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WORKSHOP REPORT

Research Strategies and Priorities to Improve the Lives of People With Schizophrenia: Executive Summary of the Ernst Strüngmann Forum on Schizophrenia

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What kind of a thing is schizophrenia? What causes it? Can it be cured or prevented? These questions have challenged researchers for over 100 years. However, despite thousands of new studies every year, and major technological advances, schizophrenia research is not leading to consistent improvements in the lives of people with the disorder.[1] What might make a difference? One possibility is that a shift in the way that schizophrenia is conceptualized and approached may lead to improvements in our understanding of the condition, which could then translate into more effective methods of prevention and promotion of recovery. But, what would these changes look like, and what is necessary to make them happen? Addressing these key questions was the goal of the Ernst Strüngmann Forum, "Schizophrenia: Evolution and Synthesis," a meeting held at the Frankfurt Institute for Advanced Studies, in July 2012. For 5 intense days of discussion and debate (there were no paper presentations), an invited group of expert and experienced researchers with diverse scientific backgrounds from around the world (see Appendix for list of participants) explored novel ways of conceptualizing schizophrenia and integrating data across levels of analysis with the goal of accelerating advances in treatment development and prevention. As with all Strüngmann Forums, the topic was divided into four, more tractable, themes, each with an associated set of questions. Participants were assigned to 1 of 4 groups to consider background papers (written just prior to the Forum by selected Forum attendees). Summaries of each group's conclusions on the novel approaches to advance the field were ultimately presented to the whole group for discussion and debate.

Throughout our deliberations, we kept in mind our goal of clinical impact. This strategy is consistent with that of the recent Rand Europe Mental Health Retrosight Report on Schizophrenia.[2] That report included the following conclusions: (1) global mental health research over the past 20 years has led to a diverse and beneficial range of academic, health, social, and economic impacts; (2) clinical research has had a larger impact on patient care than basic research although there is much variability regarding this outcome in the basic research area; and (3) where scientists bear in mind clinical relevance, there is more likely to be impact. In addition, our strategy of choosing experts from across a wide spectrum of research topics and methods is supported by Retrosight's conclusion that those involved in mental health research who work across boundaries produce findings that are associated with wider health and social benefits. What follows is a summary of our deliberations over the Forum week and considerable follow-up email discussion. We have distilled these conversations into this short text, and, as the meeting organizers, we take responsibility for any omissions. We also have updated some of the recommendations with reference to recent research. A full-length description of the questions and issues that motivated the Forum can be found in chapter 1 of a recently published book,[3] with the remainder of that volume comprising the background papers that stimulated the discussions and the final summaries of the group discussions addressing the issues.

Theme 1: Which Aspects of Heterogeneity Are Useful to Translational Success?

Much evidence indicates that schizophrenia is a heterogeneous condition.[4–6] However, it is typically treated as a single disease entity for research on mechanisms (including genetics) and for clinical trials. This paradigm is obviously problematic. Schizophrenia is, of course, not technically a disease because this status requires known etiology, pathophysiology, and course. Consensus

emerged that schizophrenia is a clinical syndrome (ie, a collection of signs and symptoms that reliably co-occur). Within the clinical syndrome construct, it is understood that patients vary as to which aspects of syndrome pathology are manifest and that between-patient variability may be substantial. It was agreed that schizophrenia is an "open construct" in the sense that its boundaries and many of its features overlap with other conditions. By analogy, schizophrenia is perhaps best seen as a category, such as cancer, epilepsy, or dementia; what we now call schizophrenia is most likely a category of brain-based disorders that resemble each other to varying degrees and probably share (an undetermined proportion of) pathophysiological mechanisms. However, the actual number of disorders, and their etiologies is, at present, unknown. As a result, a recommended strategy for research is to identify phenomena that occur together, across multiple levels (eg, biology, cognition, sign/symptom, subjective experience), so as to more precisely characterize heterogeneity and foster individualized treatment approaches.

