SCHIZOPHRENIA:

COULD IT BE PREVENTED?

A SATELLITE MEETING OF THE 2014 ANNUAL MEETING OF THE SOCIETY OF BIOLOGICAL PSYCHIATRY

MAY 7, 2014

NEW YORK HILTON MIDTOWN

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WELCOME MESSAGE

Early detection of psychotic disorders has recently become a focus for research and clinical development, leading to a major conceptual shift in psychiatry, and to the development of a preventive approach to psychiatric disorders. Based on emerging evidence that treatment delay has a negative impact on outcome, specialized programs to reduce the duration of untreated psychosis and develop specifically adapted treatments have been initiated worldwide. To this effect, it is essential to understand the underlying causes and mechanisms in order to identify key biomarkers profiles, and to develop novel therapeutic and preventive measures based on the etio-pathophysiology.

Our Symposium brings together a panel of distinguished leaders in the field, who will present the state of the art of schizophrenia research with focus on pathophysiological mechanisms, genetic and environmental risk factors and their interaction during neurodevelopment. Dialogs between academia and industry on innovative solutions to therapeutic targets will contribute to shape the perspectives on preventive measures.

Details regarding the course of the Symposium as well as our speakers and chairs are listed below. We trust that they will meet with your interest, and that we will have an opportunity to share experience, expand our networks, discuss collaborations and cultivate friendships.

We thank you for joining us and look forward to a fruitful event.

The Organizing Committee

Prof. Kim Q. Do
Prof. Hirofumi Morishita
Prof. Patricio O'Donnell
Prof. Akira Sawa

ACKNOWLEDGMENTS

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the Organizing Committee is very grateful to the following institutions:

CHUV Lausanne University Hospital

www.chuv.ch

UNIL | Université de Lausanne

www.unil.ch

alamaya foundation for research in schizophrenia

www.alamaya.net

The Johns Hopkins Schizophrenia Center

www.hopkinsmedicine.org/psychiatry/schizophrenia

Icahn School of Medicine at Mount Sinai

The Friedman Brain Institute

http://icahn.mssm.edu/research/institutes/brain-institute

PROGRAM

07:45-8:10 **Arrival and Registration**

08:10-08:15 **Organizers' Welcome**

08:15-08:30 **Michel Cuenod –** Lausanne University, Switzerland
Introduction

Session 1: Pathophysiological Mechanisms
Chairs: **Akira Sawa** (Johns Hopkins University, Baltimore) &
Julio Licinio (South Australian Health and Medical Research Institute)

08:30-09:05 **Eric Nestler –** Mount Sinai School of Medicine, New York
Epigenetic mechanisms of neuropsychiatric disorders

09:05-09:40 **John H. Krystal** – Yale University, New Haven
Glutamate microcircuit and microcircuit dysfunction in schizophrenia: potential therapeutic implications

9:40-10:15 **Bruce McEwen –** Rockefeller University, New York
Stress and the brain: structural remodelling via novel mechanisms

10:15-10:45 Break

10:45- 11:20 **Kim Do** – Lausanne University, Switzerland
Redox dysregulation in schizophrenia: a translational approach

11:20-11:55 **Patricio O'Donnell –** Pfizer Inc.
Cortical disinhibition in schizophrenia

11:55-12:30 **Anthony Grace** – University of Pittsburgh
Dopamine system dysregulation by the hippocampus and the pathophysiology of schizophrenia

12:30-13:30 Lunch

Session 2: Risk Factors and Potential Role of Critical Periods
Chairs: **Nitin Gogtay** (NIMH, Bethesda) & **Hirofumi Morishita** (Mount Sinai, New York)

13:30 -14:05 **Nick Brandon –** AstraZeneca
Translating the schizophrenia genome - Lessons from DISC1 and ZNF804A

14:05 -14:40 **Alan S. Brown** – Columbia University, New York
Prenatal risk factors: specificity for schizophrenia

14:40 -15:15 **Takao K. Hensch** – Harvard University, Cambridge
Balancing plasticity / stability in neurodevelopment

15:15-15:50 **Larry J. Seidman** – Harvard University, Boston
A developmental perspective on timing of preventative interventions for schizophrenia

15:50-16:10 Break

Session 3: Innovative Solutions to Novel Drug Targets
Chairs: **Alain Beaudet** (CIHR, Ottawa) & **Philippe Conus** (Lausanne University)

16:10 -16:45 **Akira Sawa –** Johns Hopkins University, Baltimore
Stress response and homeostatic cascades in adolescent brain: potential for novel drug discovery

16:45 -17:20 **Daniel C. Javitt** – Columbia University, New York
Glutamate-based early intervention in schizophrenia

17:20-18:00 **Joseph T. Coyle –** Harvard University, Boston
Synthesis of Perspectives

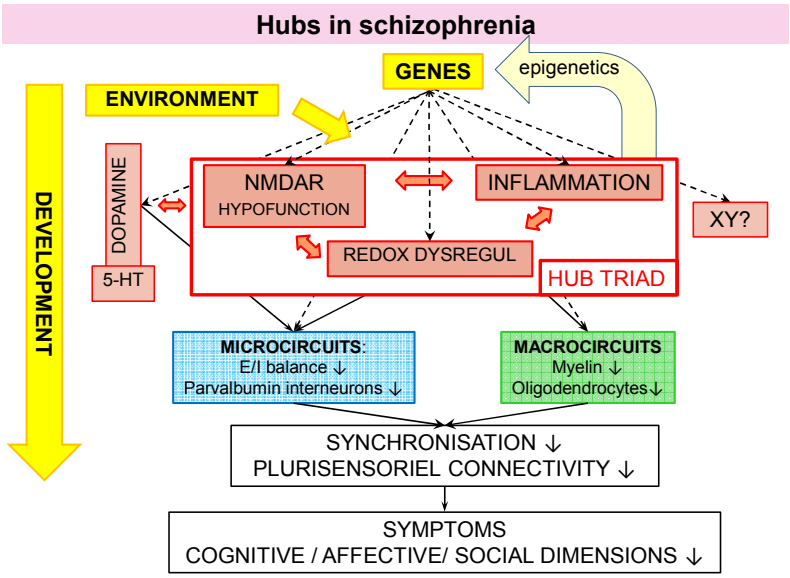
INTRODUCTION

PROF. MICHEL CUENOD

Michel Cuénod is a Swiss MD with experience in psychiatry, and a neuroscientist trained in neurophysiology, neurochemistry and neuromorphology. He was professor of neurobiology and served as director of the Brain Research Institute at the University of Zurich (Switzerland) from 1984 to 1998. Since 1998, he has been invited professor at the University of Lausanne.

