

How Can Risk and Resilience Factors Be Leveraged to Optimize Discovery Pathways?

Craig Morgan, Michael O'Donovan, Robert A. Bittner,
Kristin S. Cadenhead, Peter B. Jones, John McGrath,
Steven M. Silverstein, Heike Tost,
Peter Uhlhaas, and Aristotle Voineskos

Abstract

Based on wide-ranging discussions and specific examples drawn from the interests and expertise of the group, this chapter addresses the question of how knowledge of risk and resilience in relation to the etiology of schizophrenia can be leveraged to optimize discovery of preventive and therapeutic approaches. It explores the challenges and gaps in knowledge that have emerged as a result of recent, significant progress in understanding the factors that confer risk for schizophrenia. The fuzzy boundaries of schizophrenia and overlap in risk factors between schizophrenia and other mental disorders are highlighted, as is the predominant focus on risk rather than on resilience. Examples of research in genetics (including epigenetics) and neuroimaging are provided which examine putative mechanisms and pathways that could be leveraged to develop novel interventions.

Implications for prevention and intervention are considered from the point of view that heterogeneity and nonspecificity in schizophrenia present opportunities both to disentangle shared pathways that underpin a wide range of disorders and to develop novel approaches to prevention and intervention. The chapter concludes with recommendations that highlight key areas for future research.

Introduction

If we want to move closer to the prevention of complex disorders like schizophrenia and implement effective treatment, we must first understand the matrix of risk factors that underlies the etiology and pathogenesis of such syndromes.

Considerable progress has been made in understanding the factors that confer risk for schizophrenia and, more broadly, psychosis since the disorders were first described, beginning with family, adoption, and twin studies and now including studies of molecular genetic and environmental factors. Nonetheless, considerable gaps remain in our knowledge of individual risk factors, of how these combine and interact across levels to increase risk, and of the developmental pathways and mechanisms through which they impact on neural systems and circuits to produce the clinical phenomena of psychosis. These gaps limit our ability to utilize existing data to inform the development of strategies to promote resilience and reduce risk, at both population and individual levels.

How can current knowledge of risk and resilience factors be leveraged to optimize discovery pathways, and thereby better inform prevention and intervention? From the start, consideration of this question forced us to ponder what is currently known about schizophrenia and to set this in the context of past assumptions and future challenges.

Past assumptions:

- Schizophrenia was a relatively homogenous disease construct, albeit with subtypes.
- Schizophrenia affected men and women equally and had a flat epidemiological profile across time, place, and persons.
- Schizophrenia had a small, manageable set of risk factors.
- Neuroscience would reveal a readily interpretable mechanism of action, which would lead to effective treatments.

Current understanding:

- Schizophrenia is a poorly understood group of disorders that defies ready simplification based on symptoms, putative neurobiology, or etiopathogenesis.
- Schizophrenia affects men more than women, and the incidence of the disorder varies significantly by place and social group (e.g., within nations and between nations, between ethnic subgroups).
- Risk factors for schizophrenia (e.g., genes, prenatal exposures) are associated with a wide range of other brain-related adverse health outcomes (especially neurodevelopmental disorders).
- Common mental disorders like anxiety and depression often precede and coexist with schizophrenia.
- Isolated and transient psychotic experiences are prevalent in the community.

Future challenges:

- Acknowledge that genetic and nongenetic risk factors linked to schizophrenia will probably be shared with many other mental health outcomes (i.e., lack of specificity for exposures).

- Acknowledge that psychotic experiences are shared with a subgroup of the general population and a range of common mental disorders.
- Acknowledge that individuals can pass through a pluripotential phase of illness evolution, at which stage a number of outcomes are possible, and that a clinical staging model may offer new options for treatment and prevention.
- Consider heterogeneity and nonspecificity not as problems but rather as opportunities to unravel shared pathways that underpin a surprisingly wide range of brain-related outcomes.
- Acknowledge that interventions, which target these nonspecific outcomes, may deliver attractive and cost-efficient benefits with respect to overall disease burden.

Simply put, the agenda for schizophrenia research needs to be recontextualized. We must widen the category of observation and generate new metaphors and semantic labels to help leverage this perspective.

Constructs of Schizophrenia and Psychosis

Before we can understand risk and resilience, it is necessary to define the target disorder(s) or syndrome(s) of interest. Should a narrow (e.g., DSM-IV schizophrenia) or broad (e.g., nonaffective psychosis, all psychotic disorders including bipolar disorder) focus be taken? This is a key issue for future research and is discussed by Corvin et al. (this volume). Our discussions focused on the *broader spectrum of psychosis* in light of (a) the robust evidence from genetics and risk factor epidemiology that indicates a shared risk architecture across the psychosis spectrum, (b) clinical overlap and uncertain boundaries between different types of psychotic disorders, especially in the early phases of disorder (Murray et al. 2004), and (c) evidence from general population samples that isolated and transient psychotic experiences are common and are associated with similar risk factors to those identified for clinically defined disorder (van Os et al. 2009).

For some research questions, it may be appropriate to take an even broader perspective. For example, why do some copy number variants (CNVs) increase risk for a broad range of neurodevelopmental disorders, such as learning disability, epilepsy, autism, and schizophrenia (Van Den Bossche et al. 2012)? When referring to existing research, we are necessarily bound to use the groups and categories that were the focus of study (i.e., in some specifically schizophrenia, in others all psychotic disorders, whereas in still others psychotic experiences in nonclinical samples).

Risk and Resilience

Within the fields of medicine, human genetics, and epidemiology, there is an understandable tendency to focus on the identification of factors that increase the probability of adverse health outcomes (i.e., risk factors). Often, the identified variables are risk indicators or proxy markers (i.e., variables that index exposure to risk-increasing exposures) rather than factors that directly impact on risk. Some of the identified exposures in schizophrenia and psychosis research are at this broad level; for example, migrant or minority ethnic status (Fearon and Morgan 2006) and urban birth (Krabbendam and van Os 2005). The task for the research community is to use these broad markers or clues to help identify the direct risk-modifying factors. Insofar as the primary focus has been on risk, only limited attention has been paid to resilience and protective factors. As discussed by Jones (this volume), resilience may be most usefully defined as *the degree of adaptability when faced with adversity*. As such, both protective factors and resilience can be conceptualized as factors that reduce risk following exposure to a candidate risk factor (i.e., statistically as effect modifiers). This noted, risk dominates the existing literature to such an extent that most of the data are framed in terms of risk rather than protection or resilience.

Incidence and Risk

It is now established that the incidence of schizophrenia and other psychoses varies markedly across and within populations (McGrath 2007). Most notably, the incidence is higher in men, in densely populated urban areas, and in some migrant and minority ethnic populations; that is, in groups of people who happen to comprise an ethnic minority in a given geographical region (McGrath et al. 2004). Further, observational epidemiological studies have identified a large number of putative risk factors and risk indicators at multiple levels (from the societal to the molecular), with risk and odds ratios (OR) commonly ranging from around two (e.g., obstetric complications; Clarke et al. 2006) to around ten (e.g., family history; Mortensen et al. 1999). Specifically in relation to genetic risk, molecular genetic studies currently provide strong support for associations with at least some single nucleotide polymorphisms that confer weak increments on risk ($OR < 1.2$) and at least some CNV deletions and duplications which are rare but confer much stronger effects on risk in the small proportion of cases who are carriers ($OR > 3$) (e.g., deletions at 22q11 are associated with a 30-fold increased risk; Sullivan et al. 2012a). The list of candidate factors is extensive and, in addition to genes, a nonexhaustive list of the most robust includes older paternal and maternal age, obstetric complications (especially hypoxia), developmental delays, childhood adversity (especially abuse and bullying), and cannabis use (especially at a young age and with variants high in THC). The range of nongenetic candidate factors has been

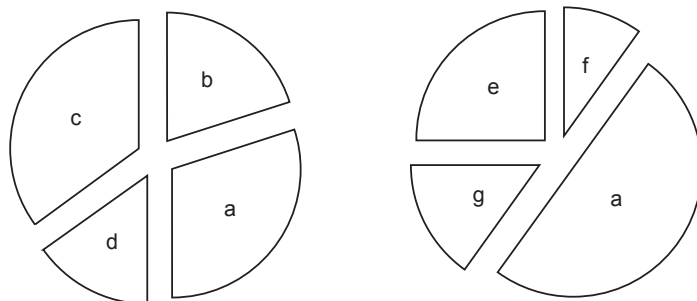


Figure 9.1 Hypothetical examples of clusters of risk factors that together may constitute a sufficient cause of psychosis: (a) genes, (b) trauma, (c) adversity, (d) substance use, (e) paternal age, (f) obstetric complications, and (g) viral infection.

regularly summarized in the literature (Murray 2003; van Os et al. 2010) and tends to converge on early development (i.e., childhood preadolescence) as a key phase for exposure.

