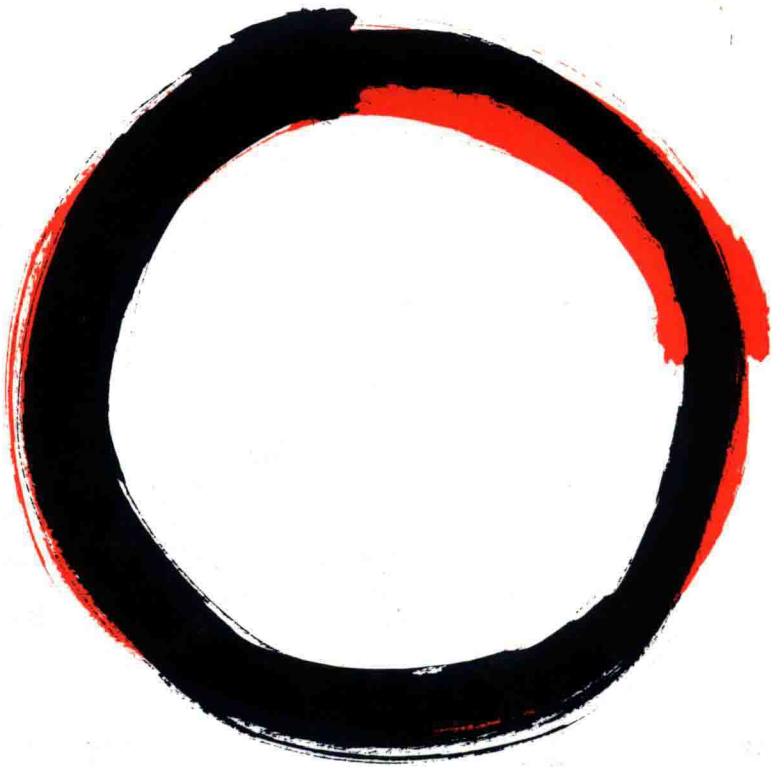
Schizophrenia

Evolution and Synthesis

EDITED BY
Steven M. Silverstein,
Bita Moghaddam, and
Til Wykes



STRÜNGMANN FORUM REPORTS

Schizophrenia

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Edited by

Steven M. Silverstein, Bita Moghaddam, and Til Wykes

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The Ernst Strüngmann Forum

Founded on the tenets of scientific independence and the inquisitive nature of the human mind, the Ernst Strüngmann Forum is dedicated to the continual expansion of knowledge. Through its innovative communication process, the Ernst Strüngmann Forum provides a creative environment within which experts scrutinize high-priority issues from multiple vantage points.

This process first begins with the identification of themes. By nature, a theme constitutes a problem area that transcends classic disciplinary boundaries. It is of high-priority interest, requiring concentrated, multidisciplinary input to address the issues involved. Proposals are received from leading scientists active in their field and are selected by an independent Scientific Advisory Board. Once approved, a steering committee is convened to refine the scientific parameters of the proposal and select the participants. Approximately one year later, the central meeting, or Forum, is held to which circa forty experts are invited.

Preliminary discussion for this theme began in 2010, when Steven Silverstein brought the initial idea to our attention. Together with Bita Moghaddam and Til Wykes, the resulting proposal was approved by the Scientific Advisory Board and from June 27–29, 2011 the steering committee was convened. The committee, comprised of Anil Malhotra, John McGrath, Andreas Meyer-Lindenberg, Bita Moghaddam, Steven Silverstein, and Til Wykes, identified the key issues for debate and selected the participants for the Forum, which took place in Frankfurt am Main, from July 22–27, 2012.

A Forum is a dynamic think tank. The activities and discourse that accompany it begin well before participants arrive in Frankfurt and conclude with the publication of this volume. Throughout each stage, focused dialog is the means by which participants examine the issues anew. Often, this requires relinquishing long-established ideas and overcoming disciplinary idiosyncrasies, which otherwise could inhibit joint examination. When this is accomplished, however, new insights begin to emerge.

This volume conveys the synergy that arose out of myriad discussions between diverse experts, each of whom assumed an active role. It contains two types of contributions. The first provides background information to key aspects of the overall theme. Originally written in advance of the Forum, these chapters have been extensively reviewed and revised to provide current understanding on these topics. The second (Chapters 5, 9, 13, and 17) summarizes the extensive group discussions that transpired. These chapters should not be viewed as consensus documents nor are they proceedings. Instead, their goal is to transfer the essence of the discussions, expose the open questions that still remain, and highlight areas in need of future enquiry.

An endeavor of this kind creates its own unique group dynamics and puts demands on everyone who participates. Each invitee contributed not only their time and congenial personality, but a willingness to probe beyond that which is evident. For this, I extend my gratitude to all.

A special word of thanks goes to the steering committee, the authors of the background papers, the reviewers of the papers, and the moderators of the individual working groups: Robert Buchanan, Michael O'Donovan, Patricio O'Donnell, and Richard Keefe. To draft a report during the week of the Forum and bring it to its final form in the months thereafter is never a simple matter. For their efforts and tenacity, I am especially grateful to Aiden Corvin, Craig Morgan, Kevin Mitchell, and Vera Morgan—the rapporteurs of the discussion groups. Most importantly, I extend my sincere appreciation to Steven Silverstein, Bita Moghaddam, and Til Wykes. As chairpersons of this 13th Strüngmann Forum, their commitment ensured a most vibrant intellectual gathering.

A communication process of this nature relies on institutional stability and an environment that encourages free thought. The generous support of the Ernst Strüngmann Foundation, established by Dr. Andreas and Dr. Thomas Strüngmann in honor of their father, enables the Ernst Strüngmann Forum to conduct its work in the service of science. The Science Advisory Board guides this work and ensures the scientific independence of the Ernst Strüngmann Forum. Supplemental financial support for this theme was received from the German Science Foundation, and the Frankfurt Institute of Advance Studies provided the backdrop for this intellectual exercise.

Long-held views are never easy to put aside. Yet, when this is achieved, when the edges of the unknown begin to appear and gaps in knowledge are able to be defined, the act of formulating strategies to fill such gaps becomes a most invigorating exercise. We hope that this volume will convey a sense of this lively endeavor. Most importantly, we hope that this joint examination of schizophrenia will lead to a novel conceptualization of the disorder and accelerate advances in treatment development and prevention efforts.

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Schizophrenia

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

Steven M. Silverstein, Bita Moghaddam, and Til Wykes

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?