Michel Cuénod was president of the *European Neuroscience Association* and is one of the founders of the *European Journal of Neuroscience*. As Secretary of the *Human Frontier Science Program*, he promoted international cooperation in molecular biology and neuroscience. He is recipient of many prizes and awards: the "Prix César Roux" of the Medical School of Lausanne, the "Robert Bing Preis" Award for Neurology of the Swiss Academy of Medicine, and the "Marcel Benoist Preis", the highest scientific distinction awarded by the Swiss government. He was named Doctor Honoris Causa of the University of Geneva in 1994, and member of the Swiss Academy of Medical Sciences in 1996. He received the Medal of the Human Frontier Science Program in 1999, and became an honorary member of the Swiss Society for Neuroscience in 2007.

INTRODUCTION



A general scheme of a central hub in schizophrenia pathophysiology will be discussed in order to put in perspective the presentations of today's symposium. An interacting triad made of NMDA receptor hypofunction, inflammation and redox dysregulation due to the convergence of genetic and environmental risk factors during brain development leads to excitatory/inhibitory imbalance in prefrontal and hippocampal microcircuits and to oligodendrocytes/myelin impairments. These deficits are at the origin of the problems of synchronization and connectivity observed in schizophrenia. Obviously, this scheme does not cover all aspects of a highly complex disease, but should put coherence in some of them. The involvement of the early developmental gene x environment interaction suggests that prevention could represent a valuable approach, provided it is applied at the time of the environmental impact(s). However, to counter the damaging consequences of environmental factors, it will be critical to have reliable biomarkers and safe preventive treatments.

SESSION 1

CHAIRS

PROF. AKIRA SAWA

Dr. Akira Sawa is a psychiatrist and neuroscientist. He currently serves as the director of Johns Hopkins Schizophrenia Center where his colleagues and he work on clinic, research, professional education, and public outreach towards better care and cure for schizophrenia. In addition, as a part of the overall center, Dr. Sawa runs P50 Silvo O. Conte center, which studies synergistic interaction of genetic and environmental stressors towards cortical brain maturation and the pathology schizophrenia by taking multifaceted translational approach. In addition, Dr. Sawa maintains his research program (Molecular Psychiatry Program).

1990: MD from University of Tokyo; 1990-1996: Residency in psychiatry, clinical fellowship, PhD research training, University of Tokyo Hospital; 1996-2002: Research fellowship (postdoctoral fellow, research associate, instructor) under Dr. Solomon Snyder, Neuroscience, Johns Hopkins University; 2002-present: Assistant, Associate, and Full Professor, Psychiatry, Johns Hopkins University; 2011-present: Director, Johns Hopkins Schizophrenia Center

PROF. JULIO LICINIO

Julio Licinio, M.D., FRANZCP, is Deputy Director for Translational Medicine and Head, Mind and Brain Theme at the South Australian Health and Medical Research Institute and Strategic Professor of Psychiatry, Flinders University in Adelaide, South Australia. He is also a Research Professor at the University of Southern California, in Los Angeles, Clinical Professor of Psychiatry at University of Adelaide, Visiting Professor of Psychiatry at University of Minho, in Braga, Portugal and Professeur Associé at Université de Paris – Descartes. He was previously Professor and Director, John Curtin School of Medical Research, The Australian National University (ANU). Professor Licinio is originally from Brazil and lived for over 25 years in the United States, where he had clinical and research training in endocrinology and psychiatry at University of Chicago, Albert Einstein College of Medicine and Cornell. He worked for over 20 years at Yale, NIH, UCLA, University of Miami and ANU, with leadership positions in those institutions. He is founding and Chief Editor of three Nature Publishing Group journals, *Molecular Psychiatry* (Impact Factor: 14.897 number 1 worldwide), *The Pharmacogenomics Journal* (Impact Factor 5.1) and *Translational Psychiatry*. Professor Licinio's translational and genomics research spans the lab and clinic examining obesity, depression, and their interface.

PROF. ERIC NESTLER

Dr. Nestler is the Nash Family Professor of Neuroscience at the Mount Sinai School of Medicine in New York, where he serves as Chair of the Department of Neuroscience and Director of the Friedman Brain Institute. He received his B.A., Ph.D., and M.D. degrees, and psychiatry residency training, from Yale University. He served on the Yale faculty from 1987-2000, where he was the Elizabeth Mears and House Jameson Professor of Psychiatry and Neurobiology, and Director of the Division of Molecular Psychiatry. He moved to Dallas in 2000 where he served as the Lou and Ellen McGinley Distinguished Professor and Chair of the Department of Psychiatry at The University of Texas Southwestern Medical Center until moving to New York in 2008. Dr. Nestler is a member of the Institute of Medicine and a Fellow of the American Academy of Arts and Sciences. The goal of Dr. Nestler's research is to better understand the molecular mechanisms of addiction and depression based on work in animal models, and to use this information to develop improved treatments of these disorders.

EPIGENETIC MECHANISMS OF ADDICTION: WHAT WE CAN LEARN ABOUT MENTAL ILLNESS

Drug addiction can be viewed as a stable form of drug-induced neural plasticity, whereby long-lasting changes in gene expression mediate some of the lasting behavioral abnormalities that define an addicted state. Recent work has begun to define the detailed mechanisms by which drugs of abuse alter the transcriptional potential of particular genes through the actions of specific transcription factors and accompanying alterations in the accessibility of genes within their native chromatin structure in brain reward regions *in vivo*.

This work will be illustrated by consideration of one drug-regulated transcription factor, ΔFosB, which is induced in a cell type-specific manner in brain reward regions by virtually all drugs of abuse and mediates sensitized responses to drug exposure. We have defined genome-wide changes in histone acetylation and methylation, DNA methylation, and related chromatin modifications in brain reward regions that accompany ΔFosB induction in response to chronic drug administration. This work has identified numerous chromatin signatures that mark either altered steady-state levels of gene expression or genes with primed or desensitized responses to subsequent drug exposure or other stimuli.

Such gene discovery efforts have provided important information concerning the basic mechanisms of transcriptional regulation in the brain *in vivo*, and have improved our understanding of how drug administration, through transcriptional and epigenetic mechanisms, alters the synaptic structure and function of brain reward neurons that underlie addiction-related behaviors. These advances can now be mined to develop improved diagnostic tests and treatments for addictive disorders, as well as applied to other forms of mental illness, in particular, schizophrenia.

