Published in final edited form as:

Neurobiol Dis. 2013 May ; 53: 1–2. doi:10.1016/j.nbd.2013.01.021.

Schizophrenia research in 2013: are we making progress?

Takeshi Sakurai¹, Leslie A. Shinobu², and Akira Sawa³

¹Medical Innovation Center, Kyoto University Graduate School of Medicine

²Takeda Pharmaceutical Company Ltd

³Department of Psychiatry, Johns Hopkins University School of Medicine

Abstract

The diagnostic category of schizophrenia encompasses a range of disabilities with distinct phenotypic features typically manifesting in young adulthood. Classically the purview of psychiatrists, it is now apparent that close cross disciplinary collaboration and iterative comparison of datasets is a must if we intend to make significant in-roads in preventing both the slide into full blown disease and ensuring that susceptible individuals maintain best quality of life as they age. For example, understanding whether there are specific development windows that permit environmental triggers acting on specific genetic backgrounds to unmask and ensconce the relevant phenotypes is one area where epidemiology, clinicians, and basic neuroscientists likely possess key pieces of the puzzle. A mind-set shift towards coherent collaborative strategies aimed at uncovering fundamental neurobiological principles that govern the dynamic way in which the brain continually moulds and reshapes structure and function could speed progress in the field.

Editorial:

Schizophrenia is a psychiatric disorder, with distinct phenotypic features, that is still diagnosed based on characteristic clinical manifestations (DSM IV-TR, with the new DSM-V draft to be finalized in 2013); there are no relevant fully validated biomarkers or laboratory-based tests (Kapur et al 2012). It is also currently viewed as a disorder of developmental origin, typically appearing in young adulthood.

Our understanding of the full range of alterations in brain structure and function that occur during the genesis of this disorder and how they can be modified by both genetic make-up and internal and external environmental context is just beginning to take off. Genetic studies, in particular, are fast providing new clues to the underlying biological changes that contribute to risk for developing/unmasking the relevant clinical phenotypes. There is evidence to make the case that the disease course is determined by a given individual's unique developmental trajectory – from conception through to adulthood, across the aging spectrum. Because of this complex interplay, pinpointing key “tipping points” that define the neurobiological changes that drive the development of and maintain the schizophrenic phenotype remains a major challenge (Insel 2010).

We open this issue with three papers that alert us to specific environmental factors that seem to play key roles in unmasking vulnerabilities in different phases of life. First, Hamlyn et al. ask the question, from an epidemiologic point of view, whether there are modifiable non-

genetic risk factors that impact early brain development. The authors chose to focus on non-genetic risk factors shared by both schizophrenia and autism since these disorders share common genetic risk factors. Through literature survey, advanced paternal age, pregnancy and birth complications, and migrant status, appear as identifiable additional shared risk factors (Hamlyn et al, this issue). Second, Saito et al. review studies that support the contention that cannabis use in adolescence is a major risk factor for schizophrenia. During adolescence, the brain goes through dramatic changes, which include myelination and synaptic pruning. The endocannabinoid system plays crucial roles in more than one of these processes. In this article, the role of the endocannabinoid system, especially the cannabinoid receptor type 1 mediated signaling cascade, is detailed from both basic and clinical science points of view (Saito et al, this issue). Following these two articles, Harvey et al. examine epidemiologic evidence from the other end of the spectrum. Although developmental in origin, schizophrenia currently evolves into a chronic disorder with life-long consequences mediated by declining cognitive function and variable impact on activities of daily living (Robinson et al 2004). It has long been suggested that chronic institutionalization further negatively impacts the disease course - a perception that led in large part in the 1970's to the widespread closing of the locked mental health wards and institution of community-based treatment programs. Disentangling the particular clinical and biologic features that are determinants of long hospitalization from the effects of hospitalization and medication is no easy task, but Harvey et al. tackle this issue (Harvey et al, this issue).

