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P624. Risk Prediction for Posttraumatic Stress Symptoms Following Trauma Exposure

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Background: The renin-angiotensin system has been implicated in post-traumatic stress disorder (PTSD), but the underlying brain mechanism(s) are unclear. Increasing evidence demonstrates that impaired prefrontal cortex (PFC) function can contribute to the maladaptive fear memory in PTSD. Given the high expression of PFC expressing AT2R neurons, here we sought to examine the role of PFC expressing AT2R cells in fear-related behavior.
Methods: Immunohistochemistry plus retrograde tracing and whole-cell patch-clamp recording were performed using the AT2R-eGFP reporter mouse to characterize the PFC AT2R-eGFP+ cells and their limbic connections. Pavlovian fear conditioning combined with real-time PCR was used to detect the AT2R mRNA expression.
Results: AT2R-eGFP+ cells were highly expressed in the PFC (142.1±13.13 cells/mm2). PFC AT2R-eGFP+ cells were majorly glutamatergic neurons (88.1%). Receptor activation with AT2R agonist compound-21 decreased the frequency of spontaneous excitatory postsynaptic currents. Retrograde labeling revealed some of the AT2R-eGFP+ neurons project to the basolateral amygdala, an important brain structure for modulating fear-related memory. The AT2R mRNA expression was increased after fear retrieval (1.061±0.4063 Control v.s. 2.967±0.6256 retrieval, $p<0.01$). Furthermore, the expression of brain-derived neurotrophic factor, a key molecule in fear memory that is involved in the AT2R signaling pathway, was also increased after fear retrieval (1.034±0.2992 Control v.s. 2.501±1.381 retrieval, $p<0.05$) and extinction retention (1.083±0.319 Control v.s. 3.048±1.238 extinction retention, $p<0.01$).
Conclusions: These findings provide neuroanatomical and behavioral evidence for PFC expressing AT2R neurons during the retrieval and extinction of fear memory. Future studies are needed to further investigate how the AT2R neurons in the PFC contribute to fear-related behaviors.
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Keywords: Fear Memory, Renin Angiotensin System, Prefrontal Cortex

P623. Role of Locus Coeruleus Expressing Angiotensin Type 1 Receptors (AT1R) Neurons in Fear Learning and Stress-Induced Anxiety

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Background: The locus coeruleus (LC), which plays critical roles in modulating anxiety-like behaviors, has been shown to express the renin-angiotensin system (RAS) component angiotensinogen (AGT) and AT1R, but the role of RAS in LC is unknown. Here, we examined the role of LC expressing AT1R neurons in fear- and anxiety-related behaviors.
Methods: RNAscope® technology was used to analyze cellular mRNA expression of AGT while chemogenetics combined with behavioral testing in AT1R-Cre mice mouse was used to examine the role of LC-AT1R cells in fear memory and stress-induced anxiety. Immunohistochemistry plus retrograde tracing was used to characterize LC AT1R-eGFP+ cells and limbic circuit connections.
Results: AGT mRNA and AT1R-eGFP+ immunoactivity were found in LC. Retrograde labeling revealed some of AT1R-eGFP+ neurons send projections to the basolateral amygdala, an important brain structure for modulating stress and fear-related anxiety responses. Silencing the LC AT1R-expressing neurons with the DREADD-CNO system prior to fear extinction training impaired the extinction of learned fear as shown by increased percent freezing during the training (time×drug interaction, $F(7, 70)=3.219$, $p<0.01$, $n=6$). Furthermore, restraint stress-induced anxiety behavior was attenuated by LC AT1R + neuron inhibition, as shown by increased % time in center (2.97±1.14 Saline v.s. 8.6±1.4 CNO, $p<0.05$, $n=6$) in the open field test and increased open arm entries (5±1.3 Saline v.s. 12±1.1 CNO, $p<0.05$, $n=6$) in the elevated plus-maze test.
Conclusions: These findings provide new evidence for an angiotensinergic LC cell type and position the LC AT1R as a potential mediator of noradrenergic regulation in learned fear and stress-induced anxiety.
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Keywords: Anxiety, Fear Memory, Renin Angiotensin System, Locus Coeruleus

