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Schizophrenia

The Nature of the Problems and the Need for Evolution and Synthesis in Our Approaches

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Overview

What is schizophrenia? What are its causes? Can it be cured? Can it be prevented? These fundamental issues have confronted the field of schizophrenia research and treatment for over 100 years. Our ability to improve the lives of people with the disorder, however, has not improved at nearly the same rate as the accumulation of new knowledge about it and technological advances to study it. Paradigm shifts may thus be needed to accelerate progress. This was the aim of the Ernst Strüngmann Forum, “Schizophrenia: Evolution and Synthesis,” to which a group of researchers were invited to explore novel ways of conceptualizing the disorder, integrating data across levels of analysis, and accelerating advances in treatment development and prevention efforts.

In this introductory chapter, we introduce the questions and issues that motivated the Forum, in terms of fundamental problems facing the field of schizophrenia research and treatment, and discuss the specific issues identified for debate and the questions which served as starting points for deliberation. We briefly summarize the debate and conclusions of each of the four thematic groups and highlight issues that emerged during the final plenary discussion.

Rationale and Motivation for Challenging Current Paradigms in Schizophrenia Research and Treatment

Schizophrenia is a diagnostic term which describes a serious mental disorder that affects approximately 1% of the population worldwide; current global
prevalence is calculated at over 20 million people (McGrath et al. 2008). Common clinical features of the condition include hallucinations, delusions, bizarre behavior, affective dysregulation and/or blunted affect, difficulties in social cognition and interpersonal functioning as well as cognitive impairment. Schizophrenia is typically diagnosed in late adolescence or early adulthood; it is often associated with lifelong disability, especially when appropriate services are not provided, and accounts for high levels of expenditures. In the United States, for example, it is estimated that as many as 10% of all mentally disabled persons are diagnosed with schizophrenia (Rupp and Keith 1993), and the diagnosis accounts for 75% of all mental health spending and approximately 40% of all publicly funded disability payments (Martin and Miller 1998). Among people with the diagnosis, 80–85% are typically unemployed at any given time; those who do obtain a job typically work for a few hours per week and quit or are fired after several weeks or months (Silverstein and Bellack 2008).

Schizophrenia imposes an immense financial burden on individuals, families, and societies. In the United States alone, the cost of treating people diagnosed with schizophrenia has been estimated to be USD 62.7 billion (~ EUR 50 billion) per year, including direct treatment costs and lost business productivity due to patient and family caretaker work absence (Wu et al. 2005). European studies also indicate high costs for treatment, although estimates are lower in southern European countries that use primarily older, less expensive medications, and where patients tend to live with families instead of in residential facilities. For example, Salize et al. (2009) calculate that the mean total cost per year, per patient, was EUR 36,978 in Zürich, EUR 16,868 in Mannheim, but only EUR 2,958 in Granada. These European cost estimates, however, represent only the direct costs of treatment; they do not include indirect costs such as lost work productivity of patients and families, or legal costs, which typically double the overall cost estimate. In the most recent comprehensive analysis of costs, Andrews et al. (2012), in a report prepared for the U.K. Schizophrenia Commission, estimated that the average annual cost per person with schizophrenia to society is GBP 60,000 and to the public sector GBP 36,000. In short, by any standard, schizophrenia is a major individual, family, and public health problem.

In recent years, numerous advances in research technology (e.g., in molecular biology and brain imaging) have resulted in an accumulation of new findings about schizophrenia. Despite this, the general sense in the field is that we are no closer to an integrated understanding of the disorder or to better methods to treat it (e.g., Insel 2009). Progress has not been made on a number of critical issues. For example, diagnosis is still made relatively late in the course of the neurodevelopmental trajectory—typically when persistent psychotic symptoms emerge, but many years after cognitive, academic, and social decline has begun. Our ability to predict who will develop the condition is poor, and etiology is essentially unknown. These issues, together with poorly developed
prevention and the fact that we still do not know whether schizophrenia represents one or more disorders, means that treatment is by trial and error. Even more shocking is that although medical illness-related mortality has decreased significantly in the general population, and life span has increased significantly for people with medical diseases (e.g., diabetes, heart disease, cancer), mortality for people with schizophrenia has not decreased over the past 100 years. Moreover, the average life span for a person with the condition is 25 years less than for people without it, and this has not changed for at least 50 years. In fact, treatment outcomes in some domains are arguably equivalent to what they were 100 years ago, the effect size of the difference between active treatments and placebo has decreased, and few patients are able to work or live independently (see Insel 2009, 2010; Kemp et al. 2010). Despite psychopharmacological developments over the past 20 years, increased effectiveness has not been demonstrated over medications that were developed in the 1950s and 1960s (Davies et al. 2007; Lewis and Lieberman 2008), treatment noncompliance is high (Lieberman et al. 2005), and several major pharmaceutical companies are eliminating new drug development efforts that target psychotic disorders. Similarly, despite many psychosocial treatment developments over the past 20 years, meta-analyses of some widely used interventions indicate small or near-zero effect sizes (e.g., Lynch et al. 2010), with inverse relationships between study quality and effect size (e.g., Wykes et al. 2008).