PROF. JOHN H. KRYSTAL

Dr. Krystal is the Robert L. McNeil, Jr., Professor of Translational Research and Chair of the Department of Psychiatry of the Yale University School of Medicine and Chief of Psychiatry at Yale-New Haven Hospital. He is a graduate of the University of Chicago, Yale University School of Medicine, and the Yale Psychiatry Residency Training Program. He has published over 400 papers and reviews on the neurobiology and treatment of schizophrenia, alcoholism, post-traumatic stress disorder, and depression. His research program unites psychopharmacology, neuroimaging, and molecular genetics. His work on brain glutamate systems contributed to the identification of novel treatment mechanisms for depression, alcoholism, and schizophrenia that are now in development. He is the Director of the NIAAA Center for the Translational Neuroscience of Alcoholism and the Clinical Neuroscience Division of the VA National Center for PTSD. Dr. Krystal received a number of awards including the Joel Elkes Award of the American College of Neuropsychopharmacology, the Anna-Monika Foundation Prize for Depression Research, and the NIAAA Jack Mendelson Alcoholism Research Award. He is also a member of the Institute of Medicine of the U.S. National Academy of Sciences. He was Chairman of the NIMH Board of Scientific Counselors (2004-2007), served on the NIAAA National Alcohol Advisory Council (2008-2012), and president of the American College of Neuropsychopharmacology (2012). Since 2006, he edited a leading psychiatry and neuroscience journal, *Biological Psychiatry* (IF=9.25).

GLUTAMATE MICROCIRCUIT AND MICROCIRCUIT DYSFUNCTION IN SCHIZOPHRENIA: POTENTIAL THERAPEUTIC IMPLICATIONS

This presentation reviews emerging evidence that there may be opposing disturbances in the regulation of glutamatergic neurotransmission in schizophrenia and affective disorders and that drugs with opposing effects on glutamatergic neurotransmission might be needed to treat each disorder. This presentation will begin by briefly reviewing evidence that schizophrenia is associated with glutamate synaptic deficits associated with evidence of deficits in NMDA glutamate receptor function and deficits in GABA neurotransmissions. These deficits are consistent with clinical evidence that glycine transporter 1 (GlyT1) inhibitors and drugs that attenuate glutamatergic disinhibition (mGluR2 agonists, lamotrigine) might play an adjunctive role in the treatment of schizophrenia. In contrast, depression appears to be associated with glial deficits in glutamate uptake, potentially resulting in overstimulation of presynaptic inhibitory glutamate receptors (mGluR2) and overstimulation of postsynaptic NMDA receptors. This model is consistent with the efficacy of mGluR2 antagonists in animals models of depression and the emerging efficacy of NMDA receptor antagonists, particularly ketamine, for the treatment of depression.

PROF. BRUCE MCEWEN

Bruce S. McEwen, Ph.D., is the Alfred E. Mirsky Professor and Head of the Laboratory of Neuroendocrinology at The Rockefeller University. He is a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He served as President of the Society for Neuroscience in 1997-98. As a neuroscientist and neuroendocrinologist, McEwen studies environmentally-regulated, variable gene expression in brain mediated by circulating steroid hormones and endogenous neurotransmitters in relation to brain sexual differentiation and the actions of sex and stress hormones on the adult and developing brain. Current work combines molecular, anatomical, pharmacological, physiological and behavioral methodologies, with translation to the human condition. He served on the MacArthur Foundation Research Network on Socioeconomic Status and Health. He is a member of the National Scientific Council on the Developing Child which focuses on healthy brain development as a key to physical and mental health. He is the co-author of a book with science writer, Elizabeth Lasley, for a lay audience called "The End of Stress as We Know It" (2002) and another book with science writer Harold M. Schmeck,Jr., "The Hostage Brain" (1994), both available as eBooks.

THE BRAIN ON STRESS: STRUCTURAL PLASTICITY AND VULNERABILITY VIA NOVEL MECHANISMS

Stressful experience can precipitate major psychiatric disorders such as schizophrenia and major depression. The brain is the central organ of stress and adaptation to stress because it perceives and determines what is threatening, as well as the behavioral and physiological responses to the stressor.

The adult, as well as developing brain, possess a remarkable ability to show structural and functional plasticity in response to stressful and other experiences, including neuronal replacement, dendritic remodeling, and synapse turnover. This is particularly evident in the hippocampus, where all three types of structural plasticity have been recognized and investigated, using a combination of morphological, molecular, pharmacological, electrophysiological and behavioral approaches; and new information takes this to the level of epigenetics. The amygdala and the prefrontal cortex, brain regions involved in anxiety and fear, mood, cognitive function and behavioral self-regulation, also show structural plasticity.

Acute and chronic stress cause an imbalance of neural circuitry subserving cognition, decision making, anxiety and mood that can increase or decrease expression of those behaviors and behavioral states. In the short term, such as for increased fearful vigilance and anxiety in a threatening environment, these changes may be adaptive; but, if the danger passes and the behavioral state persists along with the changes in neural circuitry, such maladaptation may need intervention with a combination of pharmacological and behavioral therapies, as is the case for chronic or mood anxiety disorders. There are important sex differences in how the brain responds to stressors that are in urgent need of further exploration. Moreover, adverse early life experience, interacting with alleles of certain genes, produce lasting effects on brain and body via epigenetic mechanisms. While prevention is most important, the plasticity of the brain gives hope for therapies that take into consideration brain-body interactions.

PROF. KIM Q. DO

Prof. Kim Q. Do is a neurobiologist, director of the Center for Psychiatric Neuroscience (Department of Psychiatry, Lausanne University Hospital) and head of the Unit for Research in Schizophrenia (URS). Her current major interest lies in bridging basic neuroscience with problems of clinical psychiatry. In 1999, she set up the URS laboratory and developed an interdisciplinary approach promoting active collaboration between specialists in basic neurobiological research and clinicians. Her research program is aimed at a better understanding of the causes and mechanisms leading to schizophrenia phenotypes in order to identify markers for early diagnosis, new drug targets as well as preventive and therapeutic measures. Based on an innovative hypothesis, she could demonstrate that oxidative stress/redox dysregulation induced, among others, by glutathione deficit, may represent a "hub" on which both genetic and environmental risk factors converge during neurodevelopment, leading to the impairment of neural connectivity and synchronization, as well as to cognitive deficits. With her collaborators, she showed in several experimental models that, during the development of the brain, this oxidative stress has structural and functional consequences similar to those observed in patients. Prof. Do received the NARSAD Independent Investigator Award in 2006, and the NARSAD Distinguished Investigator Award in 2010 (with Prof. Patricio O'Donnell).