In parallel, a large number of studies have identified cognitive and biological markers of risk: cognitive deficits in a number of domains that pre-date onset by many years (Kates 2010; Reichenberg et al. 2010; Welham et al. 2009); brain structural abnormalities, notably reduced gray matter volume prior to onset and ventricular enlargement (Steen et al. 2006); sensitization of the mesolimbic dopaminergic system (Collip et al. (2008); and HPA axis (Mondelli et al. 2010b; Pariante et al. 2004 axis. Despite these gains in our understanding of the risk architecture of psychosis, known risk factors explain only a small fraction of the liability. Psychosis is evidently multifactorial, with roots in early neuro- and sociodevelopment. No single factor, as far as we know, is either sufficient or necessary to cause onset. Instead, clusters of (overlapping) causes (see Figure 9.1) most likely work together (in varying combinations) to bring about the disorder (Schwartz and Susser 2006). Moreover, it may be that heterogeneity and overlap of clinical presentation mirrors heterogeneity and overlap in clusters of causes that lead to onset.

Specificity

A key issue related to incidence and risk is specificity. Many of the risk factors for psychosis are nonspecific and overlap with other disorders and syndromes (e.g., bipolar disorder, depression, anxiety, and posttraumatic stress disorder). As illustrated in Figure 9.2, continuities (e.g., shared genes) and discontinuities (e.g., premorbid IQ) in risk exist between schizophrenia and bipolar disorder (Demjaha et al. 2012). Many of the social risk factors recently implicated in psychosis are associated with a wide range of disorders and other adverse outcomes. For example, childhood adversity, broadly defined, is associated with nearly every mental disorder as well as with a wide range of negative outcomes,

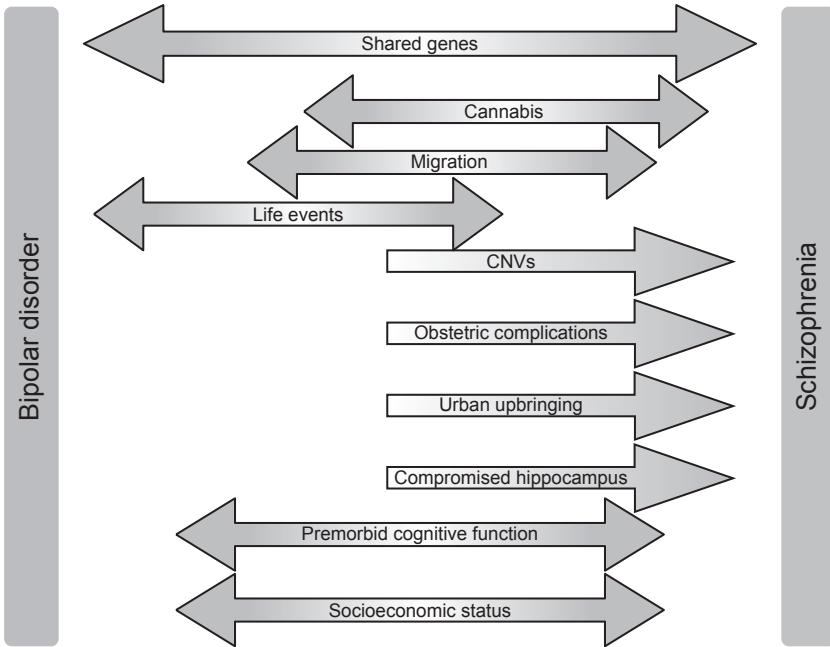


Figure 9.2 Shared and distinct risk factors for schizophrenia and bipolar disorder (reprinted from Demjaha et al. 2012, with permission of Oxford University Press).

including school exclusion, poor educational attainment, subsequent unemployment, re-victimization, substance use and abuse, and offending behavior (Kessler et al. 2010; McLaughlin et al. 2010). Complicating the picture further, much of the evidence that implicates social risk factors (e.g., trauma) has been based on studies of psychotic experiences in general populations (Varese et al. 2012). These studies show that psychotic experiences in these samples are strongly associated with common mental disorders, primarily depression and anxiety (Varghese et al. 2011). Similar overlaps have been observed in relation to cognition and biomarkers (Kelleher et al. 2012a).

There has been a tendency to view this heterogeneity and overlap in risk as a problem and a challenge for efforts to understand distinct disorders. However, nonspecificity is common across medicine; risk factors often operate across multiple diseases (e.g., cardiovascular, diabetes, cancer). Nonspecificity is generally observable in nature and as such should be viewed and embraced as an opportunity to understand shared pathways and interventions. For example, adverse environmental experiences and genes which lead to impaired brain function may combine to create a generalized vulnerability platform, or pluripotent risk state. Over time, early nonspecific symptoms and signs may develop from which (depending on the presence of other risk or protective factors)

more specific clinical disorders may emerge, either alone or as multiple comorbidities. This implies that if interventions could be targeted at this early state (i.e., before the signs of specific disorders appear), substantial public health benefits spanning a range of health outcomes could result (McGorry 2007).

Interactions and Causal Pathways

Science strives to find simple, parsimonious hypotheses that are better suited to the scientific method (e.g., falsification). However, those which examine one risk factor at a time do not reflect the reality of biology. Interactions can exist between (a) genes (epistasis), (b) genes and the environment, as well as (c) two or more environmental risk factors. Risk factors can be linked with additional contingencies that result in unexpectedly complicated pathways. This necessitates moving beyond efforts that isolate independent causal factors to consider interactions and causal pathways; that is, to elucidate webs of causation along pathways to psychosis.

Currently, there is intense interest in exploring interactions and causal pathways, most notably in relation to gene–environment interactions (van Os et al. 2008). Not surprisingly, a growing body of data points to complex interrelationships between many of the candidate factors noted above, including putative though not robustly supported interactions between genes and environmental exposures, e.g., AKT1 and cannabis use (van Winkel 2011); environment–environment interactions, especially across levels of analysis, e.g., cannabis use and urbanicity (Kuepper et al. 2011); cumulative impacts of multiple exposures, e.g., trauma and social adversity (Morgan et al. 2008; Varese et al. 2012); and mediation along causal pathways, e.g., sexual abuse via revictimization and affective dysregulation (Bebbington et al. 2011).

Recognizing these complex interrelationships constitutes an important initial step toward the dissection of the risk architecture for psychosis. They have the potential to inform us on the contexts (e.g., fragmented neighborhoods) within which individual-level exposures (e.g., social isolation) impact on risk, on how specific risk factors cluster and add up to increase risk, and on the developmental trajectories which, at each point, increase the probability of disorder. The potential implications for prevention are clear: efforts could be targeted at key stages of development and at specific groups or areas. However, modeling these interrelationships is statistically complex and controversial (with notable potential for Type I error), requiring large samples with data on a range of exposures.