Fifteen years ago, many researchers thought that genetics, in the form of a relatively small number of genetic abnormalities, would provide the answers to guide treatment. It now appears, however, that the number of genome “lesions” may be over one million, and thus it is becoming increasingly difficult to develop and maintain an understanding of the genetic basis of schizophrenia. Moreover, many genetic findings have not been replicated. The extent to which this is due to greater than expected human variation, heterogeneity, and/or false positives is unknown. Another technique that offered much promise 15 years ago, and which spawned a great deal of investment, was functional magnetic resonance imaging (fMRI). These studies have added to our appreciation of the complexity of the pathophysiology of the condition, by demonstrating that schizophrenia is not the sum of multiple localized and independent brain dysfunctions but rather the result of altered connectivity between and within brain regions, as well as altered coordination and modulation of brain activity (Phillips and Silverstein 2003). Imaging findings have also contributed to the appreciation of significant heterogeneity within the disorder as well as to the sobering realization of the considerable overlap with healthy people in aspects of brain function. Nonetheless, despite important insights into brain function in schizophrenia from imaging studies, the origins of these problems, how they generate symptoms and the subjective experiences of the disorder, and how to treat them are far from clear. Therefore, as with genetics, the gap between our knowledge base and a comprehensive grasp of the nature of the disorder and how to treat it remains large.
In addition, in spite of major investments in the study of cognitive impairment—a factor thought to be closer to the basis of the condition than symptoms or behaviors—it remains difficult to isolate specific deficits from generalized cognitive impairments and motivational deficits, thus limiting our ability to understand the neural basis of the abnormalities. Behavioral studies of cognition generally have larger effect sizes than psychophysiological or neurobiological studies (Heinrichs 2001), which is the opposite of what was expected to occur with the application of techniques such as fMRI to studies of cognitive impairment in schizophrenia. Moreover, in both the behavioral and physiological domains, it is typical for an abnormal finding to be present in only 30–70% of patients, thus raising questions about the meaning of the deficit for the condition (Heinrichs 2001). Often, issues of diagnostic specificity are ignored, despite the fact that some of the most consistent findings from imaging studies (e.g., reduced hippocampal volumes) have been found in other populations (e.g., people who experienced childhood physical or sexual abuse; Bremner et al. 2003). This suggests that some findings may reflect nonspecific factors, such as chronic stress.

Unlike nonpsychiatric disorders (e.g., coronary artery disease), where the relationship between epidemiology and pathogenesis is generally understood, in schizophrenia, research on the interaction of these factors has, for the most part, remained separate (McGrath and Richards 2009). This has seriously limited the development of comprehensive theories of the disorder that integrate societal, environmental, biological, and developmental perspectives. Recent studies, however, indicate important roles for factors such as cannabis use, stress, negative family environments, physical and sexual abuse, viral exposure, and racial discrimination as well as other forms of chronic social defeat in increasing the risk for schizophrenia (e.g., González-Pinto et al. 2011; Kirkbride et al. 2008; Lysaker et al. 2007; Tienari et al. 2004). Therefore, frameworks that conceptualize the development of schizophrenia within a societal context need to be developed.

Progress in addressing these issues requires more than just incremental additions to the existing research base. We believe that new paradigms coupled with an integration of data from multiple levels of analysis (and new methods of doing this) are necessary. This Forum was viewed as a step forward in this larger process. Our expectation was that by the end of the Forum, progress would have been made in (a) identifying factors (e.g., paradigmatic, disorder-related, institutional, financial, societal) that are preventing breakthroughs and (b) exploring alternative and novel ways to conceptualize, model, diagnose, treat, and research the disorder. Below, we summarize the different themes of the Forum, the specific questions that served to spark each of the groups’ discussions, and the outcomes of those discussions.
Group 1: Which Aspects of Heterogeneity Are Useful to Translational Success?

Issues

For many years, schizophrenia has been viewed as a single condition. However, there is no finding that is pathognomonic of schizophrenia, and the best available evidence indicates that specific abnormalities (e.g., in cognition, psychophysiology, neuroanatomy) are found in only 30–70% of patients (Heinrichs 2001). Genetic data increasingly indicate that schizophrenia is a heterogeneous disorder (Mitchell and Porteous 2011; Sebat et al. 2009). This suggests that what we now call schizophrenia may in actuality be a final common pathway of multiple etiologies, or a class of disorders that share some clinical similarities. This view is consistent with recent initiatives to redefine what we now call schizophrenia in terms of basic processes (Insel et al. 2010). The mission of the first discussion group (Corvin et al., Chapter 5, this volume) was to consider this and other evidence related to how schizophrenia is currently conceptualized. Guiding questions included:

- What are the core features of schizophrenia?
- Why has more progress not been made on the homogeneous–heterogeneous question, and what needs to occur to resolve this issue definitively?
- What are the most promising dimensions (e.g., genetic, cognitive, brain function) upon which efforts to clarify heterogeneity can be based?
- Within each dimension, to what extent do findings reflect basic widespread impairments (e.g., reduced cognitive coordination, reduced context-based modulation of neural processing due to NMDA receptor hypofunction, and reduced activity of parvalbumin-containing GABA interneurons) versus multiple independent abnormalities?
- In what ways do we need to revise our understanding of schizophrenia based on findings of genetic overlap with bipolar disorder and symptomatic overlap between childhood schizophrenia and autism spectrum disorders?
- How can we develop a theory of schizophrenia such that it is understood at multiple and interacting levels (e.g., biological, cognitive, phenomenological) in an integrated fashion?

Summary

In their deliberations, Corvin et al. (Chapter 5) began with the idea that schizophrenia is not a disease, because a disease is defined as a phenomenon with known etiology, pathophysiology, and course. Consensus emerged that schizophrenia is, at best, a syndrome, or a collection of signs and symptoms that
statistically occur together. The group agreed that schizophrenia is an “open construct” in that its boundaries and many of its features overlap with other medical and psychiatric disorders. Corvin et al. also agreed that schizophrenia is best considered a category, such as dementia, epilepsy, or cancer. That is, what we now call schizophrenia is most likely a category of brain syndromes that bear some outward resemblance to each other, probably by virtue of sharing pathophysiological mechanisms. However, the number of individual syndromes that make up the category is unknown, as are the etiologies of the syndromes. With this in mind, a major agenda for research and treatment is to focus on identifying phenomena that go together, across multiple levels (e.g., biology, cognition, symptom, subjective experience), so as to better describe heterogeneity and move toward personalized treatment. Given that schizophrenia can be studied at so many levels, a key question is: Which levels of analysis are most important?

Consensus emerged that several levels are particularly important. The first level concerns etiological factors, such as genetics, and consequences of infection, such as inflammation, that affect brain function. A second level concerns pathophysiology, where cellular (e.g., neuropil loss), molecular (e.g., reduced GABA, excessive dopamine), and circuit (e.g., reward circuitry, effective connectivity) issues were all considered important. The third level can be broadly construed as the behavioral domain, including learning and other cognitive factors. The fourth, and most debated, level concerns observable or subjective phenomena, such as deficit symptoms (e.g., a loss of motivation) or an altered sense of self.

