purified using the Qiagen RNeasy kit. The samples were hybridised to an Agilent SurePrint G3 Rat Gene Expression microarray. Using JMP Genomics 6.1, quality controls were checked and the expression data analyzed to identify genes with different expression profiles. The genes with different profiles were imported into Ingenuity Pathway Analysis to identify pathways affected by ovariectomy and/or estrogen treatment.

Ovariectomy significantly altered the expression profiles of 145 genes, while estrogen treatment altered the expression profiles of 332 genes. Compared to ovariectomised rats, estrogen-treated rats showed changes in gene expression patterns predicted to affect the activity of translation initiation and elongation (p<0.001) as well as the downstream effects of the master regulator, mechanistic target of rapamycin (mTOR; p=0.002).

Importantly, while there was some overlap in altered expression profiles between the ovariectomised animals and those receiving estrogen, these results highlight that removal of sex steroids by ovariectomy substantially differs from estrogen treatment. These data suggest that the effects on translation and mTOR, combined with the effect of estrogen at estrogen responsive elements will have profound and wide-ranging effects in the frontal cortex. This supports the concept that sex steroids play a role in modulating pathways associated with psychosis and schizophrenia, including several neurotransmitter systems (e.g. dopamine, serotonin, noradrenaline, glutamate).

**PM484**

BQCA Allosteric Modulation of [3H]NMS Binding to Human Cortex is Reduced in a Subgroup of Schizophrenia and Modulation by Divalent Cations

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**Abstract**

Muscarinic M, receptor (CHRM1) positive allosteric modulators represent a promising approach to treating the cognitive deficits of schizophrenia. Hence, we decided to extend studies using cloned receptors and animal models to study CHRM1 ortho- and allosteric binding in human cortex. Therefore, we measured the displacement of [3H]NMS (0.13nM) with acetylcholine (0—1mM) in the presence of BQCA (positive allosteric modulator; 0—3µM) using tissue from muscarinic receptor deficient schizophrenia (MRDS) subjects (defined by a marked loss in [3H]pirenzepine binding to cortical CHRM1 (~75%), other schizophrenia subjects, and non-psychiatric control subjects). This is a measure of the response of CHRM1 to positive allosteric modulation. CHRM binding sites have been shown to be ion dependent and hence we repeated our experiments using cortex from subjects without psychiatric illness and [3H]NMS (0.13nM) or [3H]pirenzepine (7nM) in the presence or absence of Zn2+ (10mg/ml) and Mg2+ (10mg/ml). As with cloned CHRM1, BQCA increases the affinity of the CHRM1 orthosteric site for acetylcholine in human cortex (logIC50: 0µM BQCA≈−4.95, 0.3µM BQCA≈−5.50, and 3.0µM BQCA≈−6.21). The effect of BQCA was reduced in MRDS subjects (p<0.01; Cohen’s d=−0.948), but not of sufficient magnitude to suggest allosteric modulators will not elicit a response in MRDS subjects. Zn2+ reduced specific [3H]pirenzepine (p=0.025 cohen’s d=−1.625) and [3H]NMS (p=0.0003 cohen’s d=−5.54) binding; Mg2+ and Zn2+ enhanced acetylcholine displacement of [3H]NMS binding (logIC50: 0mg/ml Mg2+ or Zn2+=−4.091; 10mg/ml Mg2+=−4.436; 10mg/ml Zn2+=−7.294), but Mg2+ reduced and Zn2+ enhanced displacement of [3H]pirenzepine binding (logIC50: 0mg/ml Mg2+ or Zn2+=−4.656; 10mg/ml Mg2+=−4.380; 10mg/ml Zn2+=−5.029). Additionally, both Mg2+ and Zn2+ enhanced the effect of BQCA on [3H]NMS (logIC50: 0mg/ml Mg2+ or Zn2+=−0.193; 10mg/ml Mg2+=−1.082; 10mg/ml Zn2+=−1.694), but not [3H]pirenzepine (logIC50: 0mg/ml Mg2+ or Zn2+=−0.227; 10mg/ml Mg2+=−0.256; 10mg/ml Zn2+=−0.229), binding. Our data suggests that both orthosteric and allosteric sites of CHRM1 have complex and differing responses to divalent cations.

