that grow up quite normally until they undergo the normal adolescent maturation. At this time, they exhibit a number of morphological, neurochemical, physiological and behavioural alterations that include deficits in PV interneurons. About 50% of prefrontal cortical interneuron show oxidative stress, as revealed by labelling with 8-oxo-DG, while other interneuron types are not affected. Treating the NVHL rats with the glutathione precursor N-acetyl-cysteine (NAC), the NADPH oxidase inhibitor apocynin, or the glutathione reductase mimic ebselen, reversed or prevented the PPI deficits typically observed in this model. NAC treatment also reversed electrophysiological alterations including the translatable finding of reduced mismatch negativity in adult NVHL rats. Overall, the data suggest oxidative stress plays a critical role in a model with PV interneuron deficit, that oxidative stress is pervasive in PV cells, and that antioxidant approaches may be beneficial to reverse some deficits.

**Speaker 4: Kim Do, Switzerland**

**Title:** Receptor for Advanced Glycation End-product (RAGE) as linking mechanism between neuroinflammation and oxidative stress

Daniella Dwir, Jan-Harry Cabungcal, Pascal Steullet, Michel Cuenod, Kim Q. Do

**Abstract**

**Institution:** Center for Psychiatric Neuroscience, Dept. of Psychiatry, Lausanne University Hospital, Switzerland

**Background:** In schizophrenia pathophysiology, increasing evidence point to a critical role of redox dysregulation / oxidative stress leading to impairments of fast spiking parvalbumine interneurons (PVI) which are essential for gamma oscillations generation, thus contributing to cognitive deficit. Animal models of psychosis including the ketamine/PCP, NHVL, DISC1, GluN1-KO and gclm KO models converge in showing increase in oxidative stress markers and PVI impairment in prefrontal cortex. PVs surrounded by perineuronal net (PNN), also express matrix metalloproteases (MMPs) which are induced in inflammatory and activated in oxidative stress conditions, potentially leading to PNN degradation. Evidence also indicates the implication of immune dysregulation in schizophrenia, highlighted by anomalies in peripheral immune cells and association with immune-related genes in genome-wide association studies. In a transgenic mouse model with glutathione (GSH) synthesis deficit (gclm KO), we investigate the interaction between oxidative stress and neuroinflammation in early development and its effect on PVI/PNN circuitry in adulthood.

**Methods:** In gclm KO versus WT mice, we compared by immunohistochemistry the expression of oxidative stress markers (8-oxoDG), microglia markers (Iba1, CD11b and CD68), Receptor for Advanced Glycation End-product (RAGE) and the metalloprotease MMP9 in anterior cingulate cortex (ACC) at peripuberty (P40) and adulthood (P90). Mice were treated with dopamine reuptake inhibitor (GBR12909; P10-P20) to mimic environmental insults which induce additional oxidative stress.

**Results:** GBR treatment in young mice led to increased 8-oxoDG and microglia activation, decreased PVI and PV-PNN immunoreactivity in adult gclm KO, showing a tight interaction between the oxidative stress and pro-inflammatory state and a long-term effect of an early oxidative insult. Microglia activation was more pronounced at peripubertal stage compared to adulthood, suggesting a developmental vulnerability in gclm KO. We explored the role of RAGE, which is activated by ligands produced by oxidative stress, and found increased RAGE shedding in neurons as well as increased MMP9-IR in gclm KO at P40. Interestingly, a specific inhibitor of MMP9 prevented RAGE shedding and microglia activation in the ACC of P40 gclm KO, demonstrating the critical involvement of MMP9 in this process. MMP9 inhibition might thus also limit oxidative stress and PVI/PNN deficit.

Conclusion: RAGE shedding via MMP9 is a key regulatory mechanism by which oxidative stress interacts with neuroinflammatory condition. This pathological interaction in early development might be a potential trigger of adulthood PVI and PNN impairments observed in schizophrenia.

**S22: Stress, time and the brain a dynamic role in neuro psychiatric pathophysiology and treatment**

**Chair:** Maurizio Popoli, Italy

**Co-Chair:** Tomoyuki Fruyashiki, Japan

**Speaker 1: Nuno Sousa, Portugal**

**Title:** The temporal dynamics in the stressed brain

**Abstract**

The notion that there is a single and constant stress neuromatrix is no longer sustainable. In fact, acute stressors trigger an activation of particular neuronal networks, which after prolonged maladaptive stress exposure shift to other brain regions outside those networks. This suggests that there is a distinction between the acute- and the chronic-stress neuromatrix. During this talk, a new working model to understand the shift between these networks will be presented; in this model there are independent, albeit interacting, steps, which are modulated by factors that may explain the dynamics of the chronic stress brain construct: i) susceptibility; ii) response and initial injury; iii) transition to chronicity; iv) maintenance of a “stressed-brain”.

As a result, in the chronic stress stage, perception and salience of a stressor is a modified emotional and hedonic construct, where threat/value assessment and memory traces of stressful experiences are incorporated, eventually in an “altered mode”. Indeed, according to this model the transition from acute to chronic stress entails also a transition in the salience of a stressor from a simple sign of external threat/challenge into a pathological construct. Thus, the understanding of the factors that modulate these networks and their interplay will allow for a more comprehensive and holistic perspective of how the brain shifts “back and forth” from a healthy to a stressed pattern and, ultimately, how the latter can be a trigger for several neurological and psychiatric conditions.

**Speaker 2: Zhen Yan, USA**

**Title:** Bi-phasic Effects of Stress on Synaptic Physiology and Cognitive Behaviors

**Abstract**

Stress has a profound and divergent impact on cognition and emotion, however the neuronal basis underlying the complex actions of stress hormones remains elusive. Our recent years of research have found that acute stress, via glucocorticoid receptor (GR) activation, facilitates working memory via a long-lasting potentiation of the membrane trafficking and synaptic function of NMDARs and AMPARs in prefrontal cortex (PFC), which is dependent on a mechanism involving the induction of serine and glucocorticoid-inducible kinase (SGK) and the activation of Rab4 that mediates receptor recycling (Yuen et al., 2009, PNAS; Yuen et al., 2011, Mol. Psychiatry; Liu et al., 2010, JBC; Lee et al., J.
Physiol., 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 temporopolar-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