Because the biological bases of symptoms such as amotivation and hyperreflexivity (i.e., hyperawareness of normally tacit aspects of bodily or mental experience) are relatively unknown, skepticism was expressed as to how useful these constructs are at present for moving the field forward. However, there is a long tradition of a focus on symptoms, and research indicates that phenomena such as altered self-experience (Lysaker and Lysaker 2010; Nelson et al. 2013; Sass and Parnas 2009), despite its relatively unknown etiology, constitute some of the best predictors of schizophrenia; that is, who develops schizophrenia versus who develops bipolar disorder (Nelson et al. 2012). In addition, recent work suggests that disturbances in self-representation contribute to excessive inflammatory activity, thereby providing a potential link between psychological and biological abnormalities in schizophrenia (Barnsley et al. 2011; Corlett 2013). Therefore, a challenge to the field is to understand the psychological phenomena involved in schizophrenia and to advance integration across biological and psychological levels, in an effort to characterize heterogeneity. Methodological issues in studying covariation between phenomena at multiple levels were discussed, and the benefits of traditional linear model (e.g., correlational) approaches versus those that can model nonlinear relationships (e.g., coefficients of mutual information) were outlined. Finally, there was significant cross-fertilization with the discussions of other groups on
(a) the emerging view that schizophrenia is a lifetime disorder with evidence of impairment from birth, and the extent to which the dimension of “premorbid” developmental course can capture variance in heterogeneity relevant to current research and clinical efforts (see C. Morgan et al., Chapter 9, this volume); (b) the extent to which pathophysiological mechanisms can and should be studied individually without the need to model multiple clinical features, and how this can help us understand heterogeneity (see Mitchell et al., Chapter 13, this volume); and (c) which aspects of heterogeneity are most relevant for designing better treatments and treatment programs (see V. Morgan et al., Chapter 17, this volume).

**Group 2: How Can Risk and Resilience Factors Be Leveraged to Optimize Discovery Pathways?**

**Issues**

Much evidence indicates the presence of abnormalities that predate the diagnosis of schizophrenia. This includes enlarged ventricles in infants at genetic risk, “pandysmaturation” in infants at genetic risk, persistence of infantile motor activity into childhood, and poor motor, academic and social functioning in childhood and adolescence (Fish and Kendler 2005; Gilmore et al. 2010; Schenkel and Silverstein 2004; Schiffman et al. 2006; Walker et al. 1999). This evidence suggests that, for many people at least, schizophrenia involves a lifelong abnormality that may express itself differently over time, perhaps as a function of developmental changes in brain structure, regional activation level, and function. However, a simple unfolding of neuropathology is unlikely to account adequately for the life histories or clinical presentations of patients. For example, it is now known that environmental (e.g., toxic and psychosocial) factors affect whether schizophrenia develops and how it looks when it develops (for details, see C. Morgan et al., Chapter 9). In their discussions C. Morgan et al. aimed at integrating data across levels of analysis for the purpose of synthesizing a lifespan developmental perspective of schizophrenia, and, in doing so, addressed questions such as:

- How do environmental factors interact with genetic variables to increase or decrease the likelihood of first and later psychotic episodes?
- Do developmental data suggest a core dysfunction that accounts for multiple manifestations across the lifespan (e.g., motor, cognitive, phenomenological)?
- To what extent does abnormal subjective experience, and the concomitant distress associated with such changes, lead to further alterations in biological processes that increase the likelihood of psychosis emerging?
• Why has there been such a separation of pathophysiology from epidemiology research (e.g., on social defeat, poverty, physical and sexual abuse, drug abuse, exposure to specific viruses), and what can be done to change this?
• What do current results indicate about social and lifestyle factors and the development of schizophrenia, and what research needs to be done to understand this better?
• What needs to happen to improve our understanding of the genetic basis of schizophrenia?
• What is the role of epigenetic factors in schizophrenia?

Summary

Discussion in the group began with the recognition that if we want to prevent and treat disorders like schizophrenia, we must first understand the matrix of risk factors that underlies the etiology and pathogenesis of these syndromes. There has been considerable progress in our understanding of risk for schizophrenia and, more broadly, psychosis over the past 40 years, and this has spawned special clinics for young people considered to be at ultrahigh risk for psychosis. To date, however, most evidence suggests that although we can delay the onset of schizophrenia for one to two years in people in an at-risk mental state, we cannot prevent its eventual onset (Yung and Nelson 2011; Morrison et al. 2012). Exceptions to this include one relatively small study that used fish oil high in omega-3 fatty acids (and so, with anti-inflammatory properties) as the primary intervention (Amminger et al. 2010), and a study of a form of cognitive behavioral therapy specifically designed to address cognitive biases commonly found in people who develop schizophrenia (van der Gaag et al. 2012). In the latter study, however, the intention to treat analysis (i.e., including all subjects who entered the trial) did not reach statistical significance. Thus far, medication has not been shown to prevent schizophrenia. This discussion led to several insights and recommendations. One, agreed upon by all other groups, was that intervening at the point in time when a person begins to display prodromal indicators of schizophrenia is too late. Rather, recognizing that many psychiatric disorders share the same risk factors, an alternative—but largely untested approach—is to intervene much earlier (e.g., 9–13 years of age), when academic and behavioral difficulties typically emerge. The idea was that if we can prevent further deterioration of social and cognitive functioning during this “pluripotent risk state” (i.e., a phase during which a set of difficulties could develop into any of a number of later disorders), we are more likely to prevent schizophrenia, as well as several other conditions.

A second focus of discussion centered on the need to study the interaction of risk factors. Clearly, even the most promising risk factors only increase risk to a small degree. However, combinations and interactions of factors (e.g., genetic abnormalities, low intelligence, childhood abuse, stressful home
environments, and drug use) are far more likely later to be associated with schizophrenia. Identifying protective and harmful interactions may also help us characterize heterogeneity and risk, as well as formulate rational public policies that are likely to reduce significant numbers of future cases of schizophrenia. Conversely, given the emerging recognition that psychotic phenomena in the general population are far more widespread than traditionally thought (e.g., Rössler et al. 2007), there needs to be an increased focus on factors, and their interaction, that promote resilience and reduce the likelihood of developing schizophrenia.

