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* 1

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 A receptor alpha1 subunits (PV-α1 KO mice). Electroencephalography (EEG), PV+ immunohistochemistry, perineuronal net (PNN) labeling and redox balance were compared to cortical 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 excitation 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 metallopeptidases 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* 1, Pascal Steullet1, Joseph Coyle2, Michael Didriksen2, Kathryn Gill1, Anthony Grace3, Hensch Takao1, Anthony LaMantia6, Lothar Lindemann7,
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Background: Parvalbumin inhibitory interneurons (PVIs) 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), methylazoxymethanol 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 relevant to diverse etiological aspects of these disorders, oxidative stress was always present. Specifically, oxidative stress was negatively correlated with the integrity of PVIs 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 consequence, redox dysregulation has successfully been targeted to protect PVIs 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 PVIs and PNN against oxidative stress in SR KO mice.

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

3.3 DISTURBANCES IN NEURAL OSCILLATIONS, GLUTAMATE, AND GABA: EFFECTS OF KETAMINE AND COMPARISON TO SCHIZOPHRENIA
Lawrence Kegeles1, Erin Stolz2, Xiangling Mao1, Najate Ojeil1, Raphael Massuda1, Mariana Pedrini4

Abstracts for the Sixth Biennial SIRS Conference

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Background: In schizophrenia (SCH), proton MRS studies of the medial prefrontal cortex (MPFC) show elevated glutamine (Gln) or the combination of Glu and Gln (Glx) in unmedicated patients. Studies in healthy human subjects demonstrate ketamine-induced acute increases in MPFC Glu or Gln. Together, these findings raise the question of potential disturbances in excitation-inhibition balance in the illness, possibly arising from NMDA receptor deficits in GABAergic interneurons. We investigated these questions following acute ketamine administration by using repeated 15-minute MRS acquisitions of Glx and GABA with simultaneous EEG and comparing the results with the same modalities acquired in SCH.

Methods: We enrolled 11 healthy volunteers (age 18–55) who were given a constant i.v. infusion of ketamine 0.5 mg/kg over 40 min during a combined EEG and 1H MRS study. Gx and GABA were acquired in the pregenual MPFC using a 3T GE system and a J-edited PRESS sequence. Sequential MRS acquisitions each of 15 min duration (90 min total) were obtained before, during, and following the infusion. EEG was recorded using an MRI-compatible 64-channel system with direct current BrainAmp MR amplifiers (Brain Products GmbH). Post-ketamine EEG data were analyzed in frontal electrodes for gamma and delta alterations. EEG and MRS data were also acquired in 12 patients with SCH with these systems.

Results: Neurochemicals Glx and GABA showed acute increases within 15–30 minutes following the initiation of ketamine infusion, more pronounced for GABA (13% increase, p = .04 by paired t test). Gamma amplitude in left and right frontal electrodes increased in the first 15-minute average after initiation of ketamine (p < .05), with no evidence of earlier gamma decrease. Left delta amplitude increased linearly following ketamine (p < .01). Peak GABA concentration correlated inversely with average left delta amplitude in the immediately subsequent 15-minute acquisition. Data in SCH showed similar elevations in GABA and gamma amplitude.

Discussion: These data show the feasibility of attaining time resolution of Glx and GABA changes in the several-minutes range with standard PRESS J-edited 1H MRS, and simultaneous sub-second resolution with EEG. There were no indications in these frontal electrodes of very early GABAergic inhibition leading to disinhibition of Glx, which may occur in other brain regions following ketamine administration. The GABA, Glx, and EEG alterations found here following ketamine administration are consistent with stable alterations reported in unmedicated patients with SCH and are compatible with an NMDA receptor deficit mechanism in the illness. They show homeostatic rebalancing at elevated levels as found in SCH itself. Excitation-inhibition rebalancing at abnormally elevated levels may pose a risk of neuronal damage that persists in untreated psychosis.

3.4 NEURAL OSCILLATIONS AND EXCITATION/INHIBITION BALANCE IN SCHIZOPHRENIA: A DEVELOPMENTAL PERSPECTIVE
Peter Uhlhaas*1
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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...