Because, from a research perspective, schizophrenia is approachable on so many levels, an important issue is which levels of analysis are of primary importance. Consensus emerged on 4 critical foci. The first is etiological factors, such as genetics, and consequences of infection, such as inflammation, that affect brain function. Second is pathophysiology, where molecular (eg, neurotransmitter receptors), cellular (eg, pruning), and circuit (eg, maintenance of cell assemblies supporting processes such as predictive coding, perception, memory, and learning) mechanisms were considered important targets for research and treatment. Third is behavior, including cognitive and social cognitive factors. Phenomenology is the final level, including issues such as deficit symptoms (eg, a loss of motivation) or an altered sense of self. In short, it was recommended that there be a greater focus on characterizing the psychological phenomena involved in schizophrenia and integrating this information with our accumulating understanding of its neurobiology, in a renewed effort to characterize the condition(s) and understand between-patient differences.

Another issue highlighted regarding heterogeneity was the need to better characterize covariation over time between phenomena at multiple levels and the benefits of modeling data in terms of nonlinear relationships (eg, using coefficients of mutual information).[7] For example, cognitive functioning may demonstrate significant decline in the period prior to initial diagnosis (and this may occur earlier than originally thought),[8,9] and then assume trait-like status in several domains,[10] while also demonstrating state-sensitivity in others,[11] and trajectories of change over time in different domains of disability can differ, both in childhood[12] and later in life.[13] There was also significant agreement that schizophrenia is most often a developmental condition, with differing expressions across the lifespan starting from birth or earlier. Increased attention to the domain of premorbid functioning, perhaps now (based on current evidence) better viewed as early morbidity, may capture variance relevant to mechanisms, and functional and treatment outcomes in research on fully developed cases. This domain may also be relevant to modification of early detection and intervention strategies.

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

Fundamental to preventing and treating schizophrenia is a better understanding of the array of risk factors that predispose to its multiple conditions. Better understanding is needed because current evidence suggests that while we may be able to delay the onset of schizophrenia for 1–2 years in people in an at-risk mental state, we may not be able to prevent its eventual onset.[14,15] One conclusion from these findings is that it is too late to intervene at the point when a person starts to exhibit prodromal indicators of schizophrenia (ie, the current best-practice approach). Therefore, an alternative, albeit untested, approach is to intervene much earlier (eg, 9–13 years of age) when academic and behavioral difficulties typically emerge. The concept is that if further deterioration of social and cognitive functioning can be prevented during this "pluripotent risk state" (ie, a phase during which a set of difficulties could develop into any of several disorders), we may be able to reduce the incidence of new cases of schizophrenia, as well as of other psychological conditions. In addition to potential prevention of psychosis, early intervention would also address aspects of dysfunction and symptoms that have already begun to manifest themselves.

Currently, even the most promising individual risk factors seem to increase risk by only a very small amount. Combinations and interactions of factors (eg, risk alleles, gestational insults, impaired cognition, adverse experiences in childhood, cannabis use) are far more likely to be associated with later schizophrenia than any single factor alone, so one recommendation is to investigate interactions between risk factors. Identifying both protective and risk-increasing interactions may also help better characterize heterogeneity and risk and could lead to rational public policies focused on prevention. Public health efforts at prevention at this level may also have benefits related to a number of physical and mental disorders and substance abuse.

A consistent emphasis at the Forum was the need to increase integration between different fields of study as opposed to the standard paradigm of a silo approach to science. For example, we need to invest more in understanding the pathophysiological consequences of genetic and epigenetic alterations. At the "meta" level, there has been inadequate crosstalk between disciplines such as epidemiology, sociology, and the neurosciences. For example,

despite tantalizing clues, we do not yet understand how specific factors (eg, child sexual abuse) increase the risk of developing schizophrenia. As another example, we have a poor understanding of how risk for alterations in specific mechanisms (eg, hypothalamic-pituitary-adrenal axis dysfunction, viral infection, inflammation) is increased by social and environmental factors (eg, urban environments, poverty, social defeat). There is also the long-standing issue of how the neurobiological and cognitive aspects of schizophrenia produce the subjective experiences of psychotic symptoms and phenomena such as altered experience of the self.[16] Greater interdisciplinary work between investigators working in computational modeling, neurobiology, psychology, and neurophenomenology is the most promising approach to understanding the complexity of schizophrenia development.