In addition to the group’s call for greater study of the positive predictive value of interactions between risk factors, there needs to be greater integration of disparate fields of study. For example, integrating our understanding of genetic markers with their corresponding pathophysiological sequelae is in its infancy but has shown great promise. On a larger scale, C. Morgan et al. note that there has been insufficient exchange between fields such as epidemiology, sociology, and the neurosciences. This has led to a situation where we do not yet understand, for example, how, in terms of biology, certain risk factors (e.g., child abuse) increase the risk of developing schizophrenia later in life. Similarly, we do not yet fully understand the extent to which the incidence of alterations in specific mechanisms (e.g., hypothalamic-pituitary-adrenal axis dysfunction, viral infection) are made more likely by social and environmental factors (e.g., urban environments, poverty), although emerging evidence is beginning to reveal such relationships. There is also the longstanding issue of how the biological and cognitive factors associated with schizophrenia lead to the subjective experiences of psychotic symptoms and phenomena, such as disturbed experience of the self (Renes et al. 2013). To help resolve this issue, C. Morgan et al. stress the importance of and need for more cross-fertilization between scientists in fields such as computational modeling, neurobiology, and neurophenomenology. Greater clarity is also needed to distinguish better between concepts such as social adversity, social disadvantage, and social defeat.

Another important conclusion reached by C. Morgan et al. was that the traditional separation of child and adult psychiatric services negatively affects clinical care and research by forcing people to be seen in two different systems; it also minimizes exchange between researchers and clinicians in the different fields. They recommend that this separation be eliminated and envision a system wherein research on, and treatment of, mental and behavioral difficulties that emerge in childhood and adolescence would be informed by an understanding of factors that mediate and moderate the transition to adult forms of psychopathology. Specifically, they suggest that child, adolescent, and adult services be merged so that the population at greatest risk for psychosis can be better targeted and followed throughout the full developmental course. Finally, consensus emerged that it is not necessary for all preventive efforts to be carried out in psychiatric clinics. Already, school-based interventions have shown effectiveness for treating social and academic difficulties.
in young people. More efforts are needed, however, to examine the effects of these programs on young people in a pluripotent risk state, for improving cognitive, academic, and social functioning, and for reducing behavioral disturbance and later incidence of serious mental disorder (for elaboration on these issues, see Chapter 9).

**Group 3: How Can Models Be Better Utilized to Enhance Outcome?**

**Issues**

Much research on schizophrenia, especially in terms of neurophysiology and drug development, is done using rodents and, to a lesser extent, nonhuman primates. Indeed, as in other medical conditions, research on basic neurophysiology and drug development has required, and benefited from, decades of research on animals. However, schizophrenia has a number of features (e.g., language disturbances, altered sense of self) which suggest that it is a distinctly human condition. Therefore, the mission of this discussion group was to address the role of different types of modeling for furthering our understanding of, and ability to treat, the disorder. Their given questions were:

- To what extent is schizophrenia continuous or discontinuous with behavior disorders in animals?
- How can animal studies continue to enhance our understanding of the development and progression of schizophrenia and gene–environment interactions?
- Are there differences in the extent to which animal and neural network models can account for cognitive versus emotional abnormalities in schizophrenia?
- What kinds of animal research are necessary to develop new treatments?
- When treatment development is based on animal studies (i.e., when human subjective experience of the self and world is excluded), is there a limit to which treatments can be effective?
- To what extent do disturbances in the experience of the self lead to further abnormalities in biological processes, and how can interactions such as these be modeled in nonhuman systems?
- To what extent can nonhuman models account for the gene–environment interactions that are observed in schizophrenia?

**Summary**

Mitchell et al. (Chapter 13) affirmed the utility of animal models in investigating specific neurobiological underpinnings of schizophrenia. Importantly, however, this stance contrasts with the widely held idea that animal models
can, or should be able to, recapitulate the disorder in its entirety or be used as a proxy for drug screening. Mitchell et al. note that it is obviously not possible to generate an animal model of the full syndrome of schizophrenia, given its etiological and phenomenological heterogeneity, and considering the uniquely human expression of many of its symptoms. Moreover, if schizophrenia is an open construct, the boundaries and features of which are difficult to delimit even in humans, then attempting to generate an animal model that recapitulates the disorder as a whole becomes entirely unrealistic. Furthermore, the expectation that a particular pathophysiological disturbance will manifest in an overtly similar behavioral impairment in animals and humans is not always justified. Manipulations that do not demonstrate face validity, in the sense of demonstrating an identical phenomenon in animals and humans (e.g., impaired prepulse inhibition), should thus not be rejected as irrelevant to understanding the condition, as long as it can be demonstrated that a biological process relevant to humans is being modeled. Based on these considerations, Mitchell et al. propose that the term “animal model” be used to refer to an animal that has been manipulated in a specific way that is either known to be of etiological relevance to schizophrenia or that is thought to recapitulate a phenotype of relevance to some aspect of schizophrenia phenomenology. In short, animal models can be useful to isolate and manipulate hypothesized etiological factors and their interactions, within and across levels of analysis. In this way, the group’s discussions demonstrated how heterogeneity can be useful and lead to rapid advances in understanding the biology of schizophrenia, with obvious treatment implications.

Two recurring themes relevant to understanding and modeling heterogeneity are:

1. Many factors (including chance, intrauterine environment, social environment) determine how genes are expressed, and thus people with similar genetic factors may develop different clinical presentations.
2. Small changes at the micro level can interact and cascade to lead to macro-level changes in brain function, which are different from person to person.

