within the infralimbic cortex, learned helplessness (cLH) rats had the same numerical density of synapses, immunolabeled for either the postsynaptic density marker PSD95 or the presynaptic protein synaptophysin, as controls. However, importantly, PSD95 immunolabeling intensities were substantially lower in cLH rats. In contrast, the resilient rats (cNHL) had 25% more PSD95 immunolabeled intensity than either cLH (learned helplessness) or control rats without an increase in synaptophysin-labeled terminal frequency. These results suggest that depression-like behavior may differentially modulate excitatory synapses. Preliminary investigations have demonstrated the feasibility of using this technology in postmortem brain tissue from the ACC in major depressive disorder patients and controls, to assess the number of synapses labeled with PSD95, density of PSD concentrations, and the size of excitatory synapses. This study could provide novel data that could substantially contribute to our understanding of the role of glutamatergic function in MDD.

Speaker 2: Wensheng Wei, China
Title: CRISPR screening in the study of human disease
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Abstract
Genome editing techniques have revolutionized the way that researchers study genes and their functions in eukaryotic systems and model species. Here we report the development of the whole genome CRISPR/Cas9 knockout library and its application in the identification of new drug targets through function-based screening and high-throughput sequencing analysis. Representative screenings will be presented, especially for the identification of host components important for Clostridium difficile infections and HCV infection. In addition, we have recently developed CRISPR/Cas9-mediated genomic deletion screening for long non-coding RNAs using paired-gRNAs, further expanding CRISPR toolbox for mammalian genetics. The application of these powerful genetic screening strategies will have broad application in the discovery of disease mechanisms and drug targets.

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Speaker 3: Sung Yon Kim, Republic of Korea
Title: Optical tools for studying neurocircuit formations in behavior

S11: New findings about what dopamine does in the prefrontal cortex: relevance to schizophrenia
Chair: Bita Moghaddam, USA
Co-Chair: Hitoshi Hashimoto, Japan

Speaker 1: Bita Moghaddam, USA
Title: A novel role for dopamine regulation of cortical information processing.

Abstract
Dopamine neurotransmission in the prefrontal cortex (PFC) is critical to cognitive processes such as attention, working memory as well as behavioral flexibility and has been implicated...
in cognitive deficits observed in addiction, schizophrenia, and ADHD. These cognitive processes and deficits have been linked to network oscillations in PFC. However, experimental evidence describing a causal relationship between the activity of dopamine neurons and oscillations in the prefrontal cortex is lacking. In freely moving TH::Cre rats, we optogenetically stimulated dopamine neurons in the ventral tegmental area (VTA) and simultaneously recorded local field potentials (LFPs) in the medial prefrontal cortex (mPFC). Dopamine neurons were stimulated using bursting paradigms that resemble the activity patterns of these neurons during motivated behaviors. We found that burst activity of VTA dopamine neurons is sufficient for increasing the power of high gamma (> 55 Hz) but not low gamma (35–55 Hz) oscillations in the mPFC. In addition, a corresponding elevation in the power of theta oscillations (4–11 Hz) was observed at the peak of high gamma power. Thus, bursting of dopamine neurons might modulate cortical network activity relevant to goal-directed behaviors and cognitive processes via this coordinated increase in PFC high gamma and theta power. Examination of single unit activity and spike-field coherence is ongoing and will provide further insight into the effects of VTA dopamine neurotransmission on PFC network activity.

**Speaker 2: Pascal Steullet, Switzerland**

**Title: Effects of dopamine on high-frequency neuronal synchrony in the prefrontal cortex: relevance to schizophrenia.**

