Aims: This project aims to assess whether systemic treatment with ketamine may improve the behavioural response in an animal model of a treatment resistant condition.

Methods: Male Sprague-Dawley rats received subcutaneous injections of ACTH (100ug/rat/day) or vehicle during 14 days. On the 14th day the animals were exposed to the pre-test session of forced swim (FST) and after 24h they were exposed to the open-field test (OFT) followed by the FST test session. The animals received an intraperitoneal injection of ketamine (15mg/kg) or vehicle or imipramine (3 injections of 15mg/kg) 1h before the test session.

Results: The immobility time during the pre-test was increased on the group treated with ACTH (F(14,37)=3.484; *p<0.05; Dunnett). Ketamine, but not imipramine, reduced the immobility time when exposed to the test session (F(14,37)=4.002; *p<0.05; Dunnett). The OFT showed that the drugs did not increase the locomotor activity.

Conclusion: The data suggest that ACTH treatment can induce a pro-depressive-like effect, which highlights its role as an inducer of a treatment-resistant condition. The results reinforce the potential antidepressant-like effects of ketamine in a treatment resistant condition, thus corroborating the literature findings. Further studies are necessary to investigate the mechanisms which ketamine induces its effects on treatment resistant rats.

Keywords: depression, antidepressants, ketamine, treatment resistant.

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PS143
Resetting of neuronal maturation in the adult brain: a novel candidate cellular mechanism of electroconvulsive treatment
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Abstract
Despite a long history of clinical use and well-known high efficacy for depression, the mechanism of action of electroconvulsive therapy (ECT) remains poorly understood. Accumulating evidence suggests that the regulatory mechanism of neuronal maturation could be a promising target for treating psychiatric disorders. In the present study, to explore the cellular mechanism of ECT, we examined the effect of electroconvulsive stimulation (ECS), an animal model of ECT, on the maturation status of granule neurons in the hippocampal dentate gyrus of adult mice. Single or a few times of ECS immediately reduced expression of mature neuronal markers in almost entire population of granule neurons and induced immature neuron-like functional properties such as higher excitability. The phenotypes of the ECS-treated neurons resembled those of the intermediate developmental stage. Repeated ECS stabilized such immature-like phenotypes without causing further phenotypic changes toward the younger stage. This stabilization process required NMDA receptor activation likely supported by an excitatory shift of synaptic excitation/inhibition balance in the ECS-treated neurons. These results demonstrate that brief neuronal activation by ECS and subsequent enhancement of excitability can consistently reset mature hippocampal neurons to the particular immature state. The global increase in neuronal excitability accompanying this resetting could improve perturbed neuronal activity in pathological conditions and thus may be relevant to highly effective antidepressant action of ECT.

PS144
Dopamine D1 receptor in the medial prefrontal cortex mediates behavioral resilience under stress in mice
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Abstract
Physical and psychological stress can cause not only emotional and cognitive disturbance, but also behavioral resilience to stress, depending on the duration and severity of stress. Whereas rodent studies have extensively examined neural mechanisms about how stress induces harmful behavioral consequences, mechanisms that underlie stress-induced behavioral resilience remains poorly understood. Using social defeat stress in mice, we previously reported that social defeat stress preferentially activates the dopaminergic pathway to the medial prefrontal cortex (mPFC), and that repetition of social defeat stress attenuates this activation, leading to social avoidance. Here we show a role of dopamine D1 receptor in mPFC excitatory neurons for stress-induced behavioral resilience. Repeated social defeat stress reduced mRNA expression of dopamine D1 receptor in mPFC only in mice susceptible to social defeat stress. Knockdown of D1 receptor in whole neuronal populations in mPFC by viral delivery of artificial miRNA enabled single social defeat stress to induce social avoidance. Simultaneous expression of miRNA-resistant D1 receptor mutants in mPFC neurons abolished the effect of D1 knockdown. These data indicate that D1 receptor in mPFC neurons is critical for stress-induced behavioral resilience. Neuron type-specific knockdown of D1 receptor in mPFC revealed that excitatory neurons, but not GABAergic neurons, are the site of action of D1 receptor for stress-induced behavioral resilience. Furthermore, morphometric analyses showed that single stress induces dendritic growth of apical dendrites of mPFC layer 2/3 pyramidal neurons and increases spine density on these dendrites through D1 receptor. Collectively, our findings show that short-term stress induces dendritic remodeling of mPFC pyramidal neurons and behavioral resilience through dopamine D1 receptor.

PS145
Anxiety-like and depressive-like behaviors in rats administered ACTH during early postnatal period
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Abstract
Objective: Negative life experience such as chronic neglect and maltreatment in the early postnatal period can lead to
psychiatric disorders such as depression and anxiety disorder in human. The aim of the present study was to clarify emotional properties in rats repeatedly administered ACTH during the early postnatal period.