We then shift attention to what is happening inside the brain. Each of the next three papers focuses on a different set of anatomic constructs relevant to the study of schizophrenia. Seshadri et al. have focused specific alterations in circuit-based synapses (Seshadri et al, this issue). Inan et al. review the role of cortical interneurons in the pathology of schizophrenia (Inan et al, this issue). Takahashi et al play a framework for thinking about how disruption of nerve connectivity and inflammation as a result of glial cell dysfunction may contribute to the pathophysiology of the disorder. In the last article, Mouri et al. review available animal models that may be useful to study neurobiology of schizophrenia (Mouri et al, this issue). The animal modeling repertoire for this disorder now includes a variety of chemical, genetic, environmental and other manipulations that alter function in specific brain regions/circuits. The range of models with reasonable face validity (the ability to recapitulate one or more core phenotypic features of the human disease) has increased significantly, although we need to pay attention to pitfalls in linking between mouse and human behaviors (Young et al 2010). Testing environmental/behavioral strategies for ameliorating specific behavioral phenotypes is now possible. Genetic manipulations may allow us to explore specific hypotheses of direct relevance to the molecular bases for the disorder.

In total, the articles in this issue underscore the acute need for continuing to ferret out links between the underlying genetics, developmental windows when the environmental milieu is particularly influential, the principles underlying the brain's adaptive repertoire in terms of metabolism, structure, and function, and an individual patient's natural clinical course. In addition, as the reader will appreciate, it is increasingly apparent that the clinical moniker likely encompasses a spectrum of disorders now grouped under the same set of clinical definitions, but which will eventually be redefined based on specific underlying pathophysiology.

How quickly are we moving forwards in our mission to help patients? The drug development pipeline already contains molecules that have a reasonable chance of fulfilling one or more of the most urgent unmet needs in treating schizophrenia: an anti-psychotic that works well but with a least side effect profile, drugs that improve negative symptoms, and medications that improve cognitive function. However, if we ask ourselves – “can we accurately predict who is at risk for developing schizophrenia?”, “can we prevent an 18-year old with a first psychotic episode from sliding into chronic disease?” – we are soberingly far from possessing the understanding that we need to make a difference (Hyman 2012; Insel 2012). The issue is not so much a shortage of targets for drug development, rather, perhaps, the lack of a strategy for approaching the basic biology of schizophrenia with an eye to uncovering fundamental neurobiological principles that govern the dynamic way in which the brain continually moulds and reshapes structure and function. It is clear that if we continue to approach drug development one target at time, we are unlikely to make a meaningful impact any time soon. If we place more concerted effort on uncovering principles of change, we should be able to make significant progress not only in schizophrenia, but should also be able to apply the information to other study of other CNS disorders as well.

We have a serious challenge in the current research funding climate - how to most efficiently use the finite resources that are available in a way that allows us to make significant progress in the shortest amount of time. The recent move towards collaboration in the pre-competitive space is perhaps a constructive step. There are several ongoing collaborative efforts of the growing will and commitment to partner widely in meeting the challenge of solving some of our most pressing health care needs in as timely, transparent and expeditious manner as possible. Most of these initiatives involve the generation and application of so-called BIG DATA sets that lay the foundation for novel observations related to patterned change and themes for focus that are intimately tied to the function of brain networks (e.g., Hamshere et al 2012; Stein et al 2012).

Where can clinicians play a larger role in this new era of highly integrated research? Careful clinical longitudinal data (phenotyping that captures the richness of the clinical spectrum) will again become critical as the field begins to redefine patient sub-populations based on underlying genetics and specific pathophysiological processes (e.g., Maccabe et al 2013). Merging the observations of pediatric/developmental experts with those of their adult specialist counterparts will be needed so that we can really understand the continuum of clinical changes. How can basic scientists help? There are numerous entry points - from working out the molecular biology to moving translational research forward. These include human genetics, epigenetics, molecules, cell biology using patient derived cells, animal models, functional studies of brains, identifying new drug targets, medicinal chemistry etc (Marder et al, 2011). In short, there is ample room for clinicians, scientists of all kinds, epidemiologists, imagers, etc. working in collaboration to iteratively interrogate the growing trail of clues.

