

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

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##### Abstract

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**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, NVHL, DISC1, GluN1-KO and *gclm* KO models converge in showing increase in oxidative stress markers and PVI impairment in prefrontal cortex. PVIs 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 serum- 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.