In relation to public health, we need to be particularly alert for interactions between two or more risk factors that result in “qualitative” or cross-over interaction. Zammit et al. (2010a) cite the example of paternal antisocial personality traits and childhood conduct problems. When paternal antisocial personality traits are present, the more time a father spends with a child, the

higher the risk of conduct problems. In the absence of paternal antisocial personality traits, however, the more time a father spends with a child equates to a lower risk of conduct problems (Jaffee et al. 2003). Such an example seems intuitive, but one can also envisage that, at a molecular level, if there are optimal levels of a certain bioactive molecule (i.e., best function is achieved by not too little and not too much), then for individuals with low constitutive levels of that molecule, additional exposures which tend to elevate that molecule's abundance would be protective. In others with optimal or high constitutive levels of that molecule, such exposures would, however, be damaging. There are no unequivocally demonstrated examples of this in psychosis, although the apparent existence of an optimal dopamine level for some aspects of prefrontal cortical function suggests such a possibility (Mattay et al. 2003; Vijayraghavan et al. 2007; Williams and Goldman-Rakic 1995).

Another example is given by the methionine (or Met) allele from the brain-derived neurotrophic factor (BDNF) val66met polymorphism, which leads to reduced secretion of the BDNF propeptide (Egan et al. 2003). While decreased secretion of the neurotrophin and the resulting impediment of neuroplasticity may imply a resulting predisposition to mental disorder, this is not necessarily the case. In the face of a stressor, the Met allele may be protective, as the amount of BDNF available to exert potentially negative plastic effects on the brain may be reduced (i.e., the variant acts as a buffer against the stressor). On the other hand, the same stressor in an individual with the valine (or Val) allele at the same locus may elicit a response that results in a neuronal or cellular response that is qualitatively different. The Val variant of the BDNF val66met is more likely to engage a plasticity pathway when compared with the Met variant. This could result in maladaptions of the brain in the context of stress. To complicate this further, the greater plasticity associated with the Val allele may also make individuals more responsive to protective factors, such as social support and psychotherapy. According to this differential susceptibility concept (Belsky et al. 2009), the genetic profile of an individual thus shapes the plasticity or responsiveness of the brain to environmental influences in general, thereby challenging the traditional view that susceptibility variants are inherently bad.

Risk Prediction in Populations

The overlapping and distinct risk factors for schizophrenia and a range of other disorders pose a number of challenges, especially in terms of utilizing this knowledge to predict onset, to identify high-risk groups, and to guide prevention and intervention. For example, the identification of individual risk factors (or indicators), each of which may have contributed only a minimal amount to overall risk, is of limited value in developing interventions or for the purposes

of prevention. This is especially true for environmental factors and is illustrated using the example of cannabis.

Robust evidence from prospective cohort studies indicates that early use of cannabis is associated with a significantly increased risk of psychosis and related outcomes (Arseneault et al. 2004; Moore et al. 2007). This makes cannabis an attractive candidate for public health interventions (Degenhardt et al. 2009). However, because the effect size is relatively modest (e.g., Moore et al. 2007 report a twofold increase in risk) and because schizophrenia has a relatively low incidence (about 15 per 100,000 per year according to McGrath 2007), as do other psychotic disorders (Kirkbride et al. 2006), the population attributable fraction associated with this exposure is disappointing. Based on the best available epidemiological data, Hickman et al. (2009) estimated the number of individuals who would need to stop using cannabis to prevent one incident case of schizophrenia (technically referred to as a “number needed to prevent” or NNP). In people aged 20 to 24 with heavy cannabis use, they found that the NNP for men was 2800 whereas for women it was 5470. Estimates for people who use less cannabis is about four to five times higher. Considering that the best available public health interventions related to cannabis cessation have weak outcomes (i.e., these interventions themselves have high NNP), leveraging cannabis use as a means to reduce the incidence of schizophrenia becomes much less attractive. Alternative strategies related to cannabis use and the risk of psychosis may relate to (a) identifying individuals who are at increased risk due to other factors (e.g., genetic susceptibility, exposure to other risk factors, onset of academic decline, transfer to special education class due to behavioral problems), (b) reducing access to potent forms of cannabis, and (c) public health campaigns targeted at young teenagers to encourage delayed onset of first cannabis use.

In other areas of medicine (e.g., diabetes, cardiovascular), multiple risk factors have been combined into risk scores (e.g., Framingham Risk Score for cardiovascular disease), with varying degrees of complexity, aimed at predicting disease outcome (D’Agostino et al. 2001). The assumption in such models is that risk factors combine to increase the likelihood of disease or of poor outcomes. If brief and readily applicable in clinical settings, such tools may be of particular value in efforts to identify individuals at high risk of disorder and/or poor outcome.

Our discussions considered whether the development of such tools for risk factors in relation to psychosis was feasible. The various environmental factors implicated thus far are a mixture of risk indicators and risk factors measured at different levels (e.g., trauma, ethnicity, social fragmentation). As noted, further work is needed to establish how these various factors relate to each other. The limitations are illustrated in a study using data from the British 1946 Birth Cohort, in which Jones and Van Os (1998) found that combining a number of neurodevelopmental risk markers yielded a positive predictive value of only 1.2% for schizophrenia.

Based on data available presently, it appears that we need to determine whether (a) risk factors (or their combination) with stronger predictive validity exist and/or whether (b) additive models of risk assessment may not apply for psychosis, and so new concepts, analytic techniques, and algorithms may be necessary. A more restricted approach, focusing on a narrower domain of risk, may be more productive at this stage.

Take, for example, polygenic risk scores: Given the effect sizes of typical common variants in schizophrenia, if such alleles are to contribute to risk prediction it will be through examination en masse of large groups of markers rather than individual associations. One way of applying these large sets of alleles is through a method known as polygenic score analysis. As initially applied in schizophrenia by the International Schizophrenia Consortium (ISC), this approach was used to test the hypothesis that schizophrenia risk with respect to common alleles is distributed across very large numbers of genetic variants with small effect size (Purcell et al. 2009). The process involves designating, as putative schizophrenia risk alleles, those alleles that are “associated” with schizophrenia at extremely relaxed thresholds (e.g., $p < 0.5$) in discovery or risk score “training” genome-wide association (GWA) data sets. In subsequent independent “test” data sets, individuals are then assigned “polygenic scores” based on the average number of “risk” alleles weighted by their effect sizes in the training data set, and the scores for cases and controls are compared. Data from the ISC revealed that such scores were highly significant predictors of affected status in the independent schizophrenia data sets, and indeed also predicted bipolar disorder (Purcell et al. 2009). Based on the ISC training data set, the effect size for predicting case status was extremely small, but the ISC study estimated that larger training GWA studies might achieve more robust predictive values at a level that, while not of diagnostic value, might identify individuals at substantially elevated risk of the disorder at a level equal to or better than family history. If this prediction turns out to be correct, and enough data become available over the next few years to test it, such polygenic scores might be deployed to identify individuals at relatively high risk.

Ultimately, it would be optimal to combine risk factors from many domains. The high-risk paradigm offers another potential avenue for prediction, with emerging evidence for specific clinical and demographic factors that predict transition to psychosis (Yung and McGorry 1996; Demjaha et al. 2012). For example, a family history of psychosis, a recent decline in functioning, and a new onset of sub-syndromal psychotic experiences are associated with an increased risk of transition in up to 40% of individuals in the peak age (15–25 years) for the development of psychotic disorder (Cannon et al. 2008; Murray et al. 2004). In one study of individuals at high risk, when factors such as family history, a decline in social functioning, drug abuse, and delusion-like symptoms were combined, around 80% of cases who made the transition to psychosis were predicted (Cannon et al. 2008; Murray et al. 2004). Development of neurobiological measures that index vulnerability to psychosis (e.g., gray

matter volume, cortisol, neurocognitive profile, event-related potentials) is also a promising area that may lead to the development of other assessment tools for predicting risk.