An analogy was made to epilepsy, which is a heritable syndrome, but where the region of the epileptic focus can vary in people within the same family. Similarly, in schizophrenia, a genetic factor that leads to a neural circuit abnormality in one part of the brain might lead to one set of specific impairments (e.g., perceptual organization impairments resulting from occipital lobe abnormalities), whereas the same circuit dysfunction in another region (e.g., the frontal lobe) could lead to difficulties in organizing action plans, with a range of factors (including chance) determining in which region the abnormality is expressed. It is also possible that a single impairment (e.g., in dopamine signaling) could cause multiple problems (e.g., a reduced ability to learn from reward, working memory impairment). These types of complex

relationships have not yet been modeled adequately. However, it is precisely these types of variations in expression of genetic factors, and the biological events to which they lead, as well as the interaction between these events that can be studied efficiently and effectively in animal models. Mitchell et al. state that only in this way is it likely that the heterogeneous nature of schizophrenia will be understood and that treatments truly tailored to the individual will be developed.

Mitchell et al. discuss how computational and human cellular (e.g., pluripotent stem cell) models could complement animal models. For example, within a computational framework it may be possible to predict the effect of a mutation in a specific gene on neural dynamics at various scales. It may also be possible to predict the behavioral or cognitive correlates of such alterations. It is important to note, however, that inferences in the reverse direction are much more difficult, since any phenomenon at a “higher” level can be the result of several causal pathways emerging from lower levels. For example, given a particular behavioral difference, it is usually not possible to infer what change in neural dynamics led to it. Similarly, an alteration in neural dynamics might have been caused by a change in any number of molecular components. Given this complexity, Mitchell et al. note that a major goal of experimental modeling of the effects of schizophrenia risk factors is to identify points and pathways of phenotypic convergence and possibly common pathophysiological states.

In addition to explaining pathophysiology, Mitchell et al. note that animal (and other) models can be used in longitudinal studies to clarify the development of prodromal features and the typical age of onset. The recent development of powerful small-animal neuroimaging methods offers the means to follow the same individual animal over time using a technique that provides data directly comparable to that from human patients. In short, they recommend that animal and other models not be used as proxies for the syndrome as a whole, but rather that these models are more likely to achieve advances by clarifying specific processes, their interactions, and their consequences. Because this work can be done much more quickly in animals than in humans, this new paradigm for modeling is critical for the development and targeting of treatment on an individualized basis (for elaboration on these issues, see Chapter 13).

**Group 4: What Is Necessary to Enhance Development and Utilization of Treatment?**

**Issues**

As discussed earlier, outcomes have arguably not improved significantly for people with schizophrenia over the last 100 years. However, it must be noted
that only a small percentage of patients actually receive a full range of (and in some cases, any) evidence-based treatments: in the United States, for example, only 2–10% of patients who could benefit from assertive community treatment actually receive it (Lehman and Steinwachs 1998). In addition, the adoption of evidence-based practices into clinics is often slow. The mission of this discussion group was thus to address the following questions:

- To what extent are symptom severity and level of functioning driven by social factors (e.g., stigma, poor funding for mental health, unavailability of treatments, lack of evidence-based practices outside of academic medical centers)?
- Why has progress, in terms of developing new medications, apparently slowed?
- Is the continued predominance of the dopamine hypothesis based on science, inertia, and/or lack of evidence for other models?
- How can multidisciplinary work (e.g., genetics, imaging) accelerate progress?
- Why are effect sizes so small in well-designed studies of psychosocial interventions?
- Are our treatments simply not that good? Or are they good, but not acceptable to patients, many of whom may be unmotivated (e.g., due to negative symptoms, paranoia, poor insight, or severe side effects) to engage in them?
- Are the psychological models on which these are based outdated, and are there other conceptual bases upon which new behavior change methods can be based?
- To what extent could treatment outcomes be improved if there was a greater focus on social factors, in the form of, for example, widespread efforts at stigma and discrimination reduction, peer support, and education of family members, religious leaders, and other people in patients’ lives?
- How do we integrate people with schizophrenia back into society in a manner amenable to both them and the community?
- To what extent are alterations of self and subjective experience primary phenomena in schizophrenia, and what are the implications of this for treatment development efforts?
- To what extent are discoveries regarding genetics informing treatment efforts? Can this happen to a greater extent than is now occurring?
- Do treatments need to be more tailored to specific symptoms or disability dimensions?
- Should drug development and clinical trials be left to the private sector and, if not, what should a government-run effort look like?
Summary

In their discussions, V. Morgan et al. (Chapter 17) considered the fact that there is still debate about what it is that we are trying to treat, due to all of the problems in defining the construct noted above. In particular, because of the heterogeneity in etiology and/or clinical features, treatments are less than maximally effective for most patients, and thus we need to develop a way of truly personalizing treatment. Other problems include deciding on what phenomena should be treated. There has been a relative separation between developing treatments that target pathophysiological processes thought to be involved in symptoms (i.e., the traditional focus of the pharmaceutical industry) and treatments which focus on reducing disability by improving cognitive and social functioning and promoting employment and independent living. In addition, there has been too little research on combinations of treatments.

V. Morgan et al. suggest that a more rational approach to treatment would begin by defining the problem space for intervention as involving primary, secondary, and tertiary levels, with the interventions and goals differing between levels. A radical proposition was that we might be able to prevent, rather than merely treat, schizophrenia if we were able to intervene early enough (i.e., primary prevention, little of which exists now for schizophrenia). For example, and as noted in several of the discussion groups, there is reason to believe—but no data yet to confirm—that an intervention to reduce cognitive decline (between 11 and 14 years of age) could reduce morbidity as well as prevent the onset of schizophrenia in late adolescence and early adulthood. However, given that schizophrenia involves multiple risk factors, important questions remain: How many different interventions would need to be developed to prevent the syndrome, and if such interventions were developed, where would they be delivered (e.g., school, after-school program, clinic)? How would such efforts be funded? Such questions speak to the need for involvement of policy makers and the larger society in efforts to prevent schizophrenia and other forms of serious mental disorders.

Even if, ideally, effective treatments were to be developed, a major problem at present is how to ensure that people who need the treatments actually receive them. For example, while there are many effective psychosocial treatments for schizophrenia, most are unavailable in typical mental health settings, even in developed countries. In addition, some countries, particularly the United States, have few mechanisms of payment for such effective treatments. Further, owing to factors such as poor insight, low motivation for treatment, and prior negative experiences with mental health professionals, many patients with schizophrenia choose not to adhere to treatment plans or attend clinics. Complicating this, many professionals are not trained in evidence-based practices for this population. Even when they are, decision-making processes engaged in by clinicians often lack sensitivity to contextual information and the patient’s perspective, and thus often lead to less than optimal treatment or adherence with it. All
of this speaks to the need to improve the education of people who work with schizophrenia patients and to address larger societal issues.