**PM485**

Association between erythrocyte membrane fatty acids and psychopathology in individuals at ultra-high risk for psychosis

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**Abstract**

**Object**: This study investigated the relationship between erythrocyte membrane fatty acid (FA) levels and the severity of symptoms of individuals at ultra-high risk (UHR) for psychosis.

**Methods**: The study sample consisted of 80 neuroleptic-naïve UHR patients. Associations between baseline erythrocyte membrane FA levels, measured by gas chromatography, and scores on the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale, and the Montgomery–Asberg Depression Rating Scale (MADRS) were investigated. After correlation analysis in all participants, subjects were divided into three groups according to the predominance of positive or negative symptoms based on PANSS subscale scores; membrane FA levels in the three groups were then compared.

**Results**: PANSS negative symptom scores were negatively correlated with two saturated FAs (myristic and margaric acids), one ω-9 monounsaturated FA (MUFA;nervonic acid), and one ω-3 polyunsaturated FA (PUFA; docosapentaenoic acid). Negative symptom scores were positively correlated with two ω-9 MUFAs (eicosenoic and erucic acids) and two ω-6 PUFAs (γ-linoleic and docosadienoic acids). PANSS positive symptom scores were correlated only with nervonic acid. No associations were observed between FAs and MADRS scores. In subjects with dominant negative symptoms, the sum of the ω-9 MUFAs and the ω-6:ω-3 FA ratio were both significantly higher than in those with dominant positive symptoms, whereas the sum of ω-3 PUFAs was significantly lower.

**Conclusions**: Abnormalities in FA metabolism may contribute to the neurobiology of psychopathology in UHR individuals. In particular, membrane FA alterations may play a role in negative symptoms, which are primary psychopathological manifestations of schizophrenia-related disability.

**PM486**

Disrupting GluR2-GAPDH Interaction Affects Axon and Dendrite Development

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**Abstract**

**Object**: This study investigated the relationship between already mentioned neuroleptic-naïve (i.e., no prior use of antipsychotic medication) and no prior exposure to atypical antipsychotics) patients. Associations between baseline erythrocyte membrane FA levels, measured by gas chromatography, and scores on the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale, and the Montgomery–Asberg Depression Rating Scale (MADRS) were investigated. After correlation analysis in all participants, subjects were divided into three groups according to the predominance of positive or negative symptoms based on PANSS subscale scores; membrane FA levels in the three groups were then compared.

**Results**: PANSS negative symptom scores were negatively correlated with two saturated FAs (myristic and margaric acids), one ω-9 monounsaturated FA (MUFA;nervonic acid), and one ω-3 polyunsaturated FA (PUFA; docosapentaenoic acid). Negative symptom scores were positively correlated with two ω-9 MUFAs (eicosenoic and erucic acids) and two ω-6 PUFAs (γ-linoleic and docosadienoic acids). PANSS positive symptom scores were correlated only with nervonic acid. No associations were observed between FAs and MADRS scores. In subjects with dominant negative symptoms, the sum of the ω-9 MUFAs and the ω-6:ω-3 FA ratio were both significantly higher than in those with dominant positive symptoms, whereas the sum of ω-3 PUFAs was significantly lower.

**Conclusions**: Abnormalities in FA metabolism may contribute to the neurobiology of psychopathology in UHR individuals. In particular, membrane FA alterations may play a role in negative symptoms, which are primary psychopathological manifestations of schizophrenia-related disability.
Abstract
Object: This study investigated the relationship between erythrocyte membrane fatty acid (FA) levels and the severity of symptoms of individuals at ultra-high risk (UHR) for psychosis.

Methods: The study sample consisted of 80 neuroleptic-naïve UHR patients. Associations between baseline erythrocyte membrane FA levels, measured by gas chromatography, and scores on the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale, and the Montgomery–Åsberg Depression Rating Scale (MADRS) were investigated. After correlation analysis in all participants, subjects were divided into three groups according to the predominance of positive or negative symptoms based on PANSS subscale scores; membrane FA levels in the three groups were then compared.