From Risk Factors to Risk Pathways and Mechanisms

How can knowledge of risk and resilience factors be leveraged to optimize discovery pathways? That is, how can we elucidate the complex causal matrices and pathways through which identified risk factors impact on neural circuits in the pathogenesis of disorder? Achieving this necessarily requires research across multiple levels, ultimately from the societal to the individual to the molecular. Important examples exist to illustrate how this can be achieved (see McGrath and Meyer-Lindenberg, this volume) as well as the significant obstacles that can limit progress. Our discussions inevitably focused on examples drawn from our areas of interest and expertise. We do not suggest that these are the only or most important ones. Other examples include links between stress and the HPA axis (Mondelli et al. 2010a); links between stress and brain chemistry, notably dopamine (Howes and Kapur 2009; Howes et al. 2012b); and links between exposure to threat and cognitive pathways (Garety et al. 2001). One of the key themes for us was how the basic neurosciences could be more effectively engaged in the study of psychosis. Related to this, Andre Fenton (pers. comm.) provided the following “view from a basic neuroscientist”:

It will be generally valuable to recruit basic neuroscientists to study problems that are directly relevant to schizophrenia. In particular, this recruitment will be necessary to characterize the neurobiological consequences of genetic alterations that have been identified in schizophrenia. However, most basic neuroscientists will continue to be reluctant to study animal models based on genetic risk factors for the simple reason that the relevance of a particular animal model to schizophrenia is questionable. This will be particularly true for genetic models derived from genetic screens if the penetrance of the mutation is low. In this case, studying the particular gene or genetic alteration will also be of uncertain value and thus of low interest.

There are three basic ways to encourage the desired recruitment:

1. Demonstrate that the target mutation is clearly and importantly involved in schizophrenia. To run a basic neuroscience research program the animal model needs to be both well defined and relevant. Meeting this condition would allow the researcher to explore pathophysiological and behavioral consequences with confidence that the findings have relevance to schizophrenia.
2. Demonstrate that a particular behavioral or pathophysiological endpoint is crucial to a core aspect of schizophrenia—understanding that the endpoint will likely represent one or a small number of features of

the syndrome, as opposed to an animal model of the full syndrome. In this way, the research program can proceed without needing to know whether the model being studied is relevant to schizophrenia *per se*.

3. Provide a clear set of theories. Given theory, the researcher can proceed by making predictions and evaluating experimental outcomes against the theory. This will allow the go/no go decisions to be made as the research program evolves.

Examples in Genetics

One major challenge in the genetics of schizophrenia lies in translating the identification of common variation into a deeper understanding of the biological pathways involved. This challenge exists because odds ratios for identified common genetic variants are low, and thus they may not induce robust changes that can easily be modeled in cellular or animal systems. This limits the use of these findings and poses challenges for engaging the wider neuroscience community. From a neuroscience perspective, high-penetrance variants provide a much more promising basis than low penetrance variants for investigating biological mechanisms and pathways through cellular and animal studies. At present, known high-penetrance variants for psychosis are restricted to CNVs, where the typical molecular lesions span multiple (often very many) genes, any one or more of which might be relevant (Sullivan *et al.* 2012a). Therefore, the reliable identification of high-penetrance single-base mutations may offer more precision in modeling. Strategies are now underway to identify these smaller molecular lesions; for example, whole exome and genome sequencing of case-control samples, and sequencing of mother–father–offspring families for variants that arise in affected persons as new mutations. While many variants of potential interest have been identified through sequencing (Xu *et al.* 2012), thus far none has been demonstrated to have an etiological role in schizophrenia. This work is in its early stages and should these variants exist, there is good reason to be optimistic that some will be identified.

Although it is difficult to model effects at the individual level, common genetic variants still offer opportunities for engaging neuroscientists with different requirements. Existing approaches seeking multiple weak variants in biological systems have pointed to targets for investigation and even possible therapy in Alzheimer's disease (Jones *et al.* 2010b). While it is possible, or even likely, that the complexity of psychosis means these associations are distributed across more biological processes or functions (which reduces power), there is already evidence for (a) enrichment of common genetic risk factors in bipolar disorder in genes encoding types of calcium channels (Sklar *et al.* 2011), (b) schizophrenia risk factors in a set of genes whose expression is regulated by microRNA-137 (GWAS Consortium 2011), and (c) rare variants in a set of genes affiliated to the glutamate NMDA complex (Kirov *et al.* 2012). The identification of the broad processes involved has the potential

to generate specific hypotheses, which can then be more readily exploited by basic neuroscientists. Moreover, although it remains to be established, it is at least plausible that common weak and rare strong variants will often converge on the same genes, or the same biological process. This means that modeling weak genetic effects through more robust genetic lesions (e.g., gene knockout) may be a tenable approach to deriving insights into the relevant mechanisms.

Other avenues for exploiting genetic findings have not yet been fully explored. Available sample sizes are probably inadequate for gene–gene interaction studies. Samples with both rich data on environmental exposures and extensive genetic data are even smaller, limiting the possibilities to explore gene–environment interplay. With respect to genes and the environment, some large studies are underway (e.g., EU-GEI 2008).

Genetics offers further avenues for investigating pathways to disorder, including the incorporation of nongenetic data. The identification of high-risk individuals through molecular methods (see above discussion on polygenic risk scores), for example, can be expected to facilitate any number of study designs that look at trajectories to disorder and, in particular, risk and resilience factors which distinguish those at high risk who go on to develop the disorder versus those who do not or whose outcome is more or less severe. One concrete example for which there are many analogous approaches is to follow a large sample of people with a defined molecular lesion that confers high risk (e.g., a specific CNV) with detailed longitudinal phenotyping. Such approaches may not just identify risk and resilience factors *per se*, but the detailed trajectories (e.g., EEG changes or time courses of cognitive and social interaction changes) can inform the work of basic neuroscientists in generating and exploiting model systems (cf. analogous changes during animal brain development), a process which might be iterative with the model systems informing designs of human high-risk studies.

Another area that is attracting considerable interest is epigenetics, which promises to produce novel insights into the dynamic interplay of genes and environments. While researchers often use the shorthand of labeling risk as “genetic” or “environmental” (i.e., nongenetic), it has long been accepted that this simplistic dichotomy does not reflect the transactional nature of biology. In particular, it does not capture the contingencies that occur between information derived from the DNA sequence (which we inherit from our parents) and instructions from the environment (which can range from basic chemical requirements for life, to mother–infant bonding and the family unit, to broad, system-level components at the level of society). The science of epigenetics aims to capture some of the mechanisms that mediate the interaction between these two broad domains. While the boundaries of this field are still being refined, it is clear that environmentally mediated factors (e.g., altered nutrition, stress) can change the tissue-specific and developmentally specific modification of DNA (e.g., via mechanisms related to methylation, histone coding, chromatin packaging). These mechanisms allow environmental exposures to

lead to persistent changes in the patterns of gene transcription, analogous to those that result from genetic variation, which may have profound implications for cellular properties and resultant emergent properties of this tissue. Within the field of schizophrenia research, there is considerable hope that this category of observation may provide mechanisms that link an exposure (e.g., prenatal famine, early life stress exposure) and biologically relevant phenotypes (e.g., neuroendocrine responsiveness, neurotransmitter properties) (Labrie *et al.* 2012; Oh and Petronis 2008; Petronis 2010; Pidsley and Mill 2011; Rutten and Mill 2009; Toyokawa *et al.* 2012).

Examples in Neurobiology

Measures of brain structure and brain function, including structural and functional MRI as well as electrophysiological paradigms, offer particular promise for studies of pathways and mechanisms linking environmental risk factors to psychosis. In particular, when measured using these tools in longitudinal fashion in animal models and humans, the effects of environmental risk factors, genetic risk factors, or both can provide an index of risk factor effects (i.e., mechanisms of effect) on brain structure and brain function. Furthermore, these types of studies can provide a platform where preclinical studies of novel therapeutics can be tested on brain structure and brain function, as well as behavioral deficits. As outlined by Cadenhead and de la Fuente (this volume), all of these measures demonstrate evidence of change during the prodrome and first episode of psychosis, perhaps revealing early brain changes at the emergence of psychosis.

