On the other hand, β-endorphin, a cleavage product of pro-opiomelanocortin (POMC), is an endogenous µ-opioid polypeptide primarily produced by the hypothalamus. POMC neuronal cell bodies are primarily localized in the arcuate nucleus (ARC) of the hypothalamus. The terminals of these POMC neurons are distributed throughout the CNS, including the paraventricular nucleus (PVN) of the hypothalamus, which is an important area of the brain to the stress response of the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, β-endorphin released by the activation of the hypothalamic POMC neuron is believed to change innate immune function. In this study, we investigated the role of hypothalamic µ-opioidergic systems in anti-tumor immune responses using the designer receptors exclusively activated by designer drugs (DREADD) system. To perform the activation of hypothalamic POMC neurons, we generated the transgenic mice expressing Gq-coupled human muscarinic M3 DREADD (hM3Dq) protein under the control of the POMC promoter in the hypothalamus. The hM3Dq was activated by a designer drug, clozapine N-oxide (CNO). Under these conditions, CNO-induced activation of hypothalamic POMC neurons significantly suppressed tumor growth in tumor-bearing mice. This suppression of tumor growth induced by the activation of hypothalamic POMC neurons by the administration of CNO was reversed by the pre-microinjection of naloxone into the PVN. Furthermore, CNO-induced activation of hypothalamic POMC neurons significantly decreased the plasma level of corticosterone and increased the number of NK cells in the spleen. These findings suggest that β-endorphin released by the activation of hypothalamic POMC neurons may suppress tumor growth via the PVN µ-opioid receptor-mediated suppression of the stress response of the HPA axis and the activation of cell-mediated immunity associated with NK cell activation.

PS14
Gender specific gene-by-environment interaction effects of SLC6A4 polymorphism and childhood maltreatment on anxiety sensitivity
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Abstract
Purposes: Anxiety sensitivity (AS) is a well-established characteristic that predisposes to the development of panic attack and several anxiety disorders. It has been suggested that AS is interactively influenced by genetic and environmental factors such as childhood maltreatment. Serotonin transporter gene (SLC6A4) promoter polymorphism (5-HTTLPR) is regarded as a strong candidate genetic factor for AS. The aim of this study is to examine the effect of childhood maltreatment and SLC6A4 polymorphism, and their interaction on AS by gender.

Methods: Participants were 139 women and 77 men recruited from undergraduate psychology students. They were requested to genotyped for the SLC6A4 polymorphism and complete the measures for AS, Connor Davidson Resilience scale (CDRS) and childhood trauma questionnaire (CTQ). We classified the SLC6A4 polymorphism into the three functional triallelic genotypes: La/La; La/Lg or La/S; and Lg/Lg or Lg/S or S/S. The interaction and main effects of SLC6A4 polymorphism and childhood maltreatment on AS were analyzed by general linear models in all subjects and then in gender-stratified groups. All of the analyses were repeated using the classical biallelic classification without separating Lg from La

Results: High AS score was observed in female gender and participants with childhood maltreatment. In GLM analysis for AS in total subjects, there were significant main effects of gender (p=0.011) and CDRS but interaction effect between SLC6A4 genotype and childhood maltreatment was not observed. However, in separate GLM models by gender, the interaction effect was significant in females (p=0.044) but not in males. In males, there was significant main effect of childhood maltreatment (p=0.039) only. When we perform same analyses using biallelic classification, these gender specific interaction effect were not observed.

Conclusions: Our results suggest that there is gender specificity of the effects of the SLC6A4 polymorphism, childhood maltreatment, and their interaction on AS.

PS15
Can gene therapy treat anxiety? – Overexpression of Neuropeptide S using adeno-associated viral vectors
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Abstract
Objective: Anxiety disorders have a lifetime prevalence of almost 30% and pose a huge burden on both patient and society. Available treatment options commonly induce adverse effects, urging the need for novel compounds. Neuropeptide S (NPS) has attracted attention due to its anxiolytic properties in rodents. The present study investigated the impact of NPS overexpression on anxiety-related behavior by infusing a recombinant adeno-associated virus (rAAV) into the medial amygdala.

Methods: Using stereotaxic surgery, viral vectors (rAAV-NPS vs. rAAV-Empty) were injected bilaterally into the medial amygdala of male adult Wistar rats using a thin glass micropipette. Behavior was characterized using standard anxiety, locomotion and depression tests (Elevated plus maze (EPM), Light/dark box (LDB), Open field (OF), Forced swim test (FST)). Immunohistochemical stainings were performed to verify overexpression of NPS. Statistical significance of differences between treatment groups was assessed using an independent samples t-test.

Results: Results showed that the experimental group (rAAV-NPS) spent significantly more time on the open arm in the EPM paradigm compared to the control group (rAAV-Empty), indicating an anxiolytic effect of NPS (p<0.018). Importantly, this anxiolytic effect could be delineated from locomotion, since no treatment differences across conditions were observed in the OF. Similarly, no confounding effects could be found when measuring body weight or depression-related behavior. Histology revealed NPS-positive cells in the medial amygdala in the experimental but not control group, pointing towards successful transduction.

