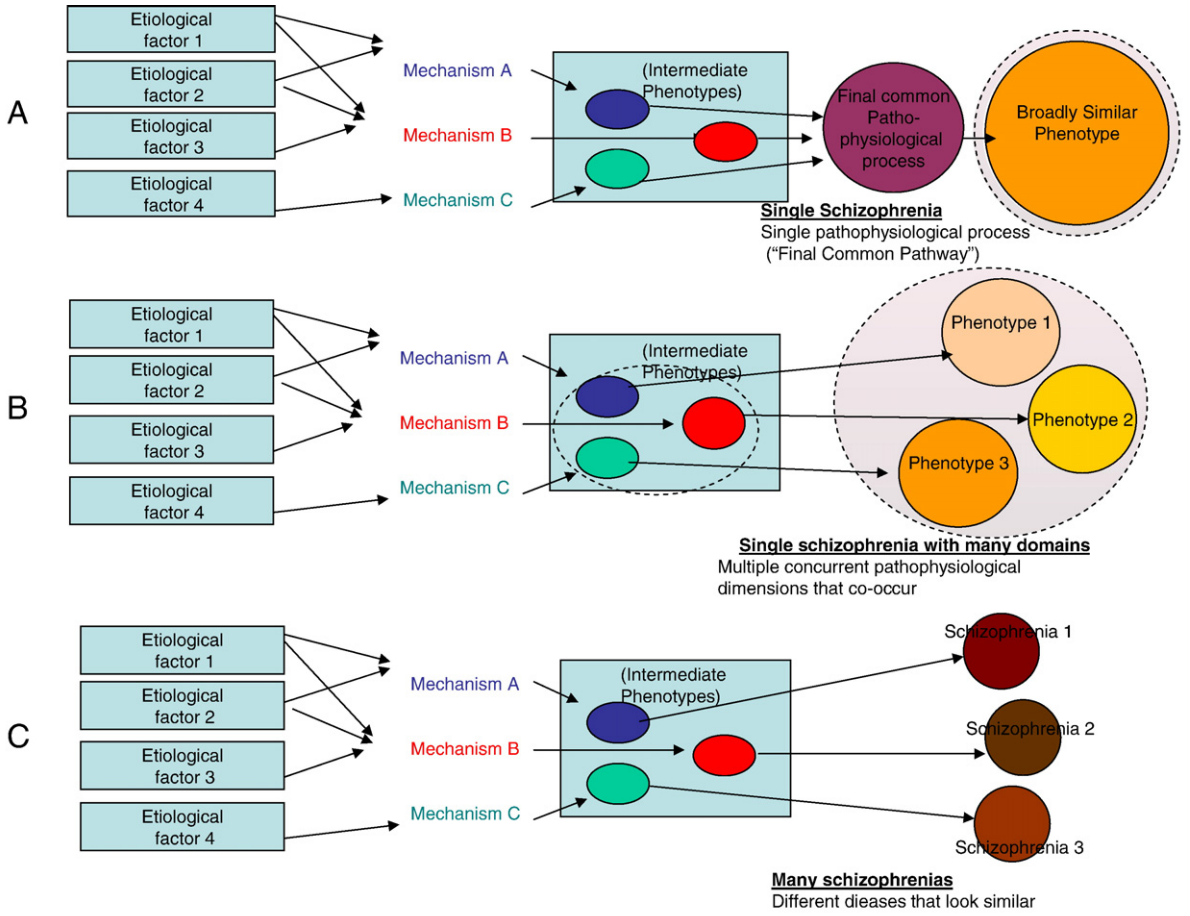


Fig. 2. Etiology to pathophysiology to illness: models of schizophrenia.

update what we know and don't know and how well we know what we know. Furthermore, it would be crucial for us to regularly take stock of findings that survive over time and those that don't (see Table 2); we often hold on to untrue findings in our field and expend enormous and obviously unproductive effort in trying to "explain them" (e.g., McGrath, 2007). To paraphrase Mark Twain in this regard (Anonymous, 2003), "it ain't what people don't know that hurts them it's what they know that ain't so".

Finally, we need to consider the possibility that there is no "one" schizophrenia, whose etiological basis we are trying to define. Perhaps, schizophrenia includes several (possibly hundreds) of different diseases whose clinical manifestations are similar. Alternatively, schizophrenia may represent a confluence of many distinct dimensions (with different etiologies); but we then need to explain why they co-occur. Fig. 2 illustrates these models along with the traditional "single common pathway" construct (Williamson, 2006) and depicts how multiple etiological factors might interact to produce neurobiological aberrations that, in turn, lead to the expression of schizophrenia.

We have accumulated a significant amount of information pertaining to the causes of schizophrenia, but our comprehension of its etiology remains limited. It is vital that we examine the reasons for this continuing gap between "findings" and "understanding".

Role of funding source

Independently prepared by authors. No external funding.

Contributors

Contributors to research and writing of manuscript. Rajiv Tandon, Matcheri Keshavan, and Henry Nasrallah.

Conflict of interest

This statement was independently developed by Rajiv Tandon, Matcheri Keshavan, and Henry Nasrallah. The content of the article is not part of the purview of Dr. Tandon's current employment by the State of Florida which bears no responsibility its contents.

Acknowledgement

We acknowledge the mentorship of Richard J. Wyatt and guidance of our many teachers and colleagues, whose collective efforts are reflected in this manuscript.

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