In the preceding decade, a particular focus of neuroimaging research in psychiatry has been the identification of neural correlates of genetic risk variants for schizophrenia in the brain using imaging genetics—a research strategy that combines molecular genetics and neuroimaging techniques (Meyer-Lindenberg and Weinberger 2006). One of the main tenets of this approach is the idea that genetic susceptibility effects are not directly expressed at the behavioral level; instead, they are mediated by molecular and cellular mechanisms that shape the structural and functional properties of neural circuits. Compared with behavior, risk-related genetic effects likely have a higher penetrance for more direct indices of these structural and functional changes, and may be studied in healthy volunteers in the absence of illness-related confounds such as medication. At the beginning, studies focused on candidate genes. Recently, attention has shifted to the examination of genome-wide significant schizophrenia risk variants, where the link to the syndrome itself has been established with sufficient confidence.

For example, a promising systems-level risk phenotype is altered functional connectivity of the dorsolateral prefrontal cortex (DLPFC) and hippocampus during working memory. Influential pathophysiological models of schizophrenia propose that genetic and environmental risk factors disturb the

normal developmental maturation of pathways that interconnect these structures (Murray and Lewis 1987; Weinberger 1987), which is thought to promote deficits in experience-dependent plasticity, abnormal functional and structural connectivity, as well as psychosis in adulthood (Harrison and Weinberger 2005; Meyer-Lindenberg 2011). Consistent with this, disturbed prefrontal-temporal functional connectivity is evident in chronic, first episode, and prodromal samples (Crossley et al. 2009; Meyer-Lindenberg 2011; Meyer-Lindenberg et al. 2005; Rasetti et al. 2011; Wolf et al. 2009). In addition, anomalies in functional connectivity of DLPFC and hippocampus have been detected in unaffected relatives of patients with schizophrenia (Rasetti et al. 2011), healthy carriers of a genome-wide supported schizophrenia risk variant (Esslinger et al. 2009; Paulus et al. 2013; Rasetti et al. 2011), and genetic animal models of schizophrenia (Sigurdsson et al. 2010). A genome-wide supported risk variant for schizophrenia and bipolar disorder in *ZNF804A* is particularly interesting in this context, as the genetic association to altered DLPFC–hippocampus functional connectivity per se has been replicated in an independent sample (Meyer-Lindenberg 2010a).

Recently, efforts have recently been extended to investigate the effects of established (but complex) social-environmental risk factors in the brain (Meyer-Lindenberg and Tost 2012). One example of the potential for interrogating epidemiology and neuroscience research is the characterization of the neural effects of urban upbringing, an established environmental risk factor for schizophrenia. Using functional MRI to examine brain response during social evaluative stress processing in healthy volunteers, a recent study (Lederbogen et al. 2011) detected an association of urban upbringing and functional alterations in the perigenual cingulate cortex (pACC), a key brain region for the regulation of negative emotion and stress (see Figure 9.3). Prior data from epidemiology suggests that the adverse effect of urban upbringing is modulated by genetic risk factors, with an excess rate of psychosis in genetically vulnerable individuals brought up in urban environments (van Os et al. 2004). From a conceptual point of view, it appears most plausible that certain genetic and environmental risk factor constellations gain their clinical momentum through converging adverse impacts on the functionality of shared neural systems. Direct proof for adverse gene–environment interactions in the brain can be provided by probing the identified functional systems in individuals stratified by genetic and social background.

In addition to the identification of neural correlates of genetic risk, efforts have been made to use neuroimaging and electrophysiological measurements (ERPs, neural synchrony, prepulse inhibition) for predicting risk status for the development of psychosis (see Cadenhead and de la Fuente, this volume; Atkinson et al. 2012; Bodatsch et al. 2011; Jahshan et al. 2012; Tost and Meyer-Lindenberg 2012). Studies with electro- and magnetoencephalography, for example, have the advantage over functional imaging of capturing neuronal dynamics with a millisecond temporal resolution. However, such approaches

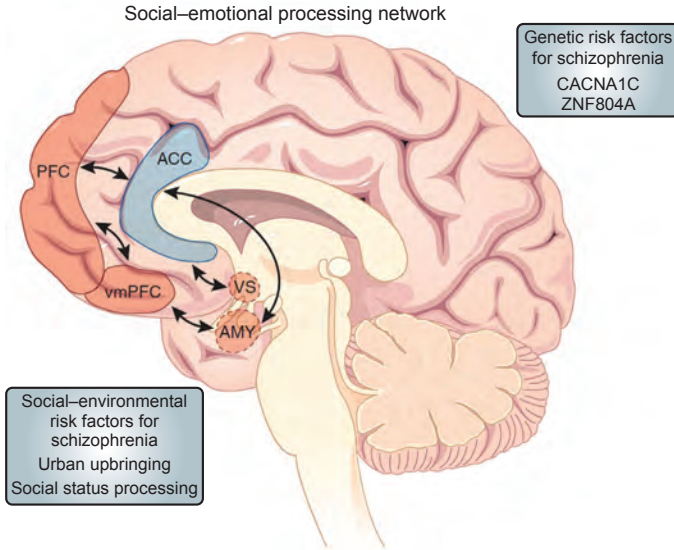


Figure 9.3 Effects of social and environmental risk factors for schizophrenia on regulatory circuits of human social-emotional processing (Tost and Meyer-Lindenberg 2012).

face several important conceptual and methodological challenges: intra-site reliability for longitudinal studies and inter-site reliability and variability of functional measures in the general population.

Analogous to the molecular genetics field, the identification of the effects of risk factors of small effect size as well as complex gene–gene or gene–environment interactions in the brain require the availability of large data archives. To test the potential of systems-level neuroscience measurements for risk prediction and biomarker discovery fully, future research needs to be conducted in multicenter studies with standardized quality assurance measures, data acquisition and processing schemes (including task paradigms), and analysis algorithms.

Research Challenges

Consideration of the previous examples (which, again, reflected our group’s experience) and our review of what is known about the risk architecture of psychosis from epidemiology led us to consider the challenges associated with an attempt to develop ambitious research programs aimed at integrating findings across multiple levels. Two implications were clear: (a) very large samples are necessary and (b) detailed information on these samples is needed across the full range of putative risk and resilience factors, from the environmental (including both individual level and area level exposures) to neurobiological to molecular. This means that research efforts need to be significantly scaled

up and broadened. Sampling and measurement (broadly defined to include the full range of assessment tools, from self-report questionnaires to neuroimaging to biological samples) constitute crucial areas for future research to address.

Sampling and Samples

What is the optimal strategy for the most efficient generation of new, large samples that will collect data across multiple levels of analysis?

A useful starting point is population-based sampling, which can set the principles for the selection of large representative cohorts and case-control samples. Population-based sampling broadly refers to the generation of a random sample (using a suitable sampling frame) from a known population (such that each person within that population has an equal chance of being selected to participate in the study) and, if not subject to selection bias, provides (relatively) precise estimates of the prevalence of exposures. This, then, sets the optimal standard for sampling to estimate risk and exposure prevalence. In some northern European countries, most notably Denmark and Sweden, the availability of register data on the whole population, and the facility to link these data to, for example, information on health service contacts and hospital admissions, sidesteps the issue of sampling altogether, as the sample is the entire population. Such systems provide considerable opportunities for studies that utilize data on whole populations across a wide range of domains, and studies from these countries have already produced a series of seminal findings that have advanced our understanding in a number of areas (e.g., Pedersen and Mortensen 2001).

Other sampling strategies are also important. Use of the Internet, for example, permits rapid generation of large samples with specific characteristics. At the Cognitive Assessment and Risk Evaluation (CARE) program at the University of California San Diego, the Internet has become an increasingly important means of recruiting early psychosis participants. Domingues et al. (2011) report that 16% of 223 subjects enrolled over a ten-year period were identified via the Internet. The number of subjects recruited per year via the Internet increased each year during the course of the study. The primary Internet site that refers to the CARE program is schizophrenia.com, a site dedicated to providing high-quality information on schizophrenia to the general public. On this site there is a link to a “Schizophrenia Screening Test and Early Treatment Resources,” which includes a screening instrument developed by Yale University and a list of prodromal psychosis programs worldwide. This method of recruitment is similar to that of many early psychosis programs worldwide.