**Abstract**

Dopamine is released in the prefrontal cortex during cognitive tasks implicating attention, working memory, decision making. During the very same cognitive processes, cortical high-frequency neuronal synchrony which favors information transfer, fast selection and binding of distributed neuronal responses also increases. The multiple modulations by dopamine of synaptic function and cell excitability in excitatory and inhibitory neurons renders however difficult a good comprehension of the effects of dopamine on prefrontal network activity. Because dopamine influences the dynamics of feed-forward inhibition and increases the excitability of fast-spiking interneurons in the prefrontal cortex, it has been proposed that dopamine could modulate fast rhythmic neuronal activity in the γ frequency range. But experimental evidences of such regulation remain scarce. In slices of mouse anterior cingulate cortex, we have shown that dopamine is able to modulate fast oscillatory activity which is generated within a local network of excitatory and inhibitory neurons and reflects rhythmic neuronal synchronization within this network. Dopamine enhances the power of such high-frequency oscillations without altering their peak frequency. Activation of either D1-type or D2 receptors positively modulates the power of these oscillations, whereas activation of D4 receptors has no effect. This suggests that dopamine improves information processing requiring high-frequency neuronal synchronization within the anterior cingulate cortex. Whether a similar dopaminergic modulation exists also within other prefrontal regions such as the medial prefrontal cortex but also in behaving animals remain to be elucidated. Nevertheless, these data provide experimental support for a potential implication of the dopaminergic system to the disturbed high-frequency oscillations in schizophrenia. Thus, a blunted prefrontal dopamine release as evidenced recently in schizophrenia patients (Slifstein et al. JAMA Psychiatry 2015) might contribute to the impaired high-frequency oscillations induced during cognitive tasks.

In addition to its neuromodulatory function, dopamine also produces during its auto-oxidation and degradation some reactive species that can be toxic if there are not properly neutralized. Thus in mice with a genetic susceptibility to oxidative stress, we have shown that an excess of extracellular dopamine during childhood (as for instance resulting from strong prefrontal dopamine release during psychosocial stresses) affects normal maturation of parvalbumin-expressing fast-spiking interneurons, a type of inhibitory neurons which are essential for generating high-frequency oscillations but which are quite sensitive to oxidative stress. As a consequence of an hyperdopaminergic during a critical period of postnatal development, the integrity of parvalbumin interneurons remains abnormal through adulthood, leading to impaired high-frequency oscillations in the anterior cingulate cortex. These data suggest then that strong dopamine release induced by severe psychosocial stresses during childhood, a risk factor for schizophrenia, can permanently affect prefrontal parvalbumin interneurons and high-frequency neuronal synchrony, particularly in individuals with a vulnerability to redox dysregulation. Altogether data suggest that either strong, chronic release of dopamine during childhood or hypodopaminergic later in life can impair high-frequency neuronal synchrony in the prefrontal cortex, both of which could be relevant to schizophrenia pathology.

**Speaker 3: Anissa Abi-Dargham, USA**

**Title: Dopamine neurotransmission in schizophrenia: new findings from combined PET and fMRI studies**

New findings about what dopamine does in the prefrontal cortex: relevance to schizophrenia, S11003: Dopamine neurotransmission in schizophrenia: new findings from combined PET and fMRI studies

**Authors: Anissa Abi-Dargham, Elsmarieke van de Giessen, Jared Van Snellenberg, Guillermo Horga, Clifford Cassidy, Mark Slifstein**

**Objectives: Prefrontal cortical hypodopaminergia has been proposed to underlie prefrontal cortical dependent cognitive deficits in schizophrenia. We undertook combined PET and fMRI studies in drug free or drug naïve patients with schizophrenia and healthy controls matched for age, gender, ethnicity and familial socioeconomic status to test: 1) amphetamine induced dopamine release in dorsolateral prefrontal cortex (DLPFC) 2) BOLD fMRI activation during a working memory task in the same subjects and 3) to examine the relationship between PET and fMRI outcome measures.**

**Methods:** PET imaging with the D2/3 radiotracer [11C]FLB457 before and following 0.5 mg/kg P.O. amphetamine. BOLD fMRI during the self-ordered working memory task (SOWT). 20 patients with schizophrenia (SCZ) and 21 healthy controls (HC) participated. We measured the percent change in binding potential (∆BPND) in DLPFC following amphetamine, BOLD activation during the SOWT compared to the control task, and the correlation between these two outcome measures.

**Results:** We observed: 1) significant differences in the effect of amphetamine on DLPFC BPND (∆BPND in HC. - 7.5±11%, SCZ: +1.8±11%, p = 0.013), 2) a significant relationship between ∆BPND and BOLD activation in DLPFC in the overall sample including patients with SCZ and HC. We also detect a significant inverse relationship between dopamine release capacity and performance on the n back working memory task in patients with schizophrenia.

**Conclusions:** These results provide the first in vivo evidence for a deficit in the capacity for dopamine release in DLPFC in schizophrenia. Furthermore, dopamine release in the DLPFC relates to working memory-related activation of this region, and to