3.2 PARVALBUMIN INTERNEURON IMPAIRMENT INDUCED BY OXIDATIVE STRESS AS A COMMON PATHOLOGICAL MECHANISM IN ANIMAL MODELS OF SCHIZOPHRENIA

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Keynote

1. CHANGING THE LENS ON MENTAL HEALTH
Alastair Campbell

Author

Overall Abstract: Alastair Campbell, talking from personal and family experience, and based on years of campaigning and study, urges a rethink of how we view mental health and mental illness.

Plenary

2. MICROCIRCUITS, MACROCIRCUITS, AND CORTICOL DYSFUNCTION IN SCHIZOPHRENIA:
A COMPUTATIONAL AND TRANSLATIONAL NEUROSCIENCE PERSPECTIVE
John Krystal

Yale University School of Medicine

Overall Abstract: Computational neuroscience may be a critical component of the effort to understand how cortical micro- and macro-circuits support behavior and express the symptoms of neuropsychiatric disorders. This presentation will present an update on an ongoing interdisciplinary effort to understand the role of compromised glutamate synaptic signaling, particularly related to the NMDA glutamate receptor, for the pathophysiology of schizophrenia. This presentation will draw on studies in animal models, healthy humans, and schizophrenia patients. It will draw parallels between the effects of the NMDA receptor antagonist, ketamine, and working memory impairment and abnormalities in cortical functional connectivity in schizophrenia. In so doing, it will highlight examples where computational approaches have affirmed hypotheses arising from experimental work or contributed new predictions that could be tested experimentally. Lastly, it will illustrate a prediction about novel therapeutics for schizophrenia that are embedded in an emerging developmental model for this disorder.

Concurrent Symposia

3. EXCITATION-INHIBITION IMBALANCES IN SCHIZOPHRENIA: MECHANISMS AND INTERVENTIONS
Lawrence Kegeles

Columbia University & New York State Psychiatric Institute

Overall Abstract: Evidence is accumulating that core features of schizophrenia (SCH) may arise from a fundamental disturbance in the cellular balance of excitation and inhibition (E-I balance) within neural circuitry. In the symposium, we will provide a comprehensive overview of E-I balance alterations in SCH with evidence from preclinical models and in vivo measurements investigating potential neurobiological mechanisms underlying these dysfunctions as well as interventions that remedy these disturbances. Takao Hensch will summarize findings on critical period plasticity and its potential role in vulnerability to schizophrenia. He will present new preclinical data on the destabilizing consequences of enhanced gamma oscillations, which reversibly prolong juvenile forms of brain plasticity by redox imbalance. Jan-Harry Cabungcal will address the role of redox dysregulation and oxidative stress in the pathophysiology of schizophrenia. He will present recent data on the relationship of deficits of the perineuronal net and oxidative stress in the anterior cingulate cortex, and evidence that redox dysregulation can be targeted with antioxidants/redox regulators across animal models. Lawrence Kegeles will present simultaneous EEG and proton MRS measurements of glutamate and GABA during ketamine administration in healthy young adults. These data will be compared with the same modalities acquired in individuals at clinical high risk and patients with SCH, showing disturbed delta and gamma band power and altered E-I balance despite homeostatic rebalancing of glutamate and GABA. Peter Uhlhaas will summarize evidence from EEG/MEG data examining the potential role of neural oscillations in the pathophysiology of schizophrenia. He will show that alterations in gamma-band oscillations are present prior to the onset of schizophrenia in at-risk individuals and related to aberrant E-I balance parameters revealed by MRS-measured levels of GABA and glutamate. Developmental data on the maturation of neural oscillations suggests that the transition from adolescence to adulthood is a sensitive period for modifications in neuronal dynamics that could potentially explain the manifestation of psychosis during this period.

3.1 ENHANCED PARVALBUMIN NETWORK ACTIVITY PROLONGS CRITICAL PERIOD PLASTICITY
Hensch Takao*

Harvard University

Background: Oscillations in neuronal activity tie the pathophysiology of schizophrenia to alterations in local processing and large-scale coordination, and these alterations in turn can lead to the cognitive and perceptual disturbances observed in schizophrenia. Here, we focus on the dual role of fast-spiking, parvalbumin (PV+) networks in the generation of gamma oscillations and critical periods of brain plasticity.

Methods: We generated a mouse model of reduced recurrent inhibition only within local PV+ cell networks by selective removal of GABA receptor alpha1 subunits (PV-α1 KO mice). Electroencephalography (EEG), PV+ immunohistochemistry, perineuronal net (PNN) labeling and redox balance were compared to control measures of brain plasticity (loss of visual acuity, formation of preference behaviors) that are typically limited to a critical period early in life.

Results: PV-α1 KO mice exhibit chronically enhanced gamma-oscillations and extended juvenile forms of cortical plasticity into adulthood. Acute pharmacological suppression of excitatory input restored E-I balance onto these disinhibited PV+ cells and returned baseline EEG power to normal levels, preventing the extended plasticity. Enhanced gamma oscillations were further found to compromise the integrity of perineuronal nets (PNNs) surrounding PV+ cells, elevating oxidative stress and the turnover of metalloproteinases and structural components of the PNN. All of these aspects were also reversed by pharmacological dampening of excitation onto PV+ cells.