Conclusions: This is the first study successfully demonstrating anxiolytic properties of NPS via transgenic overexpression. Our results are largely consistent with studies elucidating the role of NPS in acute treatments, therefore providing evidence for the
validity of both our viral vector and distinct long-lasting mechanisms of NPS. In sum, NPS remains an attractive candidate for novel compounds targeting anxiety pathophysiology.

**PS16**
Genetic variation and expression diversity of pituitary adenylate cyclase-activating polypeptide (PACAP) gene in mouse
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**Abstract**

Pituitary adenylate cyclase-activating polypeptide (PACAP) gene codes a peptide hormone that is important for regulation of emotions such as anxiety and fear. However, genetic influence on the functions remains poorly understood. Here we describe genetic variation and expression diversity of the PACAP gene to identify functional differences that influence and contribute to phenotypic diversity among individual mice (Mus musculus). We have investigated sequence variation of the PACAP gene using genome-wide single-nucleotide polymorphism (SNP) genotypes between wild-caught mice (Mus musculus domesticus, WILD) and laboratory mouse strains (LAB). SNP variations within the groups revealed a significant selective sweep around the PACAP gene in WILD, but not in LAB mice. Gene sequence comparison between the groups showed different length of a dinucleotide (GT) repeat in an intron of the PACAP gene. We found a functional role of this cis-regulatory element so that the GT repeat length affects the expression pattern of alternative splicing variants of the PACAP gene. These results indicate a contribution of the genetic variation of the PACAP gene to the expression diversity. We speculated that the genetic diversity is associated with functional diversity of PACAP gene that had a role in the establishment of laboratory mouse strains.

**PS17**
High expression of PACAP gene and the molecular mechanism found in wild-mouse strain showing elevated anxiety-like behavior
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**Abstract**

Stress response is behavioral and physiological responses, in which individual variation of the phenotypes is closely linked with the genetic variation. Wild-derived mouse strain MSM/Ms (MSM) shows higher behavioral responses to stress than laboratory mice in open-field test. Our previous study revealed that the behavioral responses to stress in MSM mice are mapped on Chr17 under the genetic background of laboratory C57BL/6 (B6) mice. In this study, we conducted fine genetic mapping using a series of congenic strains and successfully mapped a locus into about 2.3 Mb region of Chr17, in which only one protein-coding gene PACAP is located. Although there was no non-synonymous polymorphism of the PACAP gene between MSM and B6 strains, the PACAP mRNA and protein levels were significantly increased in hypothalamus of the PACAP congenic mice. This higher PACAP expression was considered as one of the reasons of the altered behavioral responses to stress because PACAP is a neuropeptide that regulates stress responses. The PACAP congenic mice showed increased serum corticosterone levels similar with B6 mice immediately after acute restraint stress, but the increased serum corticosterone levels were significantly prolonged after 1–2 hour of the stress than B6 mice. From these results, we will provide some insights into the functional mechanisms of the PACAP that alters behavioral responses to stress through stress response pathway.

**PS18**
Gray matter correlates of generalized anxiety disorder: a quantitative meta-analysis
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**Abstract**

Purpose: Increasing structural neuroimaging studies have revealed abnormalities of gray matter volume (GMV) in individuals with generalized anxiety disorder (GAD) relative to healthy control subjects (HCS) using voxel based morphometry (VBM) approach. However, the spatial localizations of GMV alterations reported in the existing studies are variable and controversial. Here, we conducted a quantitative meta-analysis for investigating the concurrence across VBM studies to clarify the consistent structural abnormalities underpinning this condition.

**Methods and Materials:** A systematic review was conducted on whole-brain VBM studies comparing GMV alterations between GAD patients and HCS in PubMed, ISI Web of Science, Embase, and MEDLINE databases from January 1996 to January 2016. Coordinates were extracted from clusters of significant GMV difference between GAD patients and HCS. Meta-analysis was performed using the Anisotropic effect size signed differential mapping (AES-SDM) software [1]. A jackknife sensitivity analysis was carried out to test the replicability of the results.

**Results:** A total of 7 datasets comprising 130 GAD patients and 146 HCS were included in the current meta-analysis. GMV enlargements were identified in the right putamen and the right superior temporal gyrus in GAD patients compared to the HCS while GAD patients showed decreased GMV in the left insula. All these findings remained largely unchanged when the jackknife sensitivity analysis was performed.

**Conclusion:** This is the first quantitative meta-analysis exploring cerebral structure alterations in patients with GAD compared with HCS. Our results demonstrated that GMV deficits in insular-limbic-temporal regions were the most consistent neural correlates in GAD, which might contribute to the understanding of the pathophysiology underlying this disorder.

**Reference**

[1] Radua, J., Rubia, K., Canales-Rodriguez, E.J., Pomarol-Clotet, E., Fusar-Poli, P., Mataix-Cols, D., 2014. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. Front. Psychiatry 5, 13.

**PS19**
White Matter Correlates of Anxiety Sensitivity in Panic Disorder
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**Abstract**

Introduction: Anxiety sensitivity refers to fears of anxiety-related sensations, and it is a dispositional variable especially