REDOX DYSREGULATION IN SCHIZOPHRENIA: A TRANSLATIONAL APPROACH

In schizophrenia pathophysiology, redox dysregulation could represent one ”hub” of convergence between genetic and environmental risk factors during neurodevelopment, leading to structural and functional connectivity impairments. The genetic vulnerability factors involve either redox regulation genes directly affecting glutathione (GSH) metabolism, or genes which indirectly lead to oxidative stress, including DISC1, PROD, G72, NRG, DTNBP1. Environmental insults known to favor major psychiatric disorders generate reactive oxygen species as well, which, if the redox regulation is impaired, could perturb the developing nervous system in a time and region specific manner. Based on oxidative stress markers in blood, fibroblasts, CSF and brain of patients suffering of schizophrenia, this hypothesis received support from genetic (*gclm* $^{-/-}$mice) experimental model whose glutathione synthesis is impaired, thus preventing an adequate redox balance regulation. This model reproduces numerous schizophrenia phenotypes including NMDA receptor hypofunction, impaired parvalbumine fast-spiking GABA interneurons (PVI), myelination, neural synchronization, and behavioral anomalies.

Interestingly, *gclm* $^{-/-}$mice also highlight childhood and peripuberty as critical periods of high vulnerability for environmental adverse insults, in analogy to known association with childhood traumatisms in future psychotic patients. Indeed, the gene-environment interaction model shows that additional oxidative challenges in juvenile and peripubertal ages, but not in adulthood, *gclm*$^{-/-}$ mice, lead to severe and permanent PVI and perineuronal net (PNN) impairment. The PNN, a specialized extracellular matrix tightly enwrapping most of PVI as they mature, plays a critical role in their protection against oxidative stress. Interestingly, *gclm* $^{-/-}$mice show during peripuberty an increase in neuroinflammation, involving microglia activation and dysregulation of the receptor for advanced glycation end-product (RAGE). Furthermore, MRS longitudinal analysis of *gclm*$^{-/-}$ mice reveals anomalies in neurochemical profile, including an increase in glutamine/glutamate ratio, also restricted to peripubertal periods. On the other hand, the long range connections may be also affected by redox dysregulation during development. Indeed, *gclm*$^{-/-}$ mice present myelin markers deficits in prefrontal cortex at peripuberty, involving the Fyn kinase pathway dysregulation which lead to impaired /delayed proliferation and differentiation of oligodendrocytes precursors.

Most importantly, an antioxidant precursor of GSH such as N-acetyl-cysteine (NAC) can prevent the morphological, biochemical, physiological alterations described above when applied from pregnancy on in *gclm*$^{-/-}$ mice. This suggests that such antioxidants deprived of side effects could potentially contribute to the prevention of the disease, if applied at the time of environmental insults.

PROF. PATRICIO O'DONNELL

Patricio O'Donnell is VP and Head of Psychiatry & Behavioral Disorders for the Neuroscience Research Unit at Pfizer, Inc. in Cambridge, Ma. Dr. O'Donnell worked as a postdoctoral fellow with Anthony Grace at the University of Pittsburgh, where he pioneered studies on the physiological properties of the nucleus accumbens, and then moved on to establishing his own research program at Albany Medical College. In 2006 he was recruited by the University of Maryland, and in 2013 he moved to Pfizer. Dr. O'Donnell's research focuses on the modulation of cortical brain circuits by dopamine, how this modulation matures during adolescence, and the mechanisms by which it becomes dysfunctional in rodent models of psychiatric disorders with the goal of identifying novel therapeutic targets. He is the recipient of numerous awards including the 2010 National Alliance for Schizophrenia and Depression Distinguished Investigator Award. Dr. O'Donnell is a fellow in the American College of Neuropsychopharmacology (ACNP), and is currently the chair of the Winter Conference on Brain Research. Dr. O'Donnell served or serves on the Editorial Boards of the Journal of Neuroscience, Neuropsychopharmacology, The International Journal of Neuropsychopharmacology, Schizophrenia Bulletin, and the Journal of Pharmacology & Experimental Therapeutics, among others, and sat on advisory committees of the National Institutes of Health. Before joining Pfizer, Dr. O'Donnell was a Professor of Anatomy & Neurobiology and Psychiatry at the University of Maryland School of Medicine.

CORTICAL DISINHIBITION IN SCHIZOPHRENIA

Strong evidence suggests schizophrenia is a disorder arising from combined genetic risk factors and environmental insults during development, with symptoms becoming evident during adolescence. A highly reproduced finding in post-mortem studies is an alteration in markers related to a subset of inhibitory interneurons that suggest loss of activity in this population. The effect of NMDA antagonists has been proposed to arise from selective blockade of receptors located in interneurons, leading to a cortical disinhibition. If this is correct, restoring inhibitory interneuron function would be a critical aspect of developing novel targets for schizophrenia.

Animal models have been useful in identifying the role of genetic and developmental manipulations on the function and connectivity of brain regions implicated in the disease. One aspect most models have in common is impaired cortical interneurons, in particular those expressing the calcium-binding protein, parvalbumin (PV). One commonly used model are rats with a neonatal ventral hippocampal lesion (NVHL), which produces prefrontal cortical deficits with adolescent onset. We have observed that cortical GABA interneurons are affected in this model, yielding cortical disinhibition in adult rats. Other models resulting in loss of interneuron function include maternal antimitotic treatment with MAM, DISC1-dominant negative mice, and in utero blockade of DISC1.

These diverse manipulations resulting in a common pathophysiological scenario (i.e., loss of PV cell function) and common behavioral deficits suggest that complex combinations of diverse etiological factors, both genetic and environmental, could result in alteration in a highly vulnerable cell population. Emerging data indicate that PV interneurons are highly vulnerable to oxidative stress in diverse animal models. It is possible that due to their high levels of activity and protracted developmental trajectory, PV interneurons can be affected by different factors at different developmental stages, contributing to a possible final common pathophysiology that could result in cognitive deficits as a consequence of diverse insults. Understanding the mechanisms in this convergence of effects will be extremely helpful in identifying novel targets for treatment.