Recognizing the relative lack of technology used in the treatment of schizophrenia, compared to treatment of other chronic disorders, V. Morgan et al. recommend increasing the use of new momentary assessment technologies, such as handheld devices that can be used for experience sampling as well as to help monitor stress levels and the onset and offset of psychotic symptoms. Such technologies can augment interventions that have previously relied on cruder methods to assess these issues. In addition, virtual reality is a powerful tool for assessment and treatment that has been used successfully with disorders such as posttraumatic stress disorder. Thus far, this has not been used much for schizophrenia, and particularly to supplement or boost treatment effects. Other new technologies which show promise include real-time biofeedback via fMRI or variants of transcranial magnetic stimulation, to help patients reduce activity in areas related to symptoms or to increase activity in areas to enhance cognitive functioning. To date, however, the limited funding typically available for treatment of people with schizophrenia means that application of such new techniques is limited outside of clinical trials conducted in academic medical centers.

V. Morgan et al. emphasize that truly effective treatment of schizophrenia requires approaching each person with the condition as a unique person with biological vulnerabilities embedded within a matrix of environmental stressors; that is, these symptoms reflect this person with these genes and this brain in this environment with these stressors. Evidence for the necessity of this approach comes from many findings, including those on stress impact (Lincoln et al. 2009), or even walking through an urban environment (Ellett et al. 2008), on symptoms such as paranoia and anxiety, as well as the links between under-stimulating environments and negative symptoms (Oshima et al. 2003, 2005). In their report (see Chapter 17), V. Morgan et al. describe a treatment planning method (PROMIS) that—unlike typical approaches which focus primarily on symptoms—organizes treatment planning around disordered physiological processes, behavioral domains, and environmental stressors and other conditions. Although they recognize the utility of animal models, as discussed by Mitchell et al. (Chapter 13), V. Morgan et al. emphasize the importance of human models in driving systems neuroscience research, and the need to have these drive other scientific efforts as well (for further elaboration on these issues, see Chapter 17).

Finally, providing interventions external to the traditional medical or other treatment contexts may be useful, especially given the negative symptoms, poor insight, and other factors that reduce attendance at clinic-based treatments. For example, individual and family treatment has been provided in the home and has been effective in reducing relapse even when medication use is minimal (Lehtinen et al. 2000). In addition, cognitive behavioral therapy can be provided in patients’ homes (Smith and Yanos 2009), as can cognitive
remediation (Ventura et al. 2013). Although schizophrenia is typically seen as a poor outcome disorder, it remains to be seen what outcomes are possible if treatment is made more “user-friendly” in both type and location.

Further Synthesis and Final Thoughts

In our final plenary session we met to assess our overall progress and provide each group with feedback on their individual reports. In this section we wish to highlight the additional themes and ideas that emerged.

The Centrality of Cognition in an Understanding of Schizophrenia

Much evidence now suggests that schizophrenia is characterized by cognitive impairment and that cognitive impairment is an early aspect of the disorder, often predating the emergence of psychotic symptoms by more than ten years (see Kahn, Chapter 14, this volume). Alternately, it was suggested that since schizophrenia patients are impaired in all aspects of cognition, all cognitive impairments may reflect a generalized impairment, and thus these are not useful portals through which to search for clues about schizophrenia. Can these competing points of view be reconciled? What is the proper role and goal of cognition studies in schizophrenia?

First, we suggest that although cognition is definitely impaired in schizophrenia, the appearance of a generalized impairment is largely an artifact of the use of measures whose scores are confounded by multiple cognitive processes (especially attention lapses) and noncognitive factors (e.g., poor motivation or medication-related sedation). Strategies have been proposed to isolate specific impairments more effectively and to identify their neural correlates (e.g., Knight and Silverstein 2001; MacDonald and Carter 2002; Silverstein 2008), but these have rarely been used. In addition, some cognitive impairments are state-sensitive; thus, whether abnormal performance is observed can be a function of phase of the disorder (e.g., Keane et al. 2013; Silverstein and Keane 2009; Silverstein et al. 2013a). Better characterization of the covariation of specific impairments with state, as opposed to being trait (and perhaps endophenotype) factors, is an important but neglected area of research; attention to this could help us model how biology and cognition relate to symptoms, recovery, and functioning, thereby increasing the yield of cognitive treatment studies. Some of these insights have already been incorporated into clinical trials of cognitive remediation, where significant changes in performance have been found (Wykes et al. 2011). In addition to localized changes in brain activity (e.g., Wykes 1998; Wykes et al. 2002, 2011) and structure (Eack et al. 2010), recent studies are finding improvements in the functioning of neural networks in schizophrenia (Penadés et al. 2013). Such studies have the potential to improve our understanding of the effects of cognitive remediation, and of how...
these effects translate into normalized subjective experience, fewer symptoms, and improved functioning.

Second, we recommend that the view of what is cognitively impaired in schizophrenia should change. Thus far, this issue has been viewed in terms of the traditional categories of neuropsychology: perception, attention, memory, learning, reasoning, executive functioning, etc. When conceived this way, everything is seen as being impaired, to some degree, and therefore as evidence of a not particularly useful (for research purposes) generalized deficit (Dickinson et al. 2008). This habit of parsing cognition into pseudo-discrete functions may not, however, be the most appropriate strategy for maximally clarifying the pathophysiologies that underlie schizophrenia. Even less productive may be the strategy of identifying a single impairment, as is often done for working memory, as the basis from which all or most other cognitive impairments in schizophrenia emerge (e.g., Barch and Ceaser 2012; Wolf et al. 2006). Several reasons and examples demonstrate why this is unlikely to be a useful strategy:

1. It is clear that disorders of perception, long-term memory, and action are involved in schizophrenia in meaningful ways (e.g., Landgraf et al. 2012).

