as robust genetic risk factors for ASD, but not all CNV carriers exhibit ASD and the severity of ASD symptoms varies among CNV carriers. Although evidence exists that various environmental factors modulate symptomatic severity, the precise mechanisms by which these factors determine the ultimate severity of ASD are still poorly understood. Here, using a mouse heterozygous for Tbx1 (a gene encoded in 22q11.2 CNV), we demonstrate that a genetically-triggered neonatal phenotype in vocalization generates a negative environmental loop in pup–mother social communication. Wild-type pups used individually diverse sequences of simple and complicated call types, but heterozygous pups used individually invariable call sequences with less complicated call types. When played back, representative wild-type call sequences elicited maternal approach, but heterozygous call sequences were ineffective. When the representative wild-type call sequences were randomized, they were ineffective in eliciting vigorous maternal approach behavior. These data demonstrate that an ASD risk gene alters the neonatal call sequence of its carriers and this pup phenotype in turn diminishes maternal care through atypical social communication. Thus, an ASD risk gene induces, through atypical neonatal call sequences, less than optimal maternal care as a negative neonatal environmental factor.

References

Hiramoto, T., Kang, G., Suzuki, G., Satoh, Y., Kucherlapati, R., Watanabe, Y., and Hiroi, N. (2011) Tbx1: identification of a 22q11.2 gene as a risk factor for autism spectrum disorder in a mouse model. Hum Mol Genet 20; 4775–4785.

Hiroi, N., Hiramoto, T., Harper, K.M., Suzuki, G., and Boku, S. (2012) Mouse models of 22q11.2-associated autism spectrum disorder. Autism S1; 1–9.

Hiroi, N., Takahashi, T., Hishimoto, A., Izumi, T., Boku, S., and Hiramoto, T. (2013) Copy Number Variation at 22q11.2-associated autism spectrum disorder. Autism S1; 1153–1165.

Takahashi, T., Okabe, S., Ó Broin, P., Nishi, A., Ye, K., Beckert, M.V., Izumi, T., Machida, A., Kang, G., Pena, J.L., Golden, A., Kikusui, K., Hiroi, N. (in press) Structure and function of neonatal social communication in a genetic mouse model of autism. Mol Psychiatry

Abstract

The objectives of the current study were to determine the extent to which previously identified increased expression of cytokines in a subgroup of individuals with schizophrenia (40%) relate to markers of oxidative stress, astrogliosis and grey matter volume reductions in postmortem tissue. We utilized a collection of dorsolateral prefrontal cortex tissue from 37 individuals with schizophrenia and 37 controls. Total glutathione was measured using a fluorometric assay. Protein levels of glutathione peroxidase (GPx) and the catalytic subunit of glutamate cysteine ligase (GCLC) were determined by Western blotting. Astrogliosis was assessed by measuring mRNA expression levels of glial fibrillary acidic protein (GFAP) using qRT-PCR, and by examining the morphology of GFAP-positive astrocytes in immunostained sections. Cortical volumes were determined in a subset of 28 individuals with schizophrenia and 22 controls using photographs of fixed postmortem sections and Cavalieri’s probe. GFAP mRNA, astrocyte morphology, GPx and GCLC protein levels were not significantly different between people with schizophrenia and controls overall. The diagnosis of schizophrenia was associated with decreased levels of reduced glutathione and reduced cortical volume. Individuals with schizophrenia who also had increased expression of inflammatory cytokines in the PFC displayed an exacerbated pathology, including decreased levels of reduced glutathione, increased GFAP mRNA, hypertrophic astrocyte morphology, and reduced grey matter volume, particularly in the superior frontal gyrus, relative to individuals with schizophrenia with low levels of inflammatory cytokines and unaffected controls. We conclude that the subgroup of individuals with schizophrenia who had elevated cytokines also show evidence of ongoing oxidative stress vulnerability and neurodegenerative processes such as astrogliosis and cortical volume loss. This has implications for clinical trials of novel therapeutics in schizophrenia, as membership of an inflammatory subgroup may influence treatment response.

S21: Schizophrenia: Oxidative Stress and Inflammation in Schizophrenia: Functional consequences

Chair: Patricio O’Donnell, USA
Co-Chair: Svetlana Ivanova, Russia

Speaker 1: Vibeke Catts, Australia
Title: Relationship between inflammatory cytokines, oxidative stress and astrogliosis markers and prefrontal grey matter volume in schizophrenia subgroups

Vibeke S. Catts 1,2, Yiru Zhang 2,3, Stu G. Fillman 1,2,3, Jenny Wong 1,2,3, Samantha J. Fung 1,2,3, Cynthia Shannon Weickert 1,2,3
1Schizophrenia Research Institute, Liverpool St, Darlinghurst, NSW 2011, Australia 2Neuroscience Research Australia, Randwick, NSW 2031, Australia 3School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, NSW 2052, Australia

Speaker 2: Celso Arango
Title: Inflammation and oxidative stress in early onset psychosis: functional and therapeutic relevance

Speaker 3: Patricio O’Donnell, USA
Title: Oxidative stress in prefrontal cortical interneurons in animal models
Patricio O’Donnell, Jan Cabungcal, Kim Q. Do
Pfizer, University of Maryland

Abstract

Immune molecules and redox pathways are receiving increasing attention for a possible role in pathophysiology of psychiatric disorders. A cell population that may present enhanced vulnerability to the deleterious effects of these mechanisms is the parvalbumin-positive fast spiking interneurons in cortical circuits. This cell population is thought to be affected in schizophrenia, as post-mortem data consistently reveals changes that can be explained by loss of function in these neurons. Remarkably, several different animal models that produce schizophrenia-relevant behavioural deficits such as altered prepulse inhibition of the acoustic startle response converge in showing alterations in this interneuron population. We explored whether oxidative stress was present and whether antioxidant treatment could reverse deficits in one such model, rats with a neonatal ventral hippocampal lesion (NVHL). This model produces animals...
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 6-enebselen, 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 points 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, GshN1-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 degradations. 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-oxoD), 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 experiences which induce additional oxidative stress.

**Results:** GBR treatment in young mice led to increased 8-oxoD 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 peripuberal 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 Fuyashiki, 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.