PROF. ANTHONY GRACE

Dr. Grace has performed translational research on the dopamine system and schizophrenia for over 30 years. He pioneered the identification and characterization of dopamine-containing neurons, and was the first to quantify their activity state and pattern that is the standard in the literature. His lab developed the MAM developmental model of schizophrenia, and showed that the hyperdopaminergic state believed to be present in schizophrenia appears to be a direct result of overdrive of the dopamine system by the hippocampus, secondary to parvalbumin interneuron loss. His lab has advanced novel GABAergic drugs that may be effective in treating schizophrenia. He showed that MAM rats, like schizophrenics, are overstressed in puberty, and peripubertal diazepam treatment may prevent the transition to psychosis in susceptible individuals. Tony has won the Lilly Basic Scientist Award from the CINP, the Efron Award from the ACNP, a NIMH MERIT award, a Distinguished Investigator award from NARSAD, and fellow of the AAAS. Tony has made a substantial impact on the field (H index 80) spanning basic and clinical research. Tony is one of a handful of individuals that not only performs important basic research, but integrates this work into testable models relevant to the human condition.

DOPAMINE SYSTEM DYSREGULATION BY THE HIPPOCAMPUS AND THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

There is a long history for the involvement of the dopamine system in schizophrenia; however, there is little evidence for a direct pathology within the dopamine system itself. Instead, research has begun to focus on the dysregulation of the dopamine system by other structures, primary among these is the hippocampus. Thus, a preponderance of evidence from human imaging studies has shown that hyperactivity within the limbic hippocampus correlates with dopamine hyperactivity and psychosis, and postmortem studies have identified a loss of parvalbumin interneurons within the hippocampus of human schizophrenia patients. We have used a developmental disruption model of schizophrenia in rats based on prenatal administration of the mitotoxin methanolazoxymethanol acetate (MAM). These rats exhibit a preponderance of behavioral, anatomical, and pharmacological responses consistent with schizophrenia, including hippocampal hyperactivity, parvalbumin neuron loss, and hyper-responsivity of the dopamine system with respect to dopamine neuron firing and locomotor response to amphetamine. Specifically, there is an increase in the number of dopamine neurons firing spontaneously, which would thereby increase the amplitude of the phasic response to stimuli, which we posit causes the schizophrenia patient to over-interpret stimuli. This increase is mediated by hippocampal hyperactivity secondary to loss of parvalbumin interneurons in this region, and consequently interference with evoked gamma band activity consistent with that observed in schizophrenia.

We found that the increase in dopamine neuron activity and the behavioral hyper-responsivity to amphetamine can be reversed by inactivation of the ventral hippocampus in rats. This can also be reversed pharmacologically by selectively increasing GABA tone in the hippocampus by administration of a hippocampal-selective GABA a alpha 5 positive allosteric modulator. However, an important consideration in addition to treatment would be the prevention of schizophrenia. There is a substantial literature suggesting that stress plays a major role in susceptibility to schizophrenia, and moreover that individuals at risk for schizophrenia that later transition to psychosis show increased response to stress peripubertally. MAM rats also show increased anxiety and increased response to stressors prepubertally, and it is known that stress can lead to hippocampal damage. We found that administration of an anti-anxiety agent during this susceptible period can prevent the development of increased dopamine neuron activity and amphetamine hyper-responsivity in MAM-treated rats. Therefore, controlling the negative impact of stress early in life may be an effective means of preventing the transition to schizophrenia in the adult.

SESSION 2

CHAIRS

PROF. NITIN GOGTAY

Nitin Gogtay, MD, received his MD from BJ Medical College in India in 1986 where he also received formal training in pathology and neuropathology. Subsequently, Dr. Gogtay spent 8 years in basic neuroscience research at Karolinska Institute in Sweden, Sydney University in Australia, and later at National Institute of Neurological Disorders and Stroke, before joining Psychiatry Residency at Cornell. He joined the Child Psychiatry Branch in 2000 and has been leading the childhood onset schizophrenia project. Dr. Gogtay's primary interest is in studying the normal and abnormal brain development, along with the clinical phenomenology and neurobiology of childhood onset psychotic disorders. Along with his research Dr. Gogtay is also the Associate Director for Clinical Research for the NIMH, in which role he provides oversight to the clinical trials funded by the NIMH.

PROF. HIROFUMI MORISHITA

Dr. Hirofumi Morishita is an Assistant Professor of Psychiatry, Neuroscience and Ophthalmology at the Icahn School of Medicine at Mount Sinai. He is also a faculty member of the interdisciplinary Mindich Child Health & Development Institute, and Friedman Brain Institute. His research focuses on understanding the mechanisms of experience-dependent brain plasticity during developmental critical period. His recent work led to the preclinical discovery of therapeutic strategies for functional recovery of vision in adulthood. His current research at Mount Sinai since 2011 aims to understand neurotherapeutic strategies for neurodevelopmental disorders. Dr. Hirofumi Morishita received his PhD from Osaka University after Psychiatry residency at National Center Hospital of Neurology and Psychiatry in Tokyo and medical school training at Kyushu University (MD). Before joining Mount Sinai, he was a postdoctoral research fellow in the laboratory of Dr. Takao Hensch at Boston Children's Hospital, Harvard Medical School. Dr. Morishita received a 2012 Travel Award from the American College of Neuropsychopharmacology, as well as funding from the Whitehall Foundation, Brain & Behavior Research Foundation, and March of Dimes Foundation.

PROF. NICK BRANDON

Nick Brandon is currently Head of Discovery Biology in the Neuroscience Innovative Medicine Unit at AstraZeneca in Cambridge, Massachusetts USA. In addition he is a co-director of the AstraZeneca-Tufts Laboratory for Basic and Translational Neuroscience. Previously he led the Psychiatry Department at Pfizer and the Schizophrenia Group at Wyeth. He has been closely involved with multiple programs which delivered compounds into clinical development through Phase 2 starts. Throughout his career, Nick has maintained a keen interest in the human genetics of mental illness, especially the role of risk genes and related pathways in setting up and driving disease processes and related pathology. His group continues to publish some of the critical papers which have led to further understanding of the risk gene DISC1 in psychiatric disease. In recent years, his labs research focused on using emerging understanding of neurocircuitry and human psychiatric genetics (iPS cells, mouse CNV models, next generation sequencing) to develop a future pipeline of targets. In 2010, Nick was awarded a Honorary Professorship from the University of Glasgow in Scotland and was elected to the membership of the American College of Neuropsychophamacology (ACNP). He has now published over 70 articles and book chapters and has recently completed editing a book 'Role of Cyclic-Nucleotide Phosphodiesterases in the CNS'.