**Methods:** Tetracosactide, the N-terminal 24 amino acids of the naturally occurring ACTH, were administered once a day at dose of 100 µg to male rat pups for 5 days on the day 21 after birth (3wACTH). Saline-injected rats were subjected as a littermate control. Emotional properties in 6- and 10-week-old rats were evaluated by the elevated plus-maze test, novelty-suppressed feeding test and sucrose preference test. And we measured the wet weight of adrenal glands in 10-week-old rats.

**Results:** Plasma corticosterone in 3wACTH significantly increased, indicating stress exposure by pharmacological intervention. Three-wACTH showed decrease of time spent in the open arms (elevated plus-maze test), the longer latency to approach a food pellet in the novel environment (novelty-suppressed feeding test) and reduction for sucrose consumption (sucrose preference test). These abnormal behaviors in 3wACTH indicated the anxiety-like and/or depressive-like behaviors, which were observed in 10, but not 6 weeks old. Moreover, adrenal atrophy observed in 10-week-old 3wACTH compared with control.

**Conclusions:** These findings suggest that pharmacological stress (namely ACTH administration) during early postnatal period might produce emotional abnormalities such as the anxiety-like and depressive-like behaviors in adulthood but not adolescent, with a critical developmental period.

### PS146 Norbin: an emerging player in the pathophysiology and treatment of depression?

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**Objective:** The neuron specific protein Norbin has recently been implicated in the pathophysiology of depression (Wang et al, 2015). Norbin positively regulates metabotropic glutamate receptor 5 (mGluR5), which is also thought to be involved in depression and has been identified as a novel therapeutic target. The aim of this study was to examine the protein expression of Norbin in a neurodevelopmental rat model of depression, and determine if any alterations in Norbin were associated with mGluR5.

**Methods:** Brains were extracted from Sprague-Dawley (SD; healthy model) and Wistar-Kyoto (WKY; depression model) rats at postnatal days (PN) 14, 35, and 98 corresponding to juvenile, adolescent and adult time-points. Immunobots were performed on prefrontal cortex (PFC) and hippocampal tissue to measure Norbin and mGluR5 protein levels.

**Results:** Norbin was expressed in both the hippocampus and PFC at all three developmental stages in both rat strains. In the hippocampus, there was a reduction in Norbin protein levels in WKY compared to SD rats, specifically at the adolescent time point (-38%). This was associated with a change in mGluR5 expression at this time point; we observed a reduction in mGluR5 dimer levels (-57%) and an increase in mGluR5 monomer expression, which remained in the adult brain (>100%). In the PFC, Norbin was dramatically increased at adolescence and adulthood in WKY rats compared to SD rats (>100%). While mGluR5 monomer levels were increased at adulthood in the PFC, no significant changes in dimeric expression were observed at any time point examined.

**Conclusion:** These findings provide support for an involvement of Norbin in the pathophysiology of depression. While further studies are required to determine the implications of these differences in Norbin and mGluR5 in WKY rats, targeting mGluR5 or Norbin at adolescence may represent an alternative therapeutic approach for the treatment of depression.

### PS147 Gunn rats show depression-like behavior and microglial activation in the hippocampus

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**Abstract** Recent studies imply that glial activation play a role in the pathogenesis of psychiatric disorders, such as schizophrenia and affective disorder. Although a number of animal studies have attempted to establish appropriate animal models for these psychiatric diseases, the numbers of established models, which show signs or symptoms relevant to the diseases, are limited. We have previously demonstrated that Gunn rats with hyperbilirubinemia show congenital gliosis and schizophrenia-like behavior. Since it is suggested that major depression involves glial activation, we examined whether Gunn rats show depression-like behavior using the forced swimming test (FST) and the tail suspension test (TST). In addition, we quantitatively evaluated microgliosis in the hippocampus of Gunn rats using immunohistochemistry analysis with the microglial marker ionized calcium binding adaptor molecule (IBA)-1.

We employed male homozygous (j/j) Gunn rats and male Wistar rats as normal control individuals. They were all 7 weeks old. In the FST, rats were placed into the water (25±1°C) for 15min. After 24 hours from the habituation, rats were put into the water for 6min. In the TST, rats were suspended from the tail for 5min. All the session were recorded by a video camera. The duration of immobility was measured based on the recorded movie.

Both the FST and TST showed that immobility time of Gunn rats was significantly longer than that of Wistar rats, indicating that Gunn rats have depression-like behavior. The quantitative immunohistochemistry analysis using Image J revealed that hippocampal immunoreactivity for IBA-1 was significantly increased in Gunn rats compared to Wistar rats. These results suggest that Gunn rat could be an animal model of depressive symptoms and activated microglia.

### PS148 Repeated restraint stress induces alteration in maturation makers of dentate gyrus neurons in BALB/c mice

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**Abstract** Stress is widely accepted as a predisposing environmental factor in psychiatric disorders, including depression and schizophrenia. We previously found “immature dentate gyrus (iDG)”, in which almost all the granule cells in the hippocampal dentate