In general, sampling for studies of biomarkers and neurobiological risk pathways have tended to be more ad hoc and purposive than described above, in part because the required sample sizes tend to be smaller and in part because of the relative practical difficulty of completing assessments (e.g.,

neuroimaging studies always require individuals to attend research facilities within which scanners are based) and consequent burden to participants. The aims are not usually to estimate main effects, but to explore pathogenic processes. Consequently studies may seek, for example, to identify individuals at the extremes of distributions (e.g., top 10% genetic liability and bottom 10%) or with and without exposures of interest (e.g., sexual abuse). This way more detailed assessments and samples relating to hypothesized psychological and biological pathways can be conducted (e.g., MRI, fMRI, cortisol, PET). Still, systems-level neuroscience research faces specific issues related to sampling bias. This arises from various sources such as technique-specific contraindications (e.g., nonremovable metal implants or electrified devices in the case of MRI), inconveniences (e.g., claustrophobia-provoking space restrictions), and the preferred location of high-end research equipment in urban areas. This can promote an underrepresentation of older, lower-educated participants with general somatic comorbidities from rural areas.

It may seem obvious, then, that the optimal strategy is to construct large population-based samples (either cohorts or case-control) in which sub-studies of psychological, biological, and genetic mechanisms based on selected subsamples can be nested within the larger study of risk and resilience factors (and their interactions). Data collected on all participants recruited to the epidemiological study can be used purposefully to identify individuals with particular characteristics; for example, individuals at high or low risk of disorder (defined according to prespecified criteria, such as cognitive decline and family history of disorder) as well as at the extremes of genetic liability. These individuals can then be assessed in greater detail on a wider range of cognitive tests (neural and social) and (potential) biomarkers. Recruitment to these nested studies will be no less challenging than recruitment to such studies generally; still, the fact that participants are drawn from a known sample means that nonrecruitment bias can be quantified in relation to all variables collected on original participants. In short, the findings from nested sub-studies of mechanisms will be more readily generalizable to a wider population (or at least the limits on generalizability will be more apparent). It is not just studies of neural pathways that can benefit from such an approach. In relation to environmental assessments, the necessarily more cursory and crude measures of environmental exposures used in large samples can be validated using more detailed assessments in subsamples (which may include independent corroboration, e.g., obstetric events, child abuse). This model is increasingly being adopted in existing cohorts (e.g., Avon Longitudinal Study of Parents and Children or ALSPAC, Dunedin, Environmental Risk Longitudinal Twin Study).

Two other design considerations came to the fore in our discussions. First, cohort studies to investigate psychosis are difficult and expensive; psychotic disorders are relatively uncommon (compared with anxiety and mood disorders) and relevant exposures or biomarkers often occur or are evident long before onset. This has, in part, fuelled interest in extended psychosis phenotypes

(i.e., transient and mild psychotic experiences, schizotypy) and endophenotypes (e.g., cognitive performance), which are more common. A number of cohort studies are ongoing that have relevant data (e.g., Avon Longitudinal Study of Parents and Children, Dunedin, Environmental Risk Longitudinal Twin Study, Christchurch Study). Individually, each study may not be large enough to provide sufficient numbers of individuals who develop a psychotic disorder. As far as we are aware, what has not been considered is combining samples, such that as participants pass through the age of risk for psychosis, the numbers meeting criteria for clinical disorder may allow for meaningful analyses. Genetics has led the way in showing how large-scale collaborations can yield samples that would have been otherwise impossible but which are essential to achieve sufficient power. Epidemiology needs to follow suit!

Second, the case-control studies noted above should not be discarded. Given what we now know about the genetic architecture of the disorders, they are likely to be the mainstay of primary identification of genetic risk factors for the disorder for which there is still a pressing need but now a clear pathway. Cheaper and more efficient than cohort studies, they offer additional advantages:

- They allow for studies of clinical disorder.
- It is possible to collect more detailed information on a wider range of exposures.
- It is possible (as above) to nest within them studies of mechanisms.
- They allow for the simultaneous study of area-level factors and their impact on incidence rates and, using multi-level modeling, for analyses of the relative impact of area and individual factors on risk.

Of course, there are many pitfalls with case-control studies; most notably, they rely on retrospective assessment of exposures, a particular problem when the recall of exposures may vary by case-control status. Various strategies can, however, be adopted to minimize recall bias (including use of corroborative evidence and, where available, contemporary records). In addition, for some exposures (e.g., child abuse) which cannot reliably be assessed at the time of their occurrence, case-control studies may be the only feasible design. Finally, case-control designs can be readily extended to include siblings and other relatives to reduce markedly unmeasured residual confounding.

In short, this points to the need for both (a) a scaling up and a mixed economy of research, in which studies of neurobiological pathways are nested within population-based studies (i.e., cohort or case control), and (b) sharing epidemiological data sets in order to have sufficient power to explore complex causal pathways (e.g., gene–environment interactions, environment–environment interactions). Regarding the latter point, while study-level meta-analysis is now well established in schizophrenia research, individual-level meta-analysis is often hindered by complex, time-consuming ethical and legal constraints related to data sharing and protecting confidentiality (van Os et al. 2009; Walport

and Brest 2011). Robust network and “cloud-based” systems, however, can now perform pooled analyses of individual-level data without sharing data; that is, individual-level data is returned to a secure central hub for “virtual” pooling but is never committed to disk nor stored on the server at any point (Wolfson et al. 2010). After careful harmonization of variables and data structure, this methodology has recently been implemented by the International Collaboration for Autism Registry Epidemiology.

Concepts and Measurement

Measure what is measurable, and make measurable what is not so.—attributed to Galileo (1564–1642)

The proposition that social risk factors are important in the etiology of psychosis is now widely accepted, largely as a result of recent studies which show that incidence is socially patterned and that various contextual (e.g., social fragmentation, ethnic density) and individual-level (e.g., trauma) exposures are strongly associated with psychosis. The conceptualization and measurement of social risk factors in psychosis research remains crude, with only limited attention paid to, for example, the nature, timing, duration, and severity of exposure. It is not uncommon, for instance, for studies of child abuse to be based on single questions with no information about age of abuse, severity, frequency, or perpetrator(s). Similarly, our understanding of the processes that are indexed by proxy variables, such as population density (the usual way in which urbanicity is operationalized) and ethnicity, remains limited. It is unfortunate that as genetics and neuroscience develop ever more sophisticated technologies for interrogating molecular and neural processes, measurements of environmental exposures remain crude and outdated. This inevitably limits efforts to delineate the precise social processes that increase risk for psychosis and, without improvement, will thwart efforts to move from (social) risk factors to neurobiological mechanisms and pathways.

A useful starting point from which to move beyond the current situation may be a taxonomy to characterize the various types of socioenvironmental factors implicated in psychosis, as a basis for better understanding interrelationships between them and for developing more (or identifying already existing) sophisticated assessments. One possible schema distinguishes:

- *social position* (status) or variables that relate to an individual’s or household’s place within a social hierarchy (e.g., social class, ethnicity, gender);
- *social experience* or variables that relate to events or difficulties such as abuse, trauma, life events, and daily hassles;
- *social interactions* or variables that capture social connections and breakdowns (e.g., social networks, support); and

- *wider social contexts* ranging from schools and neighborhoods to regions and societies, which may exert independent effects on health and which may modify the impact of variables measured at other levels.