TRANSLATING THE SCHIZOPHRENIA GENOME

The struggles of developing new drugs for mental illness are well documented. In recent years we have seen little success in progressing new molecules and mechanisms through clinical success in populations which desperately need alternatives to current treatments. There are multiple reasons highlighted as potential explanations for this faliure, ranging from non- predictability of animal models to the (lack of) selection of patients for trials. The faliure (to date) of the PDE10A inhibitor mechanism is a good example to bring out the issues with the historical drug discovery path.

In parallel with this perceived faliure, our basic knowledge of the genetics and circuitry of these disorders has increased dramatically. The genetic data emerging from groups such as the Psychiatric Genomic Consortium (PGC) is providing a rich source of potential insights and pathways for drug discovery. How as a field are we going to convert these apparent riches into medicines which really make a difference to patients?

There are likely a number of strategies we can take. We can look back at historical faliure and post-hoc determine whether we would have seen different results if we had for example stratified our patients or acted differently at decision points on a screening tree. We could also look at the cancer field and understand whether there are learnings for neuroscience from the cancer genome revolution which has taken place. We can also look at recent examples of where a genetic finding in psychiatry has led to a body of work in search of new approaches for treatment. Though not identified in contemporary genetic studies, I will focus on the risk factor Disrupted in Schizophrenia 1 (DISC1) to try and provide insight into successful approaches and pitfalls for understanding the biology and relevance of such a genetic finding. To put these learnings into practice I will then consider where we will go with ZNF804A, a genetic lead from the early GWAS studies in Schizophrenia.

PROF. ALAN S. BROWN

Alan S. Brown, M.D., M.P.H. is Professor of Psychiatry and Epidemiology at Columbia University Medical Center and Director of the Unit in Birth Cohort Studies at New York State Psychiatric Institute. He received his B.A. from Johns Hopkins University, his M.D. from Jefferson Medical College and completed residency training in psychiatry at the University of Pittsburgh, followed by a postdoctoral research fellowship in schizophrenia at Columbia University, where he also obtained an M.P.H. Dr. Brown has published extensively in the epidemiology of neurodevelopmental etiologies of schizophrenia, autism, and bipolar disorder. The focus of the work is on biomarker-based *in utero* and early childhood exposures that are prospectively documented in large population birth cohorts, including the Finnish Prenatal Studies. These studies have yielded novel associations between prenatal exposures including infection, immune dysfunction, and micronutrient deficiencies and schizophrenia among offspring. More recently, he has extended this work to autism and bipolar disorder. Furthermore, he is collaborating on translational studies of maternal immune activation and schizophrenia, and psychopharmacological trials of cytokine receptor antagonists in schizophrenia. He has received numerous NIH and foundation grants and several honors, including the A.E. Bennett Research Award, and is an Associate Editor of the *American Journal of Psychiatry*.

PRENATAL RISK FACTORS: SPECIFICITY FOR SCHIZOPHRENIA

An accumulating body of evidence from epidemiologic studies has implicated prenatal infection, nutritional deficiency, and other obstetric insults in schizophrenia. More recently, studies have examined whether these exposures are specific to schizophrenia among major psychiatric disorders. These include autism and bipolar disorder. The presentation will focus on birth cohort studies which have enabled comparisons of effects of these in utero exposures between schizophrenia and these latter two disorders.

Specifically, we have demonstrated in a large birth cohort in northern California (N=19,000 pregnancies) that serologically documented maternal exposure to influenza is associated both with schizophrenia and with bipolar disorder with psychotic features, but not with bipolar disorder without psychotic features. These findings suggest that prenatal influenza may be a risk factor for psychosis rather than for schizophrenia per se. With regard to autism, we have shown, in a national Finnish birth cohort (N=1.5 million pregnancies), that elevated maternal levels of C-reactive protein, an inflammatory biomarker, are related to an increased risk of autism and of schizophrenia in offspring. Associations between other exposures and these outcomes will also be discussed.

We shall also discuss the importance of rigorous methodology in these studies, aimed at limiting bias and confounding influences. In particular, our work has utilized prospectively documented exposures based on biomarker assays, ascertainment of cases using comprehensive database and national registries, attention to loss to follow-up, and control for potential confounding factors. The implications of this work for understanding environmental determinants that are shared, and that are unique, for each of these disorders will be discussed. This includes implications for nosology, prevention, and pathogenesis. Moreover, we shall discuss future research in this area, including our strategy of combining data from prenatal, postnatal, and later life antecedents in order to elucidate life course pathways that increase vulnerability to major psychiatric illness, as well as the potential of this work for the development of therapeutic strategies that target these risk factors.

PROF. TAKAO HENSCH

Takao K. Hensch, PhD, is joint professor of Neurology, Harvard Medical School at Boston Children's Hospital, and professor of Molecular Cellular Biology at Harvard's Center for Brain Science. After undergraduate studies with Dr. J Allan Hobson at Harvard, he was a student of Dr. Masao Ito at the University Tokyo (MPH) and a Fulbright fellow with Dr. Wolf Singer at the Max-Planck Institute for Brain Research, before receiving a PhD in Neuroscience under Dr. Michael Stryker at University of California, San Francisco in 1996. He then helped to launch the RIKEN Brain Science Institute as Lab Head for Neuronal Circuit Development and served as Group Director (and now special advisor) before returning to the United States in 2006. Professor Hensch has received several honors, including the Society for Neuroscience Young Investigator Award both in Japan (2001 Tsukahara Prize) and in the United States (2005), as well as an NIH Director's Pioneer Award (2007). He currently directs an NIMH Silvio Conte Center for Basic Mental Health Research at Harvard and has served on editorial boards of various journals, including *Neuron, J Neurosci (reviewing editor), Frontiers in Neural Circuits (chief editor), Neural Development* and *Neuroscience Research.*

BALANCING PLASTICITY / STABILITY ACROSS BRAIN DEVELOPMENT

Neural circuits are shaped by experience – the potency of which changes dynamically across the lifespan. Two important concepts have emerged from the study of such 'critical periods': 1) excitatory-Inhibitory circuit balance is a trigger; and 2) molecular 'brakes' limit adult plasticity. Notably, the cellular and molecular factors which control the onset and closure of plasticity are often linked to genes implicated in mental illness, suggesting misregulated developmental trajectories as part of the etiology. Genetic or pharmacological manipulations are so powerful that animals of identical chronological age may be at the peak, before, or past their plastic window. Thus, the critical period *per se* is plastic, and one outcome of normal development is then to stabilize the neural networks initially sculpted by experience. This talk focuses on fast-spiking parvalbumin circuits in particular, as they are consistently vulnerable to oxidative stress in schizophrenia, and therefore a primary target for novel therapeutic approaches aimed at their proper maturation and maintenance. The emerging notion that the brain's intrinsic potential for plasticity may be actively dampened (rather than passively lost), the associated biological cost of maintaining multiple brakes throughout life, why there are so many, how they interact and ultimately how to lift them in non-invasive ways may hold the key to correcting devastating neurodevelopmental disorders, recovery from brain injury in adulthood and sustaining life-long learning more broadly.