A strong consensus emerged that the traditional separation of child and adult psychiatric services negatively impacts clinical care and research by forcing people to be treated in 2 different systems. This separation also minimizes dialogue between researchers and clinicians in the different specialties. It was recommended, therefore, that this separation be eliminated and replaced by a system where research on and treatment of problems that emerge in childhood and adolescence are informed by an understanding of factors that mediate and moderate the transition to adult psychopathology. More specifically, it was recommended that child, adolescent, and adult psychiatric services be integrated so that people at high risk for psychotic disorders can be treated and followed by a consistent treatment team over time and developmental milestones.

Finally, consensus emerged that effective prevention efforts do not have to be delivered in psychiatric clinics (and that it is often optimal not to do so). For example, school-based social-emotional and cognitive interventions have shown effectiveness in addressing these problems in young people. To date, however, these interventions have rarely been applied to people specifically identified as being in a pluripotent risk state for a serious mental illness. Therefore, we do not yet know what the effects of improving cognitive, academic, and social functioning, and of reducing behavioral disturbance, would be in terms of prevention of serious mental disorder.

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

The popular notion that animal models should be able to recapitulate the disorder in its entirety or be used as a proxy for testing the effectiveness of novel pharmacological agents was rejected because it is accepted that the full syndrome is likely to have etiological and phenomenological heterogeneity and is a distinctly human disorder with respect to several core symptoms. Moreover, attempts to develop an animal model of a disorder that reflects an open construct with ill-defined boundaries are unlikely to be successful. There is also the reality that specific pathophysiological disturbances can and do manifest in behavioral impairments that can look very different in humans and nonhuman animals. Importantly, however, models that do not demonstrate face validity, in the sense of demonstrating an identical phenomenon in animals and humans, should not be considered irrelevant, a priori, to understanding the condition, as long as a biological process that is relevant to humans is being modeled. As a result of these discussions, it was recommended that the term "animal model" be used to refer to an animal manipulation that is known to address a specific *mechanism* thought to be of etiological relevance to schizophrenia or that seems to express a phenotype that maps on to some specific aspect of schizophrenia.

Two recurring themes relevant to modeling heterogeneity were (1) many factors (eg, intrauterine environment, diet, social environment) determine how genes are expressed, and thus people with similar genetic features can develop varied clinical presentations and (2) small changes at the microlevel can interact and cascade to lead to systemic changes in brain function, which can be different across people. Here, an analogy was made with familial forms of epilepsy where the site of the epileptic focus can vary even in people from the same family. In a similar way, in schizophrenia, a genetic factor that produces a neural circuitry abnormality in one part of the brain might lead to one set of alterations (eg, perceptual organization impairments resulting from occipital lobe abnormalities), whereas the same basic circuit dysfunction in a different area (eg, the frontal lobe) could lead to difficulties in organizing action plans, with a range of factors determining in which brain region the abnormality is expressed. It is also possible for disruption in the function of a small group of neurons (eg, dopamine) to lead to multiple problems (eg, impaired reward learning, working memory reduction). These types of complex relationships have yet to be modeled adequately. However, it is precisely these types of scenarios that can be investigated efficiently and effectively in animal models, thereby accelerating efforts towards personalized treatment.

An important emphasis in this discussion was on how computational and human cellular (eg, pluripotent stem cell) models could complement animal models. For example, with computational modeling, it might be possible to predict the effects of a specific gene mutation on neural dynamics at various scales. It might also become possible to predict the behavioral or cognitive manifestations of such alterations. But, inferences in the opposite direction are more problematic because any phenomenon at a "higher" level can be the result of multiple causal pathways emerging from lower levels.

An important recommendation was that an aim of modeling efforts should be to identify points and pathways of phenotypic convergence and possibly common

pathophysiological mechanisms.[17] Models can also be useful in longitudinal studies to clarify the emergence of prodromal features and variability in age of onset of psychotic and other symptoms.[18,19] The recent development of small-animal neuroimaging methods allows for following the same individual animal over time using techniques that provide data directly comparable to that from human patients. In short, it was recommended that animal and other models should not be used as proxys for the syndrome as a whole but rather that models are most likely to achieve advances by clarifying the impact of specific processes, their interactions, and their consequences on brain function. In this way, animal models can remain central to the effort to understand causal mechanisms and pathways related to human brain dysfunction.