Delineated this way, it is evident that we have lumped together very different exposures under umbrella terms with limited meaning: social defeat (Selten and Cantor-Graae 2005), social disadvantage (Morgan et al. 2008), etc. This points to the need for tools that more fully capture the nature of exposures. Where these are not available (and we should look first; see below) there is significant work to be done developing them. Of particular note here, and by way of an exception to the above, is the use of *in vivo* experience-sampling techniques, which capture in real time daily hassles and emotional responses, thus illustrating precisely the type of innovations required (Myin-Germeys and van Os 2008; Myin-Germeys et al. 2001).

While the above discussion primarily relates to social factors, a more general point should be made regarding measurement, which may once again seem obvious but merits highlighting: standardized paradigms are needed for neurobiological assessments and procedures (e.g., structural and functional MRI, electrophysiological measurements, neurocognitive batteries). Standardization, however, is not enough. Measurement of specific processes (e.g., perception, memory) must be accomplished without confounds from other processes (e.g., poor attention, low motivation) or from generalized performance impairments or other factors such as smoking or poor nutrition (Knight and Silverstein 2001; Silverstein 2008).

Rapprochement with the Social Sciences

The above leads into consideration of the relevance of the social sciences to efforts to understand the impact of social factors on risk of psychosis. There is undoubtedly considerable skepticism within psychiatry about the value of the social sciences to understanding the etiology of psychosis. This stems from a now untenable view that the onset of schizophrenia and other psychoses is unaffected by environmental factors, as well as from the legacy of mistrust that developed when many social scientists sided with, and provided ammunition for, the amorphous antipsychiatry movement during the 1960s and 1970s, which challenged the very existence of mental illness (Morgan and Kleinman 2010). As a result, despite select examples where collaborations have been enormously fruitful (e.g., for depression, Brown and Harris 1978; for social class and schizophrenia, Hollingshead and Redlich 1958), researchers have been slow to draw from the social sciences in seeking to further investigate the crude social factors recently implicated in psychosis. In relation to concepts and measurement, there is much in fact that could be gained from a rapprochement with the social sciences, most notably sociology, which is primarily concerned with precisely the factors and processes being considered in relation to

psychosis: urbanicity, social class, ethnicity, and all forms of social adversity. In short, to optimize discovery pathways, there is as much a need to engage with the social sciences as with the neurosciences.

Implications for Prevention and Early Intervention

In considering possibilities for utilizing knowledge on etiological pathways to psychosis for prevention, our discussion was shaped by Geoffrey Rose (1985:33):

I find it increasingly helpful to distinguish two kinds of aetiological questions. The first seeks the causes of cases, and the second seeks the causes of incidence. “Why do some individuals have hypertension?” is a quite different question from “Why do some populations have much hypertension, whilst in others it is rare?” The questions require different kinds of study, and they have different answers.

This seminal paper (Rose 1985) suggests that strategies for prevention can be separated into those that seek to reduce (prevent) incidence rates of disorder in populations and those that seek to identify individuals at high risk of disorder and prevent individual cases of disorder.

General Populations

In relation to psychosis, we are not close to being able to predict risk (incidence) at a population level (or at least determinants of incidence at a population level), as already noted above in the discussion of risk prediction tools. Based on a systematic review and meta-analysis of studies of the incidence of psychosis in England, Kirkbride *et al.* (2012) have done some initial work on predicting incidence rates given knowledge of the sex, age, and ethnicity of populations and population density. Such systematic reviews are particularly useful for service planning and resource allocation. However, they do not provide any information about how incidence rates may be modified.

This noted, some of what we now know about pathways to the development of psychosis (via premorbid cognitive and functional decline), and the common occurrence of symptoms of depression and anxiety and isolated psychotic experiences prior to onset (i.e., a pluripotent risk state in which a number of adverse outcomes are possible), point toward generalized strategies to intervene to prevent more severe outcomes during childhood and adolescence. This was the basis for the staging model of mental disorder developed in Melbourne by McGorry *et al.* (2006). From this perspective, and further considering the nonspecific nature of many of the environmental factors implicated in psychosis, broader public health interventions that aim to reduce exposure to risk factors, and perhaps promote resilience or protective factors, may impact on incidence of psychosis (along with other disorders and adverse outcomes).

Clearly, better prenatal care, improved nutrition, reduced pollution, more green space for exercise, and public health campaigns to reduce tobacco and drug use are positive interventions as a whole. This extends to interventions such as school-based educational programs and interventions that target children who exhibit difficulties or a decline in performance at school. A further rationale for broad-based environmental efforts to reduce serious mental disorder later in life comes from animal studies, where exposure to enriched environments in adolescence has been shown to prevent psychotomimetic drug-induced behavioral, social, and cognitive changes thought to model aspects of schizophrenia (Koseki et al. 2012). By educating school officials and providing early interventions, it might be possible to identify earlier those at greater risk for not only psychosis but also mood, anxiety, behavioral, or learning disorders and alter the potential course.

School-Based Interventions

One strategy for prevention involves targeting risk indicators (e.g., poor interpersonal skills, poor social problem-solving skills, poor stress tolerance, poor self-regulation, decline in academic function) in children who show signs of risk for future mental health problems. Such interventions can be delivered in the school classroom as well as in other settings. Importantly, children receiving these services are not specifically identified as being at-risk for psychosis; intervention may have positive effects on a range of outcomes (some of which have already been demonstrated), consistent with the idea that intervening during the pluripotent risk state may be more effective than intervening at the later stage of high risk for a specific disorder.

For example, there is a developing evidence base for social-emotional learning interventions (delivered by trained teachers as part of regular classroom curricula) that shows significant effects on positive behavior, improved social emotional competencies and academic performance as well as decreases in conduct problems and emotional distress, and these are increasingly being implemented in school settings (Durlak et al. 2011). To date, however, the effects of such programs on preventing the development of serious mental disorders that continue into (or emerge in) adulthood are not known. Recent evidence from the animal literature, however, suggests that prophylactic training of specific cognitive functions might reduce the negative effects of a later-onset schizophrenia-related brain abnormality (Lee et al. 2012). Thus, the effects of very early intervention services will be important to explore, especially in light of the relative failure of current “ultra high-risk” identification and treatment efforts to delay psychosis by more than one year (Yung and Nelson 2011). In implementing school-based programs at a relatively early age (e.g., 8–13) for children identified as being in a pluripotent risk state, two critical issues and potential barriers involve (a) avoidance of labeling and stigmatization and (b) funding for adding interventions to the school curriculum.

At-Risk and Early Psychosis Populations

When we narrow our focus from the general population to those individuals who are at greater risk of psychosis, or who are already showing early signs of psychosis, a number of novel and potentially important pharmacologic and nonpharmacologic interventions have been identified that address risk domains (e.g., stress response, inflammatory processes, nutrition) but have yet to be studied as preventative or disease-modifying strategies in the early course of psychotic disorder (for a review, see Cadenhead and de la Fuente-Sandoval, this volume). Similarly, informative biomarkers that provide insight into mechanisms of illness or serve as putative predictors of psychotic illness can serve as surrogate endpoints in clinical trial designs and provide new directions for biomedical research. To illustrate the use of neuroimaging markers in treatment development and prevention, consider the following examples:

1. Once identified, and sufficiently established through independent replication, neuroimaging phenotypes related to genetic and/or environmental risk for schizophrenia may serve as neural systems markers that may be targeted for treatment development, in a “top-down” approach to treatment. For example, knowledge from neuroimaging and neurophysiological studies that demonstrate impaired structure and function in the DLPFC (see above) provides a rationale to target this particular brain region, and its associated functional neural circuitry, while studying the effects of novel pharmacological compounds or other therapies. One example for a novel therapeutic approach is repetitive transcranial magnetic stimulation (rTMS). Prior evidence suggests favorable effects of rTMS in DLPFC on negative symptoms, cognitive function, and intermediate neural markers linked to both this particular brain region and functional alterations in schizophrenia (Barr *et al.* 2013; Boroojerdi *et al.* 2001; Gromann *et al.* 2012; Prikryl *et al.* 2012; Rounis *et al.* 2006). Here, established neuroimaging markers of genetic or environmental risk, such as DLPFC-hippocampus coupling, may be used as functional readouts to examine whether novel therapies are efficient in modifying this particular neural system. If so, these markers may further be used to optimize these treatment approaches (e.g., by finding the optimal range of stimulation intensity in the case of rTMS, or the optimal dose range in the case of novel compounds). Notably, the fact that the risk marker itself is biological in nature does not mean that these features can only inform primarily biological interventions. In all these efforts, the brain is best conceptualized as an intermediate observation level where genetic and environmental risk factors converge and increase illness risk by their complex combined effects on shared neural subsystems. The same principle applies to the validation and optimization of psychotherapeutic approaches; for example, in the

context of the effects of behavioral therapy on established neural risk markers, such as amygdala hyperactivity in depression and anxiety disorders (Bryant et al. 2008; Siegle et al. 2006).