Results: PANSS negative symptom scores were negatively correlated with two saturated FAs (myristic and margaric acids), one ω-9 monounsaturated FA (MUFAs:nervonic acid), and one ω-3 polyunsaturated FA (PUFAs: docosapentaenoic acid). Negative symptom scores were positively correlated with two ω-9 MUFAs (eicoseneoic and erucic acids) and two ω-6 PUFAs (γ-linoleic and docosahexaenoic acids). PANSS positive symptom scores were correlated only with nervonic acid. No associations were observed between FAs and MADRS scores. In subjects with dominant negative symptoms, the sum of the ω-9 MUFAs and the ω-6:ω-3 FA ratio were both significantly higher than in those with dominant positive symptoms, whereas the sum of ω-3 PUFAs was significantly lower.

Conclusions: Abnormalities in FA metabolism may contribute to the neurobiology of psychopathology in UHR individuals. In particular, membrane FA alterations may play a role in negative symptoms, which are primary psychopathological manifestations of schizophrenia-related disability.

PM487
Presynaptic protein Piccolo knockdown in the prefrontal cortex induces cognitive and emotional impairment in mice.
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Abstract
Object: In the prefrontal cortex, the phosphorylation level of synaptic vesicle binding protein Synapsin significantly decreased in the Piccolo knockdown mice, but the remarkable abnormalities were not observed on the shape of dendrite and spine and on the expression level of Synaptophysin, NMDAR1 and PSD-95 in the mice. In the behavioral analysis, the Piccolo knockdown mice showed decreased cognitive dysfunction including object recognition, spatial learning and working memory. Furthermore, the locomotor activity in the novel environment increased in the Piccolo knockdown mice, and its hyperlocomotion was improved by the treatment with atypical antipsychotic drug risperidone. Similarly, the impaired prepulse inhibition of the acoustic startle responses in the Piccolo knockdown mice was ameliorated by risperidone.

These results suggest that Piccolo in the prefrontal cortex regulates the release of the neurotransmitter from the presynaptic membrane, and it consequently plays a functional role in the synaptic plasticity, cognitive memory and emotional activity. Furthermore, our observations indicate that the mouse with Piccolo deficient in the prefrontal cortex is useful animal model for the mental disorders such as the manic symptom of bipolar disorder or the positive symptom of schizophrenia.

PM488
Activation of Galphaq proteins coupled with dopamine D1-like receptor and alpha1-adrenoceptor in rat brain membranes
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Abstract
Objectives: Previously, we reported 5-HT1A receptor- and MUscarinic acetylcholine receptor (mAChR)-mediated Gq activation in rat brain membranes (Eur J Pharmacol 726: 109–115, 2014). In this paper, it was noticed that Gq proteins were also activated by dopamine and (-)-epinephrine, although these effects were much lower than that elicited by 5-HT or carbachol. In the present study, activation of Gq coupled to dopaminergic and adrenergic receptor was pharmacologically characterized in rat brain membranes.

Methods: Receptor-mediated activation of Gq in rat brain membranes was assessed by guanosine-5′-O-[(3-[(35)S]thio)triphosphate ([35S]GTP[S]) binding/immunoprecipitation assay (Eur J Pharmacol 726: 109–115, 2014), with minor modifications.

Results: In cerebral cortical membranes, dopamine and (-)-epinephrine stimulated specific [35S]GTP[S] binding to Gq in a concentration-dependent manner, with EC50 values of 65 and 0.46 μM, to the maximal percent increase over basal binding of 99 and 70 %, respectively. The responses in hippocampus and striatum were lower than those in cerebral cortex for either compound. Pharmacological characterization using a series of dopaminergic and adrenergic compounds indicated that dopamine- and (-)-epinephrine-stimulated [35S]GTP[S] binding to Gq was mediated through dopamine D1-like receptor and α1-adrenoceptor, respectively. In these assay systems, however, some compounds behaved against all expectations. For instance, R(+)-SCH23390 and SKF83896, both of which were usually regarded as dopamine D1-like receptor antagonists, exhibited agonistic effects. The α1-adrenoceptor agonist (R)-(−)-phenylephrine did not stimulate the specific [35S]GTP[S] binding to Gq. Although oxymetazoline acted as an agonist, this effect appeared to be mediated by 5-HT1A receptor, but not by adrenergic receptors.