Discussion: Cortical gamma oscillations are associated with plasticity and cognition. Our results provide a cellular explanation of how elevated gamma oscillations may promote ectopic brain plasticity by regulating the extracellular matrix which normally stabilizes cortical circuitry. These results carry broad implications for subjects at-risk for schizophrenia who exhibit heightened gamma oscillations prior to psychosis onset (see talk by P Uhlhaas).

3.2 PARVALBUMIN INTERNEURON IMPAIRMENT INDUCED BY OXIDATIVE STRESS AS A COMMON PATHOLOGICAL MECHANISM IN ANIMAL MODELS OF SCHIZOPHRENIA
Jan Harry Cabungcal*, Pascal Steullet1, Joseph Coyle2, Michael Didriksen3, Kathryn Gill1, Anthony Grace1, Hensch Takao3, Anthony LaMantia3, Lothar Lindemann5

Abstracts for the Sixth Biennial SIRS Conference
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3.3 DISTURBANCES IN NEURAL OSCILLATIONS, GLUTAMATE, AND GABA: EFFECTS OF KETAMINE AND COMPARISON TO SCHIZOPHRENIA

Lawrence Kegeles*,1, Erin Stolz2, Xiangling Mao3, Najate Ojeil1, Raphael Massuda3, Mariana Pedrini4,

Maryam Bayatmokhtari3, Mark Slifstein*, Anissa Abi-Dargham4, Matthew Milak1, Carolyn Rodriguez2, Chi-Ming Chen2, Dikoma Shungu1

1Columbia University & New York State Psychiatric Institute; 2University of Connecticut, Storrs; 3Weill Cornell Medical College; 4Universidade Federal do Rio Grande do Sul; 5Mount Sinai School of Medicine; 6Stony Brook University School of Medicine; 7Stanford University

**Background:** Parvalbumin inhibitory interneurons (PVI) are crucial for maintaining proper excitatory/inhibitory balance and high-frequency neuronal synchronization. Their activity supports critical developmental trajectories, sensory and cognitive processing, and social behavior. Despite heterogeneity in the etiology across schizophrenia and autism spectrum disorder, PVI circuits are altered in these psychiatric disorders. Identifying mechanism(s) underlying PVI deficits is essential to establish treatments targeting in particular cognition. Based on our previous publications and new data, we propose oxidative stress as a common pathological mechanism leading to PVI impairment in schizophrenia and some forms of autism.

**Methods:** Using immunohistochemistry technique and confocal imaging analysis, we assessed the relationship between oxidative stress (as revealed by 8-oxo-DG immunolabeling) and PVI and their perineuronal net (PNN) in twelve established animal models relevant to autism (i.e., the fmr1 KO and CNV 15q13.3) and schizophrenia (CNV: 22q11, 15q13.3, 1q21, serine racemase (SR) KO, GRIN2A KO, Gclm KO) with or without additional insult (e.g., environmental: Gclm KO + GBR12909, GRIN2A KO + GBR12909, neonatal ventral hippocampal lesion (NVHL), methylazoxy-methanol acetate developmental rodent model (MAM) and poly:IC).

**Results:** When PVI deficits in the anterior cingulate cortex were found in these animal models carrying genetic and/or environmental risks related to diverse etiological aspects of these disorders, oxidative stress was always present. Specifically, oxidative stress was negatively correlated with the integrity of PVI and the extracellular perineuronal net enveloping these interneurons. Oxidative stress may result from dysregulation of systems typically affected in schizophrenia, including glutamatergic, dopaminergic, immune, and antioxidant signaling. As a convergent endpoint, redox dysregulation has successfully been targeted to protect PVI with antioxidants/ redox regulators across several animal models (e.g., Gclm KO, NVHL rats, GRIN2A KO and SR KO mice). D-serine, an allosteric modulator of brain NMDA receptor also protected PVI and PNN from oxidative stress in SR KO mice.

**Discussion:** In view of the fact that the established pathophysiologial processes dopamine excess, immune dysregulation and NMDA receptor hypofunction could all induce oxidative stress and are potentiated by additional oxidative insults, this mechanism could be central to damage of the highly metabolically active PVI and the PNN surrounding them. Antioxidant systems are therefore potential therapeutic targets, assuming that redox regulators could be applied early, during environmental impacts, long before the clinical emergence of the disease.

3.4 NEURAL OSCILLATIONS AND EXCITATION/INHIBITION BALANCE IN SCHIZOPHRENIA: A DEVELOPMENTAL PERSPECTIVE

Peter Uhlhaas*,1

1Institute of Neuroscience & Psychology, University of Glasgow

**Background:** Schizophrenia (ScZ) is a neurodevelopmental disorder that characteristically emerges during the transition from adolescence to adulthood. However, the mechanisms that underlie the expression of psychotic symptoms and cognitive deficits during this developmental period are still unclear. In my presentation, I will summarize data from EEG/MEG-work