2. To give an example of a bottom-up approach, the effects of an environmental risk factor on brain structure or function might be useful for informing, or supporting, disease prevention strategies. Following the discovery of such a risk factor in a population-based sample, neuroimaging can be used to identify the effects of this in the brain (e.g., the effects of the complex phenomenon “urbanicity” on pericingulate function; Lederbogen et al. 2011). Further decomposition of these complex environmental risk factors into causal subcomponents (vs. epiphenomena) is certainly necessary to inform true preventative approaches. Here, neuroimaging risk markers may add an additional level of observation that can be exploited to guide these efforts (e.g., if significant associations of pericingulate function with social support measures, but not socioeconomic status, were to be detected). Naturally, not all of the identified neural functional (and presumably causal) risk subcomponents will be immediately susceptible to manipulation in real-world environments to modify disorder risk. However, the combination of evidence for a risk factor from a population-based sample, coupled with follow-up validation demonstrating effects of this risk factor on the brain, can provide a powerful platform to inform public health strategies for prevention.

There are, however, a number of impediments to the effective implementation of clinical trials for novel interventions in early psychosis, such as lack of interest by pharmaceutical companies in older drugs that would not provide profits (e.g., aspirin, minocycline). In addition, there are safety concerns regarding the use of children or teenagers who are represented in at-risk populations. The latter point raises a significant issue; namely, by separating services for children and adolescents from services for adults, barriers are created that impact research, intervention, and prevention.

Interface with Child Psychiatry

There is a clear disconnect between disciplines that address child and adult psychiatry across all countries represented at the Forum: Australia, Canada, Germany, Great Britain, Ireland, The Netherlands, Switzerland, and the United States. Breaking down the boundaries between the clinical disciplines of child psychiatry, developmental disabilities, and adult psychiatry carries with it a number of potential benefits.

As noted, psychosis is a developmental disorder, the early signs of which are often evident long before the emergence of positive symptoms and behavioral

disturbance. Those who go on to develop psychosis may be known to child services. Partitioning of services into separate child and adult systems discourages combined approaches that might enhance power by marshalling all relevant forces (including datasets), inhibits the use of expertise to develop the best developmentally appropriate tools of clinical (and other) measurement for research, and is a barrier to information flow about the outcome of research. Given the evidence that certain disorders in childhood are either risk factors for, or early manifestations of, adult disorders, it can be expected that the research agenda can be fostered by longer-term clinical perspectives, even at the level of case reports that seed experimental or more detailed observational studies. The discontinuity in service provision inhibits a longitudinal perspective, both among clinicians and in more formally designed studies that aim, for example, to identify which disorders have childhood precedents, who is most at risk, and even optimal treatment of the subset of people with childhood disorders who go on to develop psychotic (as well as other) disorders. As noted, there is evidence that preventative or ameliorative interventions for adult disorders may require delivery by those who conventionally work in the childhood arenas.

In addition to a more seamless integration of child and adolescent and adult psychiatry, prevention efforts could be enhanced by closer ties between mental health experts and the following groups: special education teachers, juvenile justice program staff, social workers, developmental psychologists, and family therapists. For example, special education teachers, by definition, work with children with serious emotional disturbances and/or cognitive/academic difficulties, and a substantial proportion of whom can even be considered to be at high risk for developing a serious mental disorder. Although these teachers have many skills for improving the social and academic performance of these children and adolescents, these skills are essentially unknown to child psychiatrists and psychologists. In addition, these teachers typically lack training in the identification of risk factors for serious mental disorder and in interventions developed within psychiatry. Similarly, a stressful upbringing (e.g., dysfunctional family environment, economic disadvantage) has been shown to increase risk for schizophrenia in both genetic high-risk (e.g., Tienari et al. 2004) and non high-risk (Wicks et al. 2005, 2010) populations, and it has been suggested that insights from the fields of neuroscience, genetics, psychology, and studies of the social world could be integrated into formulations focusing on interlevel interfaces, with profound implications for training, practice, and research in the field of family processes and therapy (Sluzki 2007). We do not wish to imply that there is a problem with different professionals possessing different skills. However, it is a problem if these professionals work separately and in relative isolation, without informing each other's work or treatment/education plans.

Recommendations

Expanding on our initial set of questions, we propose the following directions for future research:

1. Research needs to target the identification of risk factors—both genetic and nongenetic—scaled up by (a) combining existing cohorts and (b) constructing large population-based samples with nested studies of neural pathways and mechanisms.
2. Related to point 1, there is a need for stronger efforts, incentivized by funders, to make available large relevant epidemiological data sets, with a high priority for data sets that have genetic data from which to draw individuals at higher risk, to the research community much earlier (following the lead taken in genetics).
3. There is a need for much stronger interdisciplinary ties and fully integrated research programs between the neurosciences, the social sciences, developmental psychology, and immunology (neuroimmunology).
4. To move beyond crude markers of environmental risk (e.g., urbanicity, ethnicity), we need to develop (or identify from the social sciences and use) more sophisticated concepts and social assessment tools to capture the complexities of social contexts and experiences over time.
5. To allow better developmental modeling by neuroscientists and the genesis of theories which then become testable in those models, comprehensive longitudinal characterizations need to be developed at the earliest possible stage of cognitive, psychological, neurophysiological, social, and environmental profiles of individuals at high risk (identified through the population and other high-risk study designs).

With respect to prevention and treatment, we identified the following needs:

1. Emphasis needs to be given to the importance of implementing public health strategies that impact on important risk factors for psychosis.
2. Promising interventions that may have failed in patients with long-standing disorders need to be tested in at-risk and early psychosis populations.
3. The effectiveness of school-based interventions that target young people in a pluripotent risk state needs to be examined in terms of improving cognitive, academic, and social functioning, and for reducing behavioral disturbance and later incidence of serious mental disorder.
4. Child and adolescent services need to be merged with young adult services to better target the population at greatest risk for psychosis and follow them through the full developmental course.

Conclusions

The scientific map of schizophrenia is not a blank sheet. Over the last few decades, major advances in understanding genetic and nongenetic risk factors have been achieved, although some of the discoveries have been a source of frustration for those looking for quick and simple solutions. For example, the genetic architecture has not delivered common polymorphisms with large effect. Early cannabis use appears to be associated with an increased risk of schizophrenia, but population-based cannabis reduction will probably not prevent many new cases. Nevertheless, genetics has finally started to shed light on possible disease mechanisms, whereas research related to trauma exposure, migrant and minority ethnic status, and city birth have put the somewhat neglected area of stress and socially mediated risk factors firmly back on the table for our field. Although much more work remains, we do not face a *terra incognita*, upon which we are doomed to stumble. Rather, we have a map, albeit a very incomplete one. Given what we now know, and with the exponential growth in neuroscience and steady access to new technology, there are good reasons to believe that the challenges we face in schizophrenia research are tractable.

To the junior researchers who are contemplating entering or remaining in this field, we wish to reassure you that you should not feel intimidated by the uncertainties surrounding psychosis, a condition that exposes some of the farthest reaches of what it means to be human. Tenacity and creativity are required to add momentum to our field, and we encourage you to participate in this important and exciting world of research.