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

Due to the heterogeneity in etiology and clinical features that currently characterize schizophrenia, treatments are less than optimally effective for most patients. What steps need to be taken so that treatment is more comprehensive and personalized? Before this question can be addressed, there is the problem of agreeing on what should be treated. To date, there has been a relative separation between developing treatments focused on pathophysiological processes thought to be involved in symptoms and treatments that aim to reduce disability by improving functioning and promoting employment, independent living and social roles. In addition, there has been far too little research on the effectiveness of combined treatments or staging treatment across the life cycle of illness. A rational approach to treatment should start by defining the problem space for intervention as involving primary, secondary, and tertiary levels, with the recognition that the treatments and their goals will likely differ between levels. Moreover, there is the important question of how and if these efforts would be funded. These questions highlight the need for involvement of policymakers and communities in efforts to prevent or cure schizophrenia.

Due to factors such as poor insight, low motivation for treatment, prior negative experiences with healthcare professionals, poor treatment response, and significant side effects of medication, many people with schizophrenia choose not to adhere to recommended drug treatment or engage in available psychosocial treatments. Compounding this problem, many professionals are not trained in evidence-based practices for this population, and even when they are, decision-making processes by clinicians often lack sensitivity to contextual information and the patient's perspective, leading to suboptimal treatment and adherence. This highlights the need to improve the education of those who work with people with schizophrenia and to address larger societal issues. Finally, financial structures are not in place to support evidence-based care in many settings.

Several new technologies have promise for use in treatment of schizophrenia. These include the use of handheld devices for experience sampling to help monitor stress levels and the onset and offset of psychotic symptoms. Such technologies can augment interventions that have previously relied on cruder assessment methods (eg, using journal entries in cognitive behavior therapy). Virtual reality is a powerful tool for assessment and treatment that has been used successfully in posttraumatic stress disorder, but this has not been used much for schizophrenia. Real-time biofeedback via fMRI or variants of transcranial magnetic stimulation to help patients reduce excessive brain activity thought to underlie symptoms, or to increase activity in regions as a means of improving cognitive functioning, are also promising avenues. To date, however, the limited funding typically available for such "blue skies" treatment of people with schizophrenia means that, for now at least, application of such new techniques is limited outside of academic medical centers.

Truly effective treatment of schizophrenia requires approaching each person with the condition as a unique individual with biological and psychological vulnerabilities embedded within a matrix of environmental stressors. Evidence for the necessity of this view comes from many findings, including those on the impact of stress[20] or walking through an urban lansdcape[21] on symptoms such as paranoia and anxiety, as well as on the links between understimulating environments and expression of negative symptoms.[22] Problem-oriented medical information systems allow treatment planning to be organized around disordered pathophysiological processes, behavioral domains, and environmental stressors, and these approaches need evaluations for cost-benefits determinations.

Providing interventions external to the usual medical contexts may be useful, especially given the negative symptoms, poor insight, and other factors that reduce attendance at clinics. For example, individual and family treatment has been provided in the home and shown to be effective in reducing relapse even when medication use is minimal.[23] Similarly, cognitive remediation has been successfully delivered in the home,[24,25] with varying degrees of professional support.[26] Although schizophrenia is associated with poor outcome in many, but not all patients, it remains to be seen what outcomes are possible if treatment is made more "user-friendly" in both type and location.