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Background: Posttraumatic stress symptoms (PTSS) are common following trauma exposure. Identification of individuals with PTSS at the time of emergency care is important to enable preventive interventions. In this study, we used baseline survey data from two large prospective cohort studies to identify the most influential predictors of PTSS at the time of presentation for emergency care and to develop a clinical decision support tool to identify individuals who develop substantial PTSS.
Methods: Self-identifying white and black American men and women (n=1,546) presenting to one of sixteen emergency departments (EDs) within 24 hours of motor vehicle collision

(MVC) trauma were enrolled. Individuals with substantial PTSS (≥33, IES-R) six months after MVC were identified via follow-up questionnaire. Sociodemographic, pain, general health, event, and psychological/cognitive characteristics collected in the ED and used in prediction modeling. Ensemble learning methods and Monte Carlo cross-validation were used for feature selection and to determine prediction accuracy. External validation was performed on a hold-out sample (30% of total sample).

Results: 25% (n=394) of individuals reported PTSS six months following MVC. Regularized linear regression was the top performing ensemble learning method. The top thirty factors together showed good reliability in predicting PTSS in the external sample (AUC=0.79+/-0.0017). Top predictors included acute pain severity, expectations of recovery, socioeconomic status, self-reported "race/ethnicity", and psychological symptoms.

Conclusions: These analyses add to a growing literature indicating that influential predictors of PTSS can be identified and risk for future PTSS estimated from characteristics easily available/assessable at the time of ED presentation following trauma.

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Keywords: Post-Traumatic Stress Disorder (PTSD), Post-traumatic Stress Symptoms, Symptom Prediction, Machine Learning, Motor Vehicle Collision Trauma

P625. Genetically Regulated Gene Expression in Chronic Pain

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Background: Chronic pain is common worldwide, with devastating social and public health costs. Many psychiatric conditions are commonly comorbid with chronic pain, which can negatively affect treatment outcomes for either condition. Mechanisms of chronic pain development are not fully understood, and treatment is often ineffective. Recent large (N∼480k) GWAS have shown that chronic pain is a complex, polygenic trait with significant CNS involvement, and multiple genetic variants have been associated. However, any functional impact and causal role of these trait-associated genetic variants are not yet known. To address this knowledge gap in the path from genotype to phenotype, Transcriptomic Imputation (TI) approaches such as Predixcan can be applied to existing large GWAS summary statistics.

Methods: Predixcan analysis was carried out on summary statistics for Multisite Chronic Pain (MCP). Briefly, gene expression is decomposed into 3 components: GReX (Genetically Regulated Gene Expression), a reverse-causal component, and a component attributed to environment/ other factors - Predixcan tests for association between GReX and MCP.

Significant association results were analysed using FUMA GENE2FUNC, highlighting pathways of interest.

Results: 146 gene associations across 49 different tissues were found, and pathways including neutrophil activity, pyrimidine and GDP-mannose metabolism, and regulation of postsynaptic processes were highlighted.

Conclusions: These analyses found genes of interest for chronic pain, prioritizing causal genes, showing tissue locations, and indicating direction of effect in relationships between gene expression changes, and chronic pain. These findings have the potential to inform treatment targets, and contribute to understanding of neurobiological contributions to chronic pain and psychiatric disorder overlap.

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Keywords: Chronic Pain, Psychiatric Genetics, Transcriptomic Imputation

P626. Epigenome-Wide Meta-Analysis of >2100 Military and Civilian Participants Reveals New DNA Methylation Patterns Associated With PTSD

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Background: Epigenetic factors, including DNA methylation (DNAm), participate in adaptation to traumatic stress, and may help to distinguish between individuals with and without PTSD. Here, we present the results of the largest epigenome-wide association study (EWAS) of PTSD to date.

Methods: This study includes 2139 participants (704 PTSD cases and 1435 trauma-exposed controls) from ten cohorts participating in the Psychiatric Genomics Consortium (PGC) PTSD Epigenetics Workgroup. PTSD was assessed by each individual cohort according to the harmonization principles adopted by the PGC-PTSD Workgroup. DNAm was assayed from blood with the MethylationEPIC BeadChip (approximately 850K CpGs assessed). A common QC pipeline was applied to each of the cohorts. Within each cohort, DNAm was regressed on PTSD, sex (if applicable), age, cell proportions, and ancestry. To provide additional insight into earlier findings, we evaluated 35 PTSD-associated CpGs from a previous PGC-PTSD EWAS.

Results: Five CpGs near BANP, NRROS, SNX29, TAGLN3, and KATNAL2 and two intergenic CpGs associated with