physiology, 2012). On the other hand, we have revealed that repeated 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 temporoammonic-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 pathophysiologically 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