The intent of this special issue is in part to help celebrate the insights of the recent past and in part to help catalyze the next phase of integrated research where genetic, epidemiologic, developmental, behavioral, clinical, and neuroscience data is considered, debated, and acted

on in concert. We need a sea change in mindset, a new urgency with which we approach the puzzle before us, and a spirit of true collaboration tinged with healthy competitiveness. We hope you will join the effort.

Acknowledgments

The research in the authors' laboratories has been supported by TK project (T.S.), by USPHS grants MH-084018, MH-094268 Silvo O. Conte center, MH-069853, MH-085226, MH-088753, MH-092443, Stanley, RUSK, S-R foundations, NARSAD, and Maryland Stem Cell Research Fund (A.S.).

References

- Hamshere ML, Walters JT, Smith R, Richards AL, Green E, et al. Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the Schizophrenia PGC. *Mol Psychiatry*. 2012
- Hamlyn J, Duhig M, McGrath J, Scott J. Modifiable risk factors for schizophrenia and autism - Shared risk factors impacting on brain development. *Neurobiol Diseases*. this issue.
- Harvey PD, Lowenstein DA, Czaja SJ. Hospitalization and psychosis: Influence on the course of cognition and everyday functioning in people with schizophrenia. *Neurobiol Disease*. this issue.
- Hyman SE. Revolution stalled. *Sci Transl Med*. 2012; 4:155cm11.
- Inan M, Petros TJ, Anderson SA. Losing your inhibition: Linking cortical GABAergic interneurons to schizophrenia. *Neurobiol Diseases*. this issue.
- Insel TR. Rethinking schizophrenia. *Nature*. 2010; 468:187–93. [PubMed: 21068826]
- Insel TR. Next-generation treatments for mental disorders. *Sci Transl Med*. 2012; 4:155ps19.
- Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012; 17:1174–9. [PubMed: 22869033]
- Maccabe JH, Wicks S, Lofving S, David AS, Berndtsson A, et al. Decline in Cognitive Performance Between Ages 13 and 18 Years and the Risk for Psychosis in Adulthood: A Swedish Longitudinal Cohort Study in Males. *JAMA Psychiatry*. 2013:1–10.
- Marder SR, Roth B, Sullivan PF, Scolnick EM, Nestler EJ, et al. Advancing drug discovery for schizophrenia. *Ann N Y Acad Sci*. 2011; 1236:30–43. [PubMed: 22032400]
- Mouri A, Nagai T, Ibi D, Yamada K. Animal models of schizophrenia for molecular and pharmacological intervention and potential candidate molecules. *Neurobiol Diseases*. this issue.
- Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004; 161:473–9. [PubMed: 14992973]
- Saito A, Ballinger MDL, Pletnikov MV, Wong DF, Kamiya A. Endocannabinoid system: Potential novel targets for treatment of schizophrenia. *Neurobiol Diseases*. this issue.
- Seshadri S, Zeledon M, Sawa A. Synapse-specific contributions in the cortical pathology of schizophrenia. *Neurobiol Diseases*. this issue.
- Stein JL, Medland SE, Vasquez AA, Hibar DP, Senstad RE, et al. Identification of common variants associated with human hippocampal and intracranial volumes. *Nat Genet*. 2012; 44:552–61. [PubMed: 22504417]
- Takahashi N, Sakurai T. Roles of glial cells in schizophrenia: Possible targets for therapeutic approaches. *Neurobiol Diseases*. this issue.
- Young JW, Zhou X, Geyer MA. Animal models of schizophrenia. *Curr Top Behav Neurosci*. 2010; 4:391–433. [PubMed: 21312408]