PROF. LARRY J. SEIDMAN

Dr. Seidman is Professor of Psychology in the Department of Psychiatry at Harvard Medical School, at the Beth Israel Deaconess Medical Center (BIDMC), and at Massachusetts General Hospital where he has conducted neuroimaging research since 1992. He is Director of the Massachusetts Department of Mental Health sponsored "Center of Excellence in Clinical Neuroscience and Psychopharmacological Research" at BIDMC. He has spent more than 30 years studying the causes of psychotic disorders and mapping the components of neurodevelopmental disorders of prefrontal cortex and executive control in schizophrenia and other disorders. He has focused primarily on cognition in schizophrenia and studies of youth "at risk" for psychosis. He has published more than 330 peer-reviewed papers and has been involved with 70 funded grants since 1978. He is Principal Investigator of a number of grants investigating the phase of clinical high risk for psychotic illnesses, and treatment of psychosis in the early phases. He has long been involved in teaching and mentoring, and has mentored more than 45 individuals with faculty appointments around the world including 4 Professors and 7 Associate Professors. He brings together his clinical and research interests in the development of projects involving early intervention and prevention of psychotic disorders.

A DEVELOPMENTAL PERSPECTIVE ON TIMING OF PREVENTATIVE INTERVENTIONS FOR SCHIZOPHRENIA

The onset of schizophrenia, like that of Alzheimer's Disease and many other illnesses, can be considered a late phase in a neurodevelopmental and or neurodegenerative evolution. Thus, while improving or developing new treatments for the first episode are very important, the search for earlier interventions may ultimately have the most promise by delaying or attenuating the illness or in the best case scenario, preventing it. Thus, the focus on defining, measuring and treating the "prodromal", clinical high-risk (HR) stage of illness holds considerable promise, but even then, illness can be quite severe and long-standing, raising questions about even earlier treatment.

Primary prevention strategies oriented to the pre-prodromal periods have not been attempted because of an absence of biomarkers or solid knowledge of pathophysiology in the period before adolescence prior to the emergence of mild psychotic symptoms (i.e., prior to the putative "prodrome"). However, there is consistent evidence of significant neuropsychological and social deficits beginning in early childhood of people who later develop schizophrenia, suggesting that a subgroup of youth may be considered vulnerable to schizophrenia and could potentially be treated. Moreover, there is a growing literature on brain structural and functional impairments in the premorbid period. However, the limits of prediction of illness, and the limits of knowledge about "preventative" treatments raise many ethical issues about earlier treatment during the pre-morbid period. In this talk, I will provide a concise literature of the premorbid and prodromal brain, cognitive and behavioral markers derived from both clinical and familial HR research, and will discuss some potential strategies for interventions. I will address these abnormalities and treatments from a developmental perspective.

SESSION 3

CHAIRS

PROF. ALAIN BEAUDET

Dr. Alain Beaudet, MD, PhD, is the President of the Canadian Institutes of Health Research (CIHR). Before joining CIHR in July 2008, Dr. Beaudet was the President and CEO of the Fonds de la recherche en santé du Québec (FRSQ), a position held since 2004. Among his many accomplishments, Dr. Beaudet was associate director (research) at the MNI. He was also Professor at McGill University's Neurology-Neurosurgery and Anatomy-Cell Biology departments. Dr. Beaudet has authored over 175 original articles and 40 monographs and book chapters. Dr. Beaudet has received numerous grants and distinctions, including the Killam postdoctoral fellowship, grants from the Medical Research Council (MRC), CIHR and FRSQ, and the Murray L. Barr Junior Scientist Award. In September 2004, he was awarded the Prix Adrien-Pouliot by the Association francophone pour le savoir (Acfas). He served as president of the Canadian Association for Neuroscience from 1995 to 1997. In 2007, France bestowed the *Order of Academic Palms* distinguished Officer's award to him and he was made Doctor *honoris causa* of Université Pierre et Marie Curie. In 2011, he became a Knight of the National Order of Quebec, the highest honour awarded by the government of Quebec. In 2012, he was awarded the Australian Society for Medical Research (ASMR) Medal. He was also inducted as a Fellow of the Royal Society of Canada. In 2013, he received a Doctorat *Honoris Causa* from the Université de Sherbrooke.

PROF. PHILIPPE CONUS

Philippe Conus is Professor of psychiatry, Head of the Service of general psychiatry and Vice Head of the Department of psychiatry at the University of Lausanne (Switzerland). He specialized in internal medicine and subsequently in psychiatry at the University of Lausanne. He spent 4 years at the Early Psychosis Prevention and Intervention Center in Melbourne Australia, where he developed a clinical and research interest in early intervention in psychotic disorders while working with Prof. Patrick McGorry. He developed a specialized clinical and research program for the early phase of bipolar disorders and became senior lecturer at Melbourne University. Since returning to Switzerland in 2003, he developed an early intervention program for psychotic disorders and started a translational program for research in this domain in collaboration with Professor Kim Do.

PROF. AKIRA SAWA

Dr. Akira Sawa is a psychiatrist and neuroscientist. He currently serves as the director of Johns Hopkins Schizophrenia Center where his colleagues and he work on clinic, research, professional education, and public outreach towards better care and cure for schizophrenia. In addition, as a part of the overall center, Dr. Sawa runs P50 Silvo O. Conte center, which studies synergistic interaction of genetic and environmental stressors towards cortical brain maturation and the pathology schizophrenia by taking multifaceted translational approach. In addition, Dr. Sawa maintains his research program (Molecular Psychiatry Program).
1990: MD from University of Tokyo; 1990-1996: Residency in psychiatry, clinical fellowship, PhD research training, University of Tokyo Hospital; 1996-2002: Research fellowship (postdoctoral fellow, research associate, instructor) under Dr. Solomon Snyder, Neuroscience, Johns Hopkins University; 2002-present: Assistant, Associate, and Full Professor, Psychiatry, Johns Hopkins University; 2011-present: Director, Johns Hopkins Schizophrenia Center

STRESS RESPONSE AND HOMEOSTATIC CASCADES IN ADOLESCENT BRAIN: POTENTIAL FOR NOVEL DRUG DISCOVERY

The concept of intervening prior to the full expression of an illness has many precedents in medicine including cardiovascular disease and diabetes. In brain diseases, recent studies on Alzheimer's disease have suggested that interventions are most likely to be effective during earlier stages of the disease, including mild cognitive impairment. In schizophrenia (SZ), a corresponding condition of mild cognitive impairment to Alzheimer's disease is defined as a prodromal stage or an at risk mental state in adolescence.

