chronic stress induces synaptic depression by increasing the ubiquitin/proteasome-mediated degradation of NMDAR and AMPAR subunits, resulting in impaired recognition memory (Yuen et al., 2012, Neuron). Moreover, females and males show different cognitive and emotional responses to repeated stress and estrogen prevents the detrimental effects of repeated stress on glutamatergic transmission and cognition (Wei et al., 2014, Mol. Psychiatry). Currently, we have found that an epigenetic mechanism involving histone modifications can be used as a potential rescue strategy for the detrimental effects of chronic stress.

Speaker 3: Scott Thompson, USA
Title: Stress and depressive disorder: the role of excitatory synapses in its origin and treatment.
Abstract
Chronic stress leads to a weakening of excitatory synaptic transmission within and between multiple brain regions. In this talk, I will discuss a model in which chronic stress impairs excitatory synapses in multiple sites with cortico-mesolimbic reward circuitry thereby producing depressive-like behavioral changes, such as anhedonia. In this model, weakening of excitatory synapses within and between the hippocampus (HC), prefrontal cortex, and nucleus accumbens (NAC) by chronic stress, ultimately resulting in decreased dopamine release from the ventral tegmental area, lowers the value of rewarding stimuli and promotes anhedonia.

Evidence of this defective circuitry—both intrinsic to the NAC and at upstream synapses within CA1 of the HC—will be presented. In the HC, weakening of excitatory synapses is mediated by loss of GluA1-type AMPARs at distal apical dendrites in the temporopolar-CA1 (TA-CA1) pathway, and is reversed by monoaminergic antidepressant treatment. Similarly, hippocampal output to the NAC is weakened and can be restored by both antidepressants and by high frequency activity-induced long-term potentiation.

Our model predicts that restoring excitatory drive in these synapses will restore the normal affective state, and we show chronic administration of fluoxetine exerts this action. We predicted that negative allosteric modulators of GABA receptors should also restore excitatory drive. Using behavioral, electrophysiological, and biochemical methods, we found that compounds that target α5 subunit-containing GABA-A receptors promoted synchronous oscillatory activity between the HC and NAC, restored excitatory strength at TA-CA1 synapses, and restored normative behavior in social interaction and sucrose preference tests following chronic stress, all within 24 hours of treatment. These data support an excitatory synapse hypothesis model in which depressive-like behavior is caused by dysfunctional cortico-mesolimbic circuitry, and suggests novel therapeutic approaches that may be capable of rapid antidepressant effects by restoring pathologically weakened synapses within reward circuits.

Speaker 4: Maurizio Popoli, Italy
Title: Stress and drugs in the brain. Time-dependent changes in synaptic function and brain architecture
Abstract
Stressful life events represent major risk factors for the development of neuropsychiatric disorders, such as mood and anxiety disorders, which account for a large share of mental health issues worldwide and represent a great therapeutic challenge. In vulnerable individuals, repeated stress or single major stressful events induce brain alterations, which involve synaptic transmission and morphology in the glutamate (Glu) system, ultimately impairing brain functions related to cognition, emotions and homeostatic mechanisms [1,2].

A wealth of neuroimaging studies have shown volumetric reduction and remodeling of neuroarchitecture in limbic/cortical brain areas of depressed subjects; at the same time chronic stress models in rodents have consistently shown reduction of synaptic spines and atrophy/remodeling of dendrites in the same areas affected in humans, thus suggesting that stress-induced maladaptive changes have a primary role in the chain of events leading to development of psychopathology. Instead, the rapid effects of acute stress on synaptic function/plasticity are often opposite, with enhancement of glutamate release/transmission, increased number of spines/synapses, enhancement of synaptic strength. The somewhat opposite modifications of acute vs chronic stress suggest a bi-phasic process, during which, at some unknown points, the stress response turns from increased excitatory activation into its opposite [3–4]. However, while the effects of chronic stress have been investigated at length in animal models, the short- and long-term consequences of acute stressors have been little or not investigated, although it has been shown that in some cases (e.g., PTSD) the first few hours after trauma are crucial for pathophysiological outcome and therapeutic intervention [5].

We have shown previously that acute inescapable stress rapidly enhances glutamate release/transmission in prefrontal frontal cortex (PFC/FC), by synaptic corticosterone (CORT) receptors-dependent non-genomic increase of readily releasable pool (RRP) of vesicles in perforated synapses [6]. Recently, we started investigating the medium- and long-term changes induced by acute stress, with the aim of looking at key determinants in the outcome of stress. Surprisingly, by using EM-stereology, we found that after 40 min of inescapable stress, the enhancement of glutamate release/transmission in PFC was accompanied by a dramatic increase (42.6%) of total number of excitatory synapses (due to non-perforated and axo-spinous synapses), an effect prevented by antidepressant treatment [8]. Spine density was elevated up to 24 h but returned to normal level later; instead dendritic arborization was already reduced 24 h after stress [9]. While confirming a bi-phasic mode in the outcome of acute stress, these results showed for the first time that a single exposure to stress can exert complex and remarkable effects on PFC architecture, both rapid and sustained in time.