Further Thoughts

Additional recommendations were developed within the context of end-of-Forum meetings among all participants. One involved exploring the similarities vs differences, or overlap vs nonoverlap, between schizophrenia and several

other conditions, which thus far have been understudied in relationship to schizophrenia, to clarify the essential aspects of the disorders that comprise the syndrome. One class of conditions highlighted was developmental disorders characterized by cognitive impairment. For example, studies show an overlap between schizophrenia and both verbal and nonverbal learning disabilities in terms of cognitive impairments and their anatomical correlates.[27–34] At the same time, schizophrenia and autism appear to represent opposite extremes on some dimensions,[35–38] and thus investigation of the pattern of similarities and differences between these disorder classes may be quite revealing. Schizophrenia is also associated with an elevated rate of conduct disorder and antisocial personality disorder diagnoses,[39] and these may share biological abnormalities, such as reduced functional connectivity involving the frontal cortex[40] and cortical thinning.[41] Physical and sexual abuse in childhood also increases risk for both antisocial personality disorder and schizophrenia,[42] and its effects include violence and reduced thalamic volumes in both disorders.[43] At a psychological level research on eating disorders has shown stereotyped ways of thinking and response to cognitive remediation approaches (including anatomical effects as revealed by fMRI) that are similar to those observed in schizophrenia.[44–46] In addition, preliminary evidence suggests that schizophrenia may share some aspects of perceptual organization impairment with body dysmorphic disorder, a condition in which approximately half of patients meet criteria for delusional symptoms.[47–50] Other examples of potentially revealing comorbidity exist as well, such as with substance abuse (including cigarette smoking) and various medical conditions.[51,52] It is important to note that the suggested strategy of increased cross-diagnostic research is not the same as the National Institute of Mental Health strategy proposed for the Research Domain Criteria (RDoC) initiative,[53] which involves identifying dimensional constructs relevant to psychopathology domains, as opposed to diagnostic categories. The 2 approaches overlap, however, in the sense of seeking to identify core mechanisms that transcend current Diagnostic and Statistical Manual (DSM) diagnostic boundaries. Further investigations of these issues may sharpen our understanding of etiological and developmental pathways to schizophrenia syndromes.

It may also be useful to study conditions that reduce risk for schizophrenia. Two examples of this are congenital blindness—where a case of schizophrenia has not been reported[54,55]—and rheumatoid arthritis, which occurs 70% less in people with schizophrenia than in other people.[52,56] Data on congenital blindness has provided clues regarding the role of crossmodal plasticity in reducing the emergence of cognitive and behavioral features associated with schizophrenia and on the role that visual processing disturbances may play in the development of schizophrenia. Data on rheumatoid arthritis may help clarify the role of lipid membranes and the glutamate system in these 2 conditions.[57]

Finally, to study many of the issues summarized in this report, very large sample sizes will be necessary. This will require generation of comprehensive databases and establishing methods for researchers to contribute to and to access data from these databases. 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,[58] ie, 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).

As discussed in the Retrosight report noted earlier, we now know how research projects are successfully translated into patient benefit (and when this is unlikely to occur). The projects with the greatest impact share certain characteristics that could be selected for, promoted, and nurtured to increase the impact of future research and therefore make more effective and efficient use of research resources. We believe that an increased focus on the consensus-driven themes, methods, and topics we reviewed in this summary report is likely to increase the impact of future research, at the individual and societal levels.

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Appendix

Meeting participants: Robert A. Bittner, Robert W. Buchanan, Kristin S. Cadenhead, William T. Carpenter, Jr, Aiden Corvin, Camilo de la Fuente-Sandoval*, Daniel Durstewitz, André A. Fenton, Jay. A Gingrich, Joshua A. Gordon, Chloe Gott*, Peter B. Jones*, René S. Kahn, Richard Keefe, Wolfgang Kelsch, James L. Kennedy, Matcheri S. Keshavan,

Angus W. MacDonald III, Anil Malhotra**, John McGrath**, Andreas Meyer-Lindenberg**, Kevin J. Mitchell, Bita Moghaddam**, Vera A. Morgan, Craig Morgan, Kim T. Mueser, Karoly Nikolich, Patricio O'Donnell, Michael O'Donovan, William A. Phillips, Wulf Rössler, Louis Sass, Akira Sawa, Jeremy Seamans*, Steven M. Silverstein**, William Spaulding, Sharmili Sritharan, Heiki Tost, Peter Uhlhaas, Aristotle Vioneskos, Michèle Wessa, Ashley Wilson*, Leanne M. Williams*, Til Wykes**.

*Authored or coauthored background papers but were not in attendance at the meeting.

**Program Advisory Committee.

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