Advance in scientific technologies have provided new tools to address the pathophysiological mechanisms that may be associated with the early phases of SZ. Furthermore, studying subjects in the early phrases of the disease can bypass concerns that biospecimens have been affected by long-term medication and other factors related to chronicity. Consequently, many "old" hypotheses that have been debated due to confounding factors, such as medication, substance use, chronic changes and aging, have been re-assessed. More importantly, new experimental evidence has led to new targets for intervention in the early phase of SZ and psychotic disorders.

In this talk, we will revisit the pathology of SZ and psychotic disorders by considering the nature of its developmental trajectory. We will focus on the pathology that develops prior to full onset of the disease. These pathological changes, which occur during adolescence and appear to be associated with altered brain plasticity, will be viewed as targets for interventions that can alter the course of the disease. We highlight translational significance of "stress-associated" cascades. These include (1) inflammation and immune mechanism, (2) oxidative stress-associated cascades, and (3) endocrinological and metabolic implications, and their interconnected functions as key pathophysiological mechanisms of SZ, in particular the early phage of SZ.

PROF. DANIEL C.JAVITT

Dr. Javitt is Professor of Psychiatry and Neuroscience at Columbia University College of Physicians and Surgeons where he directs the Division of Experimental Therapeutics and the Columbia Conte Center for Schizophrenia Research. In addition, he serves as Director of Schizophrenia Research at Nathan Kline Institute for Psychiatric Research. Dr. Javitt received his BA, *magna cum laude* from Princeton University in 1979 and his MD from Albert Einstein College of Medicine in 1983. He completed his residency in Psychiatry in 1987, and earned a PhD in Neuroscience from Einstein in 1990. He has published over 250 articles on issues related to normal brain function, cognitive neuroscience, NMDA receptors and schizophrenia. He has received awards for his research from organizations including the *American Psychiatric Association*, the *Society for Biological Psychiatry*, the *American College of Neuropsychopharmacology,* the *American College of Psychiatrists*, and the *Child Welfare League of America*. His research is supported by the NIMH, the Stanley Medical Research Institute, and other philanthropic organizations. He is a Fellow of the *American College of Neuropsychopharmacology*, and a standing member of the Institute of Medicine *Neuro Forum*.

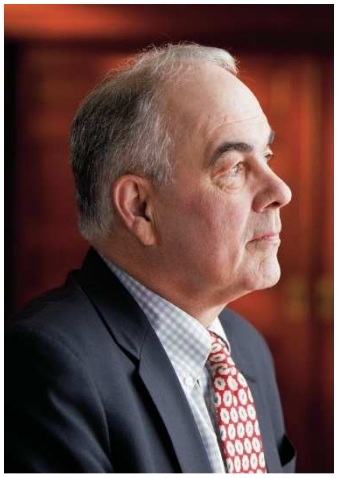
GLUTAMATE BASED EARLY INTERVENTION IN SCHIZOPHRENIA

Disturbances in N-methyl-D-aspartate receptor (NMDAR) function contribute to schizophrenia (Sz) and are indexed by objective neurophysiological disturbances. Agents such as glycine and D-serine bind to an allosteric regulatory site of the NMDA receptor complex and may be therapeutically beneficial in Sz. Two recent studies were conducted with 60 mg/kg/d (~4 g/d) D-serine to investigate utility of this agent in early stage schizophrenia.

The first study investigated D-serine effects on potential neurophysiological measures of target engagement, including mismatch negativity (MMN) and visual P1 in 35 stabilized, chronic Sz subjects, along with PANSS symptoms and MCCB neurocognitive function. D-serine patients showed a small (8.5±13.2%) but significant decline in PANSS symtpoms vs. placebo, along with a small but significant improvement in MCCB composite score **(**1.5±3.1 pts,t=2.4,p=0.023,d=0.72). Significant improvements were also observed for MMN (p=.044), with largest change occurring to frequency deviants (p=.018), and visual P1 (p=.043,d=.67), supporting use of these measures to assess functional target engagement in future trials.

The second study investigated D-serine effects (16-wk) on prodromal symptoms in 44 individuals at clinical high risk (CHR) for Sz based on SIPS/SOPS criteria. A highly significant (p=0.03;d=0.68) 35.7 ± 17.8% reduction was observed in effect was observed on SOPS negative symptoms. Furthermore, >20% improvement was observed in 9/10 subjects who completed all 16 weeks of treatment vs. only 5/11 placebo patients (p=.023). A 30.9±14.9% reduction was observed on total symptoms that approached significance (p=.07,d=.67). 2 placebo and 1 D-serine patient transitioned to psychosis during the study.

These studies support glutamate-based interventions in general, and D-serine based intervention in specific, in early stage schizophrenia. Future studies combining D-serine and redox based interventions should also be considered.



PROF. JOSEPH T. COYLE

Joseph T. Coyle graduated from Holy Cross College and then received his medical degree from the Johns Hopkins School of Medicine in 1969. Following a pediatric internship, he was a research fellow for three years at the National Institutes of Mental Health. He returned to Johns Hopkins in 1973 to complete his psychiatric residency and joined the faculty in 1975. In 1980, he was promoted to Professor of Neuroscience, Pharmacology and Psychiatry. In 1982, he became the Director of the Division of Child and Adolescent Psychiatry. From 1991 to 2001, he served as Chairman of the Consolidated Department of Psychiatry at Harvard Medical School. He now holds the Eben S. Draper Chair of Psychiatry and Neuroscience. Dr. Coyle's research interests include developmental neurobiology, mechanisms of neuronal vulnerability and psychopharmacology. He has carried out research on the role of glutamatergic neurons in the pathophysiology of neuropsychiatric disorders for over 30 years. He has published over 600 scientific articles and has edited ten books. His research has been cited over 45,000 times (*h*-index>100). He is a member of the Institute of Medicine, fellow of the American Academy of Arts and Sciences and fellow of American Association for the Advancement of Science. He is the editor of *JAMA Psychiatry*.

SYNTHESIS OF PERSPECTIVES