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S23: Oxytocin as a multidimensional pharmacotherapy in psychiatric disorders
Chair: Ronald See, USA
Co-Chair: Young Chul Chun, Republic of Korea

Speaker 1: Ronald See, USA
Title: Oxytocin attenuates drug seeking in a model of psychostimulant addiction and relapse
Abstract
Oxytocin has been proposed as a potential treatment approach in drug addiction, but little is known about the effects of oxytocin in translationally relevant models of addiction or the neurobiological substrates of the actions of oxytocin. This presentation highlights the ability of oxytocin to reduce drug taking and drug seeking in a rat model of methamphetamine (meth) addiction.

In the first set of experiments, we developed and applied a behavioral economics model of meth addiction to assess the effects of oxytocin on both meth demand and conditioned cue-induced reinstatement of meth seeking following a period of drug withdrawal. Systemic oxytocin treatment reduced both meth demand (determined by an increase in $\alpha$, the downward acceleration of a demand curve) and reinstatement of cue-induced meth seeking. Notably, oxytocin had the highest efficacy to reduce reinstatement in those rats showing the highest motivation for meth.

A second set of experiments examined the central effects of oxytocin on meth demand and reinstatement. The effects of systemic oxytocin on meth demand were completely blocked by central infusion (icv) of an oxytocin receptor antagonist, while direct application of oxytocin in the nucleus accumbens (NAc) abolished the effects of oxytocin on both meth demand and reinstatement. Finally, oxytocin activity in the NAc was found to be necessary for enhanced meth demand, as central antagonism of oxytocin receptors in the NAc blocked the effects of systemic oxytocin.

Taken together, these results show a centrally mediated action of oxytocin in reducing demand for meth and cue-induced reinstatement of meth seeking. Future development of oxytocin-based pharmacotherapy may be beneficial for psycho-stimulant addiction.

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Speaker 2: Inga D Neumann, Germany
Title: Chronic effects of oxytocin: Are we ready for its therapeutic use?

Abstract
Due to its acute pro-social and anxiolytic properties, and the attenuation of stress responses the neuropeptide OXT has received substantial interest. We have recently shown that OXT promotes social preference behaviour and prevents social phobia induced by social defeat stress in rats and mice. Further, in a mouse paradigm for social fear conditioning, OXT specifically reversed social fear – an effect which was localized within the dorsolateral septum, where social fear was associated with reduced OXT receptor binding.

In contrast to its acute effects, chronic central OXT infusion over 14 days using osmotic minipumps dose-dependently increased anxiety of male mice and reduced OXT receptor binding in the basolateral amygdala, nucleus raphe and dorsolateral septum. At lower dose, continuous chronic infusion of OXT was able to prevent a variety of chronic stress-induced mal-adaptations. We are currently studying the consequences of chronic OXT on OXT receptor-coupled intracellular signaling pathways in males and females.

Although the acute effects point towards the therapeutic use of OXT for anxiety-related disorders including social phobia more detailed behavioral and molecular studies are needed to reveal chronic effects.

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Speaker 3: Youl-Ri Kim, Republic of Korea
Title: Oxytocin as a multidimensional pharmacotherapy in psychiatric disorders

Abstract
The core pathology of anorexia nervosa (AN) is associated with abnormalities in systems related to fear and defense of appetite behavior. Anomalies in social and emotional development have been linked to oxytocin systems. In this session we will (1) review comprehensively the literatures about the possible link between oxytocin and AN, (2) present our findings of genetic and epigenetic variants of the OXTR gene, and of the impact of oxytocin on social processing and appetite in people with AN, and (3) talk about the potential of oxytocin as for AN a treatment via a reduction in the fear circuit.

Speaker 4: Junghee Lee, USA
Title: Oxytocin facilitation of social cognition skills training.

Abstract
Oxytocin (OT) can enhance the salience of social information. We evaluated whether this property of OT would enhance learning during social cognitive skills training exercises in individuals with schizophrenia. Subjects were 27 male schizophrenia outpatients who met DSM-IV-TR criteria for schizophrenia and were taking antipsychotic medications. We also evaluated potential indicators of OT effects in brain.

Methods: Subjects participated in a 6-week (12-session) course of Social Cognitive Skills Training (SCST) that focused on 3 areas: 1. Facial Affect Recognition; 2. Recognizing non-verbal gestures and vocal cues; 3. Empathy. Subjects were randomly assigned to receive either intranasal OT (40 IU) or placebo 30 minutes prior to each session. Hence, each session included both patients taking OT and placebo. We evaluated scores on social cognition measures; clinical symptoms; and neurocognition (MATRICS Consensus Cognitive Battery (MCCB)). Participants only received OT immediately prior to each training session; they did not receive OT between sessions or on the day of assessments. In a separate study we evaluated two potential biomarkers indicating OT’s target engagement in brain: pupillary response to a facial identification task and EEG mu suppression during a biological motion task. For these studies patients received single intranasal doses of OT or placebo in randomized order one week apart.

Results: 13 patients were randomized to receive OT and 14 to placebo, and there were no significant demographic differences between the groups. On the social cognitive tests, subjects receiving OT demonstrated significantly greater improvements.