2. Some impairments in perception and attention, which do not appear to be secondary to disordered working memory (e.g., reduced visual acuity), can be demonstrated in children who later go on to develop schizophrenia, and it has been proposed that these play a causal role in abnormal neural development (e.g., Schiffman et al. 2006; Schubert et al. 2005).

3. Working memory impairment has been observed in relatives of people with schizophrenia (Conklin et al. 2005), which suggests that it is an endophenotype. Some perceptual impairments, however, have not been reported in this population or among people at risk and do not appear to be present even as late as the first episode of psychosis (Parnas et al. 2001; Silverstein et al. 2006b), thus suggesting that they are indices of syndrome progression, as well as state markers (given links with specific symptoms; Keane et al. 2013; Silverstein and Keane 2009).

4. Working memory impairments in schizophrenia are small, much smaller than in some neuropsychological patients with focal lesions whose symptoms have little overlap with schizophrenia.

5. The “work” that visuospatial working memory is assumed to do includes imagining transformations (e.g., mental rotation). We know of no evidence that such abilities are grossly impaired in schizophrenia (or present in animals used to model working memory deficits).

6. Cognitive impairment in schizophrenia typically reflects a process that is not working correctly, as opposed to a true deficit in function. Thus,
clarifying in which ways these systems are altered is a more valid perspective than generating a catalog of deficits.

Based on all of the above, we suggest that what is needed is not less concern for cognitive distinctions, but more concern for newer distinctions. One useful distinction that has already been applied to schizophrenia is that between coding and coordinating neuronal interactions (Engel et al. 2010; Phillips and Silverstein 2003; Silverstein 2010). However, recent work on canonical cortical computations—algorithms based in widespread circuitry that are used to solve a variety of problems (e.g., Carandini and Heeger 2012; Fuster 2003)—provides an emerging set of fundamental computational processes (e.g., gain control) which can be usefully applied to multiple impaired phenomena in schizophrenia (Butler et al. 2008; Phillips and Silverstein 2013).

As suggested by Mitchell et al. (Chapter 13), greater emphasis needs to be placed on the discovery of pathophysiological hubs through which etiology is channeled into behavioral and phenomenological symptoms. This approach has been useful in the study of epilepsy, and it can also be useful to study cognition in schizophrenia. Mitchell et al. agree that computational studies of neuronal dynamics can help reveal possible hubs at the level of pathophysiology and, as noted by Durstewitz and Seamans (Chapter 12), this is relevant for understanding cognition. Therefore, what is needed is continued development of modeling of causal links between brain dynamics, cognition, symptoms, phenomenology, and behavior. This will require novel ways of working between disciplines and funding agency incentives to do so.

Altering our view of how and why cognition is impaired in schizophrenia has obvious implications for how cognitive impairment should be treated and for the choice of outcome variables used in clinical trials. Importantly, however, we should not necessarily or blindly assume that treatments which target these cognitive difficulties will confer direct benefits to functioning, or that an absence of cognitive effects on these measures with treatment indicates a lack of improvement in real-world functioning. Often, as has been shown in both the traumatic brain injury and schizophrenia cognitive remediation literatures, test performance (i.e., impairment) and real-world functioning (i.e., disability) are independent of each other, and the extent of their change with treatment can vary independently of each other (e.g., Reeder et al. 2004; Silverstein et al. 2005; Wilson 1991, 1997; Whyte 1998; Wykes et al. 2012).

A Greater Number of Comparative Studies with Other Disorders Is Needed

Consensus emerged that schizophrenia is not a disease, but rather a syndrome that is best characterized as an open construct. In this way, it shares similarities with phenomena such as hypnosis: it can be characterized by alterations in consciousness, cognition, behavior, and physiology, but no one aspect of it
is unique to the condition (e.g., Silverstein 1993). One implication is that it may be useful to further explore the similarities versus differences, or overlap versus nonoverlap, between schizophrenia and several other conditions, which thus far have been understudied in relationship to schizophrenia, as a means of clarifying the essential aspects of the syndrome(s).

One potential area of exploration involves the overlap between schizophrenia and other developmental disorders characterized by cognitive impairment. For example, many studies show an overlap between schizophrenia and both verbal and nonverbal learning disabilities. In terms of the former, there is an elevated rate of histories of dyslexia in people who grow up to have schizophrenia as well as in families of people with schizophrenia (Horrobin et al. 1995), and an elevated rate of schizophrenia and schizotypy in people diagnosed with dyslexia in childhood (Richardson 1994). In addition, anatomical abnormalities, as revealed by imaging, predict poor cognitive functioning in both disorders (Leonard et al. 2008), and both dyslexia and schizophrenia share specific visual processing impairments, such as in contour integration (Simmers and Bex 2001; Silverstein et al. 2009a) and magnocellular pathway processing (Revheim et al. 2006). Schizophrenia also shares social and cognitive abnormalities with nonverbal learning deficits (Silverstein and Palumbo 1995) as well as features of cognitive and social cognitive impairment (as well as genetics) with autism spectrum disorders (e.g., Lugnegård et al. 2013; Stone and Iguchi 2011). At the same time, schizophrenia and autism appear to represent opposite extremes on some dimensions (Crespi and Badcock 2008; Russell-Smith et al. 2010), and thus further investigation of the pattern of similarities and differences between these disorder classes may be quite revealing.

In addition to developmental cognitive disorders, schizophrenia is associated with a higher than normal rate of conduct disorder and antisocial personality disorder (Volavka and Citrome 2011), and these share aspects of reduced coherence in thinking and speech (Hare 1993) as well as biological abnormalities, such as reduced functional connectivity involving the frontal cortex (Motzkin et al. 2011) and cortical thinning (Ly et al. 2012). Physical and sexual abuse in childhood (Matheson et al. 2013) also increases risk for both antisocial personality disorder and schizophrenia, and its effects include violence and reduced thalamic volumes in both disorders (Kumari et al. 2013). Further investigations of these issues may sharpen our understanding of etiological and developmental pathways to schizophrenia syndromes. This would address similarities and etiological overlap between these conditions, which were proposed long ago (Bender 1959; Dunaif and Hoch 1955) but remain underexplored.

It may also be useful to study conditions which reduce risk for schizophrenia. Two notable examples of this are congenital blindness—where a case of schizophrenia has never been reported (Silverstein et al. 2012c, 2013b)—and rheumatoid arthritis, which occurs 70% less in people with schizophrenia than in other individuals (Mors et al. 1999). Data on congenital blindness has
provided tantalizing clues regarding the role of crossmodal plasticity in reducing risk for cognitive and behavioral features associated with schizophrenia, and on the role that visual impairment may play in the development of schizophrenia. Data on rheumatoid arthritis may help clarify the role of lipid membranes, such as prostaglandin-2, platelet-activating factor, and the glutamatergic system in these two conditions (Oken and Schulzer 1999).

The Implications of Schizophrenia as a Disordered System

In addition to (stem) cellular, computational, and animal models of schizophrenia, we should not rule out the possibility of “macro” models. This suggestion is based on similarities which can be observed in complex systems, be they small or large, physical, biological, or social (Bar-Yam 1997, 2002; Csermely 2008; Freyer et al. 2012; Simon 1973). This includes characteristic dimensions such as sensitivity, stability, adaptability, and cooperation. In this view, not only biological but also social systems have the potential to inform us about processes involved in phenomena at other levels, such as brain function or behavior, in schizophrenia. To illustrate this, we suggest that examining social disorganization and its sequelae (including violence) may reveal insights about system-level disturbances associated with cognitive and behavioral disorganization in schizophrenia. For example, (a) both antisocial personality disorder and schizophrenia are associated with increased risk for violent behavior (Hodgins 2008) and reduced coherence in thinking and speech (Hare 1993); (b) increased rates of aggression in childhood are related to schizophrenia and in adulthood (Hodgins 2008); and (c) schizophrenia is associated with an increased rate of antisocial personality disorder (Jackson et al. 1991). It has also been suggested that paranoia is to thought, as aggression is to behavior (Gilligan 1996); both schizophrenia and violence reflect, in part, similar forms of breakdowns in adaptive response patterns (e.g., Broen and Storms 1966). Importantly, there are societal conditions associated with both violence and psychosis, and these conditions resemble, in terms of disruption of a system, what is found in schizophrenia. For example, it has been noted that both schizophrenia (Allardycce and Boydell 2006; Faris and Dunham 1939) and violence (Bouffard and Muftić 2006; Boyle and Hassett-Walker 2008; Sampson and Groves 1989) are more likely to occur in social systems where there is more disorganization—defined by residential instability, frequent vacant housing units, family disruption, reduced homogeneity in traditions and value systems among neighbors, less communication and cooperation between families in the same neighborhood, disrupted social closure or fewer interlocking ties or networks within communities and between families, and a general reduction in social capital (De Silva et al. 2005; Hagan et al. 1996; Sandefur and Laumann 1998). Are there ways in which symptom development in schizophrenia appears to parallel (in terms of system dysfunction) that which is found in disorganized social systems? Consider that hallucinations and delusions have been
attributed to parasitic foci, where an attractor state forms and becomes isolated, and less influenced by surrounding cortical activity (Hoffman and McGlashan 1993). To the extent that this analogy is valid, what gains in our understanding of a system breakdown like schizophrenia might be won by better understanding disintegration of social systems and their sequelae? We believe that it is worth exploring whether these similarities represent more than an analogy and could even reflect causal relationships. For example, past theories and data have demonstrated excessive developmental neuroplasticity in schizophrenia and the related increased tendency for mental functioning to be molded by positive or negative features of the environment (Bender 1966; Reser 2007; Tienari et al. 2004). Rather than reflecting an isomorphism between social conditions and brain function in individuals vulnerable to such effects, it is also possible that aspects of social disadvantage may simply increase risk for outcomes such as violence and/or schizophrenia and reinforce other risk factors (Thornberry 1987; Toch and Adams 1989). We need to learn more about how this happens. In short, we suggest that the study of people with schizophrenia, or those at risk for it, could benefit from a greater understanding of brain dynamics within the context of, and in reaction to, the social environment.

At another level, future work should consider the role of the environment in planning treatment, beyond recognizing it as an etiological factor. Are there interactions between, for example, the level of social disorganization in a patient’s past or current life and symptom expression or stress-sensitivity that may be relevant to treatment? Beyond this, can the dynamics of person–environment interactions form a dimension that can be used in characterizing heterogeneity? For example, is reactivity to the environment (e.g., Sturgeon et al. 1984) a variable upon which subtyping can be based? If so, what are the implications of this for diagnosis and treatment? One goal of these efforts would be to move beyond “personalized medicine” to “embedded medicine,” in which treatment is based on person–environment interactions. The ultimate implication is that, as with other issues such as violence (Newman et al. 2004), intervention must be delivered at individual as well as community and national levels, in terms of public policy which affects social conditions that increase risk for schizophrenia. A novel paradigm that can express systems dynamics from molecular to social levels, model interactions between these levels, and characterize emergent phenomena such as schizophrenia appears necessary to move into the next phase of understanding and treatment. Finally, we also need to realize that it is unlikely that we will ever be able to predict completely who will develop schizophrenia. This is because all of the known risk factors are neither necessary nor sufficient—alone or in combination—for schizophrenia to occur. However, an increase in our understanding of the issues could be successful in lowering the risk for, rate of, or disability associated with the condition.

Finally, to study many of the issues described in this chapter, very large sample sizes will be necessary. This suggests the necessity of generating large
databases and creating methods for investigators to contribute to and access data from them, as well as incentives for researchers to engage in this type of collaborative “cloud” research, as opposed to solely working on small datasets in individual laboratories. To study a condition as heterogeneous as schizophrenia, and to understand the relationships between multiple biological, psychological, and environmental variables and their covariation over time using mega-samples, strategies from informatics and novel data analysis techniques will have to be increasingly applied to schizophrenia research. Concurrently, there is also a role for largely forgotten idiographic methods (Allport 1962); that is, for more in-depth study of individual people as a way to understand and generate novel hypotheses about the development of schizophrenia and the factors that protect against, cause, and modify expression of the condition(s).